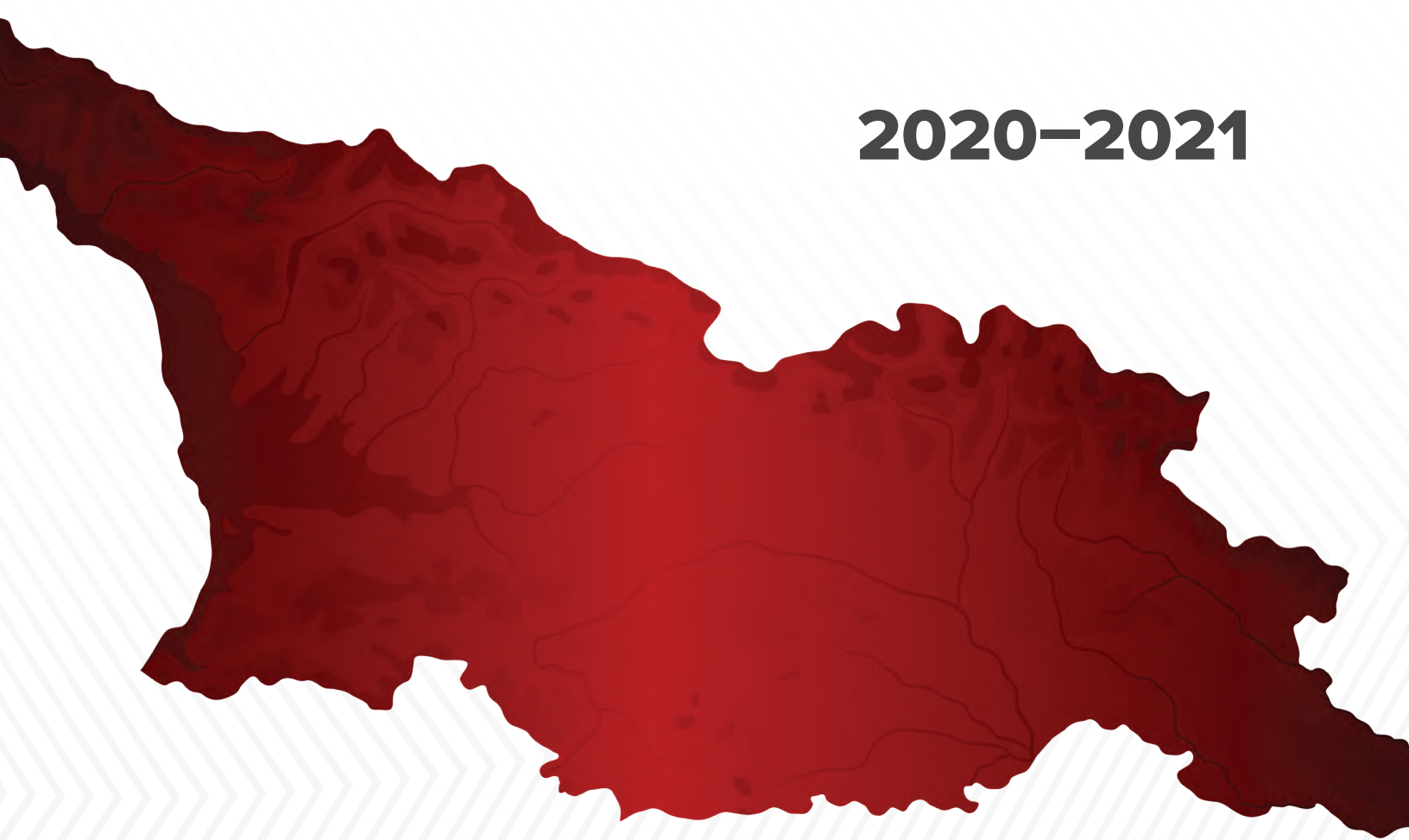




GEORGIA
HEPATITIS
ELIMINATION
PROGRAM
PROGRESS REPORT

2020–2021



MINISTRY OF INTERNALLY DISPLACED
PERSONS FROM THE OCCUPIED
TERRITORIES, LABOUR, HEALTH AND
SOCIAL AFFAIRS OF GEORGIA



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GEORGIA HEPATITIS ELIMINATION PROGRAM **PROGRESS REPORT**

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The information presented in this report is the work of individuals and does not necessarily represent the position of the US Centers for Disease Control and Prevention.

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases	IBSS	Integrated Bio-Behavioural Surveillance Study
Anti-HBc	Antibody to Hepatitis B core	IPC	Infection Prevention and Control
Anti-HCV	Antibody to HCV	M&E	Monitoring and Evaluation
CDC	Centers for Disease Control and Prevention	MoIDPLHSA	Georgia Ministry of Internally Displaced Persons from the Occupied Territories, Health, Labour, and Social Affairs
Core Ag	Core Antigen	MSM	Men who have Sex with Men
DAA	Direct-Acting Antiviral	NAT	Nucleic Acid Testing
EASL	European Association for the Study of the Liver	NCD	Non-Communicable Disease
ECHO	Extension for Community Healthcare Outcomes	NCDC	National Center for Disease Control and Public Health
EIDSS	Electronic Integrated Disease Surveillance System	NSP	Needle and Syringe Program
EQA	External Quality Assurance	OST	Opioid Substitution Therapy
FDA	U.S. Food and Drug Administration	PDI	Peer-Driven Intervention
FIND	Foundation for Innovative New Diagnostics	PHC	Primary Healthcare Center
GHOST	Global Hepatitis Outbreak Surveillance Technology	PPE	Personal Protective Equipment
GHRN	Georgia Harm Reduction Network	PSE	Population Size Estimate
HBsAg	Hepatitis B surface Antigen	PWID	People Who Inject Drugs
HBV	Hepatitis B Virus	PLHIV	People Living with HIV
HCC	Hepatocellular Carcinoma	RDT	Rapid Diagnostic Test
HCV	Hepatitis C Virus	SC	Scientific Committee
HCW	Healthcare Worker	SOP	Standard Operating Procedure
HDV	Hepatitis D Virus	SVR	Sustained Virologic Response
HIV	Human Immunodeficiency Virus	TAG	Technical Advisory Group
HR	Harm Reduction	TTI	Transfusion Transmitted Infections
		TB	Tuberculosis
		WHO	World Health Organization

ORIENTATION TO THE REPORT

This report highlights the impact of various policy changes and initiatives that occurred from January 2020 through December 2021, aimed at improving outcomes across the continuum of hepatitis C care. This report supplements the findings in the National Hepatitis C Virus Elimination Progress Report, 2015–2017 (1), National Hepatitis C Virus Elimination Progress Report, January 1, 2017–June 30, 2018 (2), and National Hepatitis C Elimination Program Progress Report, 2018–2019 (3). This report includes the following:

- Highlights of accomplishments and key findings
- Tables containing monitoring and evaluation data on key performance indicators for the reporting period
- Technical Advisory Group (TAG) recommendations
- Appendices (1–3) including clinical algorithms, diagnostics, and scientific materials

The information contained in this current progress report mirrors the following six elimination strategies presented in the larger Strategic Plan for the Elimination of Hepatitis C Virus in Georgia, 2016–2020 (4) and Strategic Plan for the Elimination of Hepatitis in Georgia, 2021–2025 (5).

- 1.** Improve Advocacy, Awareness, Education, and Partnerships for HCV-Associated Resource Mobilization
- 2.** Prevent HCV Transmission through Harm Reduction, Blood Safety, and Infection Prevention and Control
- 3.** Identify Persons Infected with HCV and Link Them to Care
- 4.** Improve HCV Laboratory Diagnostics
- 5.** Provide Comprehensive HCV Care and Treatment
- 6.** Improve HCV Surveillance

For the purposes of this report, the 2016–2020 strategic plan strategy headings will be utilized throughout, as the majority of the activities reported occurred under that strategic plan. Subsequent reports will utilize the strategies from the 2021–2025 strategic plan.

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1. Available from: <https://www.moh.gov.ge/uploads/files/2019/Failebi/25.04.2019-1.pdf>
 2. Available from: <https://www.moh.gov.ge/uploads/files/2019/Failebi/25.04.2019-2.pdf>
 3. Available from: <https://ncdc.ge/#/blog/blog-list/33a11d14-e71c-4b28-ad39-d6670090664c>
 4. Available from: https://www.moh.gov.ge/uploads/files/2017/akordeoni/failebi/Georgia_HCV_Elimination_Strategy_2016-2020.pdf
 5. Available from: <https://centre-of-excellence.easl-iff.org/>

PROGRESS TOWARDS HCV AND HBV ELIMINATION IN GEORGIA: RESULTS FROM 2021 NATIONWIDE SEROSURVEY

BACKGROUND

In 2015, the country of Georgia launched the world's first national hepatitis C virus (HCV) elimination program with a goal of reducing prevalence by 90%. To establish baseline prevalence, Georgia conducted its first nationally representative seroprevalence survey that same year. The 2015 serosurvey used a household design and recruited 6,296 adults age 18 years or older. An estimated 7.7% of the adult population had evidence of exposure to hepatitis C (anti-HCV), and 5.4% had chronic HCV infection (HCV RNA). Additionally, the chronic hepatitis B virus (HBV) prevalence was 2.9% among adults (HBsAg). Injection drug use (IDU) and blood transfusion were the risk factors found to be associated with HCV exposure, and blood transfusion and incarceration were the risk factors for chronic HBV infection. These results estimated that 150,000 people were living with chronic HCV infection at the time. Since then, the Georgia Hepatitis C Elimination Program has made great progress, treating over 76,000 people—more than half of the estimated number infected—and achieving a cure rate of 98.9%.

Hepatitis B vaccination was introduced into the national schedule in 2001, and hepatitis B birth dose (HepB-BD) was added two years later in 2003. Since then, vaccination rates among children have remained consistently high, particularly since 2010 (>90%). Vaccination for hepatitis B is prioritized for certain adult populations (e.g., healthcare workers, hepatitis C program beneficiaries), but coverage rates are low. Testing and treatment for adults living with chronic hepatitis B (approximately 80,000 adults based on the 2015 serosurvey) remain limited, and in response, hepatitis B was included in Georgia's 2021–2025 Strategy for Viral Hepatitis Elimination.

The achievements of the Georgia Hepatitis C Elimination Program and hepatitis B vaccination efforts in Georgia have been critical in developing Georgia's current public health capacity, including the ongoing response to COVID-19. However, challenges remain in identifying individuals infected with HCV and linking them to care, especially among certain key populations (e.g., persons who inject drugs). Recognizing the need to monitor progress towards HCV and HBV elimination, the Government of Georgia (GoG), led by the Ministry of Internally Displaced Persons from the Occupied Territories, Health, Labour, and Social Affairs (MoIDPLHSA) and the National Center for Disease Control and Public Health (NCDC), conducted a second nationwide serosurvey on hepatitis B and hepatitis C from June through October 2021, in partnership with the U.S. Centers for Disease Control and Prevention's (CDC) Division of Viral Hepatitis and Global Immunization Division. The serosurvey also included SARS-CoV-2, but those results will not be presented in this summary.

The 2021 serosurvey included children 5–17 years and adults 18 years of age or older. The primary objectives were to estimate exposure to and prevalence of hepatitis C and hepatitis B infection among children and adults, assess risk factors and geographic distribution associated with infection, and update information on knowledge and perceptions toward hepatitis. The results of the serosurvey were also intended to measure progress toward the WHO viral hepatitis elimination goals.



METHODS

SAMPLE SELECTION

The nationwide household survey was conducted from June through October 2021 using a stratified, multi-stage cluster design with systematic sampling. Ten strata were defined across all the regions and the capital city of Tbilisi, with 267 clusters identified and 30 households selected per cluster. Households were chosen systematically using a skip pattern, and one adult and one child of eligible age (where applicable) were selected per household using a Kish grid. The population included adults aged 18 years or older and children aged 5–17 years living in randomly selected households in Georgia, excluding the separatist regions of Abkhazia and South Ossetia. A sample size of 8,010 adults and 2,692 children was calculated based on an estimated anti-SARS-CoV-2 prevalence of 10% and an anticipated 70% participation rate to produce 95% confidence intervals. An additional 1,880 households were included for children to account for low initial enrollment.

Data collection in the field took place over a period of four months. Individual interviews were administered using a structured questionnaire with responses recorded electronically. Each participant’s data included a unique identifier (barcoded label) that was linked to their blood sample for tracking and confidentiality purposes.

INCLUSION/EXCLUSION CRITERIA

Randomly selected members of each household were eligible for participation, and those who provided voluntary informed consent (or assent paired with parental/legal guardian consent for children) were enrolled. A household was defined as a group of persons who reside in the same place and prepare meals together. Children aged less than 5 years, adults with mental illness, any participants who could not give blood because of severe illness or hemophilia, and any participants who refused participation or blood draw were excluded.

TESTING ALGORITHM

All samples were tested for hepatitis C antibodies (anti-HCV) and total antibody to HBV core antigen (anti-HBc) at the Serology Laboratory, Lugar Center for Public Health Research, NCDC. Positive samples were further tested for confirmation of chronic infection and virus characterization. Anti-HCV positive samples were tested for HCV RNA, and, if infection was identified, genotyping was also performed. Anti-HBc positive samples were tested for HBV surface antigen (HBsAg), and those positive for HBsAg were tested for HBV DNA. Test results were provided to participants within a maximum of six months of sample collection, and both HCV- and HBV-infected individuals were counseled and referred to a local provider for care and treatment.

STATISTICAL ANALYSIS

Data were weighted at cluster, household, and individual levels and adjusted by sex, age, and geographic distribution using 2014 census data to produce nationally representative estimates. Weighted proportions and 95% confidence intervals (95% CI) (Wilson, with continuity correction) were calculated and compared with 2015 survey results using a chi-square test with an alpha of 0.05. All analysis was performed in SAS version 9.4 (Cary, North Carolina, USA).

RESULTS

A total of 8,710 individuals participated in the survey, including 7,237 adults (90.3% participation rate) and 1,473 children (72.2% participation rate). Among adults, the median age was 46 years (interquartile range [IQR]: 32–60), 53.3% (95% CI: 51.3–55.2) were female, and a plurality (31.8% [95% CI: 30.6–33.0]) lived in Tbilisi. **The 2021 adult prevalence of anti-HBc was 21.7% (95% CI: 20.4–23.2), of HBsAg was 2.7% (95% CI: 2.2–3.4), of anti-HCV was 6.8% (95% CI: 5.9–7.7), and of HCV RNA was 1.8% (95% CI: 1.3–2.4).** There was a slight reduction in



anti-HBc prevalence compared to 2015 (25.9% [95% CI: 24.1–27.6]; $p < 0.001$), while the prevalence of HBsAg (2.9% [95% CI: 2.4–3.5] in 2015; $p = 0.62$) and anti-HCV (7.7% [95% CI: 6.6–8.8] in 2015; $p = 0.20$) remained stable. **There was a substantial decrease in HCV RNA prevalence from 2015 (5.4% [95% CI: 4.5–6.3], $p < 0.0001$), representing a 67% reduction in chronic HCV infection among adults since the start of the Georgia Hepatitis C Elimination Program.** Prevalence of chronic HCV infection decreased among all age groups, but most notably among those aged 40–49 years (from 9.8% in 2015 to 2.7% in 2021) and 50–59 years (from 8.7% to 1.6%). Those aged 40–49 years had the highest positivity rate (2.7%), while the lowest positivity rate was among those aged 18–29 years (0.9%). Substantial decreases were also observed for both males (from 9.0% to 3.1%) and females (from 2.2% to 0.6%).

Independent risk factors for hepatitis C in 2015 included history of IDU and receipt of a blood transfusion. Rates of both risk factors decreased in 2021: the rate of reported lifetime IDU decreased from 4.2% (95% CI: 3.4–5.1) in 2015 to 3.0% (95% CI: 2.3–3.9) in 2021, $p = 0.03$, and blood transfusions decreased from 7.0% (95% CI: 6.1–7.8) to 4.7% (95% CI: 3.9–5.5), $p < 0.001$. **Among those reporting risk factors, the proportion with chronic HCV infection also decreased substantially, from 51.1% to 17.8% among injection drug users, 13.1% to 3.8% among those who received a blood transfusion. Those with a history of incarceration also declined from 32.3% to 14.6%.**

Despite the ongoing Georgia Hepatitis C Elimination Program, awareness of the hepatitis C virus decreased from 73.0% (95% CI: 71.1–74.9) in 2015 to 66.1% (95% CI: 63.9–68.2) in 2021 ($p < 0.0001$). However, among those who had heard of the virus in 2021, significantly more were aware it could be cured with medications (77.2% [95% CI: 75.1–79.2] in 2021 vs. 70.5% [95% CI: 68.5–72.6] in 2015; $p < 0.0001$). **Additionally, as a testament to the program, among those aware of their own HCV infection, 79.9% (95% CI: 71.4–86.4) reported having been treated, up from just 28.1% (95% CI: 18.2–37.9) in 2015.** Knowledge of the hepatitis B virus remained stable between the two surveys; 34.9% (95% CI: 32.6–37.4) had heard of the virus in 2021 compared to 36.5% (95% CI: 34.4–38.6) in 2015 ($p = 0.36$). Among those who had heard of HBV in 2021, 46.0% (95% CI: 42.4–49.6) knew it could be treated with medication, compared to 42.8% (95% CI: 39.9–45.8) in 2015 ($p = 0.32$).

Among children, the median age was 10 years (IQR: 7–13), 52.3% (95% CI: 48.8–55.8) were male, and 33.0% (95% CI: 30.5–35.6) lived in Tbilisi. **The child prevalence of anti-HBc was 0.7% (95% CI: 0.3–1.6), and HBsAg prevalence was 0.03% (95% CI: 0.0–0.2), much lower than the European regional hepatitis B control target of <0.5%. Only one child in the sample tested positive for HBsAg. The child was born in 2013 when there was a HepB-BD vaccine shortage and had received only one dose of hepatitis B vaccine at 2 months of age.** No children in the sample tested positive for anti-HCV or HCV RNA.

CONCLUSIONS

The prevalence of HCV RNA among adults is now 1.8%, which corresponds to approximately 48,600 people with chronic HCV infection. Since the beginning of the Georgia Hepatitis C Elimination Program in 2015, there has been a 67% reduction in chronic HCV infections, while rates of anti-HCV, anti-HBc, and HBsAg among adults have remained relatively stable. Unlike in 2015, children were included in the current study; none tested positive for hepatitis C, and only one child tested positive for chronic HBV infection, confirming good coverage with hepatitis B vaccination and demonstrating achievement of regional hepatitis B control targets. Among those aware of their HCV infection, the proportion reporting having been treated increased from 28% to 80%. Among those reporting IDU, the proportion of chronic HCV infection has declined considerably (from 51.1% to 17.8%). These results demonstrate substantial progress toward HCV elimination in Georgia, as well as the achievement of regional control targets for hepatitis B and success of the vaccination program.

ACCOMPLISHMENTS BY STRATEGIC DIRECTION

STRATEGY 1.

IMPROVE ADVOCACY, AWARENESS, EDUCATION, AND PARTNERSHIPS FOR HCV-ASSOCIATED RESOURCE MOBILIZATION

The government of Georgia has supported communication campaigns to raise awareness about the importance of early HCV diagnosis and to ensure that all Georgians can be tested and receive highly effective treatment for free. A variety of activities were undertaken with the contribution of numerous stakeholders working across a range of settings to increase professional and public understanding of hepatitis C and to help find patients who are undiagnosed and untreated.

KEY ACCOMPLISHMENTS AND FINDINGS

- From 2020 through 2021, social media, government websites (<https://www.moh.gov.ge/> and <https://www.ncdc.ge/>), and TV media were used to provide real-time information about the Georgia Hepatitis C Elimination Program to the general population, high-risk subgroups, patients, healthcare professionals, and international partners. Activities included the following:
 - Social media:
 - ◆ Sixty HCV-related blog posts, 20 banners, 10 video blogs, and more than 10 live streaming videos of campaign activities on Facebook
 - <https://www.facebook.com/hepatitiscgeorgia>
 - ◆ Five HCV treatment providers' live chats on Facebook responding to questions
 - ◆ Five social media influencer-led live discussion sessions targeting the general population; posts shared on three popular social media groups with more than 100,000 participants
 - ◆ Two animated videos produced for social media outlets:
 - <https://www.facebook.com/hepatitiscgeorgia/videos/936870560574004>
 - <https://www.facebook.com/hepatitiscgeorgia/videos/339230304257407>
 - Television, radio, and print:
 - ◆ More than 20 television reports and shows with invited guests (hepatitis experts, Ministry and NCDC leadership, physicians, and patient associations) to provide information to the general population on HBV, HCV, how to access the Georgia Hepatitis C Elimination Program, and program progress
 - ◆ One video clip was produced for a television campaign:
 - <https://www.youtube.com/watch?v=rYHFRDkMUFg>
 - ◆ Five radio shows, 12 articles, and 10 reports in print and online media
 - ◆ Media advertisements (six radio and seven television) conducted for one month

- A small-scale pre- and post-test survey was conducted among general population (300 participants) to evaluate the effectiveness of the social media, television, radio, and print campaign. According to the survey, awareness and knowledge of key aspects of the Georgia Hepatitis C Elimination Program services and the disease have increased; low risk perception and stigma remained the most frequently named barriers to being tested or enrolling in the treatment program.
- During 2021, the Hepatitis C Cured Patient Association and their partners carried out population-based interventions, including the following:
 - Held 10 informational meetings with different target groups (e.g., vulnerable populations, ethnic minorities) throughout the country.
 - Identified 20 Elimination Program Ambassadors who participated in a train-the-trainer program on hepatitis awareness, media communication, and peer-to-peer consulting techniques led by health promotion and strategic communication specialists. The Ambassadors trained 185 people and participated in five community outreach testing campaigns conducted in five regions of the country, including among ethnic minority groups (Azerbaijani and Armenian population).
 - Disseminated 30,000 flyers and 1,000 posters during testing campaigns carried out by Hepatitis C Cured Patient Association, local governments, public health organizations, and primary healthcare specialists.
- During World Hepatitis Day 2020 and 2021 campaigns, several communication activities were conducted throughout the country, including
 - Press conference with participation from policymakers, service providers, and media.
 - Public screening campaign in the streets by the Hepatitis C Cured Patient Association and their partners.
 - Television and radio specials featuring hepatitis guest speakers.

ACCOMPLISHMENTS BY STRATEGIC DIRECTION

STRATEGY 2.

PREVENT HCV TRANSMISSION THROUGH HARM REDUCTION, BLOOD SAFETY, AND INFECTION PREVENTION AND CONTROL

Preventing new HCV infections is crucial to achieving elimination goals. Although increased awareness of the risks associated with hepatitis C transmission can support prevention efforts, coordinated efforts are also needed in other areas, including integration of HCV services at harm reduction sites; provision of services and monitoring of coverage provided at needle and syringe programs (NSP) and opioid substitution treatment (OST) programs; and robust blood bank and infection, prevention, and control (IPC) practices.

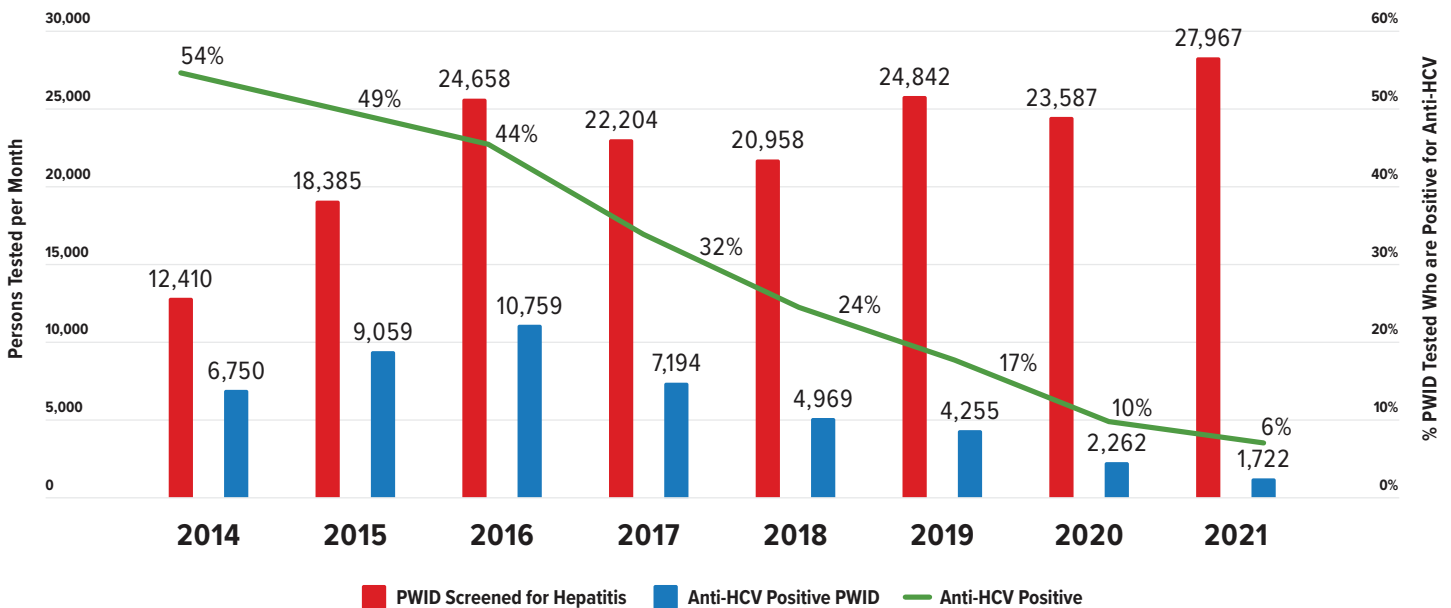
HARM REDUCTION

KEY ACCOMPLISHMENTS AND FINDINGS

- Harm reduction (HR) services have been expanded considerably in both scope and scale through the addition of service delivery locations:
 - HCV and HBV antibody screening is available at 14 NSP sites and 9 mobile units, employing over 200 HR workers. Stationary HR sites provide services to 11 cities and cover more than 45 cities with mobile outreach.
 - The screening efforts among PWID substantially increased the total number of PWID aware of their HCV infection status, from 17,103 in 2016 to 27,967 in 2021 (Georgian Harm Reduction Network data). The proportion of PWID testing positive for anti-HCV decreased from 25% in 2016 to 6% in 2021.
 - The number of PWID tested for HBsAg increased from 16,755 to 31,098 during the last five years, with positivity rates decreasing from 5.7% in 2016 to 2.5% in 2021. The overall number of anti-HBV-positive PWID identified during the last five years is 4,849.
 - HCV and HBV screening are provided as part of the pre-enrollment process at all 22 OST clinics, with a total capacity of 13,000–14,000 beneficiaries. The number of patients enrolled in the program has increased from 7,381 in 2017 to 11,515 in 2021.
 - During the last five years, among persons in the screening registry who screened anti-HCV positive at HR centers, 4,489 were tested for HCV viremia (RNA and core antigen), including 1,112 tested in 2020–2021. Overall, 3,741 PWID were confirmed as having active HCV infection, including 891 cases confirmed in 2020–2021.

- From 2017–2021, among 3,741 PWID with confirmed viremic infection after screening anti-HCV positive at HR centers, 2,764 (73.9%) completed HCV treatment, including 864 persons who received treatment in 2020–2021. Overall, sustained viral response (SVR) was achieved in 98.7% (1,932/1,958) who had an SVR test.
- HCV viremia (RNA) testing capacity was established at four HR centers through the Foundation for Innovative New Diagnostics (FIND) Decentralizing HCV Testing to Harm Reduction Sites and the HEAD-Start Project; capacity was maintained by the state Hepatitis C Program using GeneXpert equipment. From June 2018 through December 31st, 2021, 3,772 RNA tests have been completed at these 4 sites, including 1,361 tests evaluating re-infection with a positivity rate of 7.4%.
- HCV treatment services have been integrated into three NSP sites (Tbilisi, Batumi, and Zugdidi) and one suboxone OST site. At HR integrated sites, 997 PWID were enrolled in hepatitis C treatment, including 173 during 2021. Among 602 treated PWID who were tested for SVR, the SVR rate was 95.3%.
- The HR services are maintained with support of the Global Fund HIV Program and the state HIV and Drug Addiction Prevention Programs. The share of state funding for NSP services was increased from 14% to 30% between 2020 and 2021.

Figure 2.1. Number of persons who inject drugs (PWID) tested for hepatitis C, and number and percent testing anti-HCV positive in Georgia, 2014–2021, Georgian Harm Reduction Network





- Other projects conducted from 2020 through 2021 focusing on PWID include the following:
 - Survey of PWID using WHO and UNAID simplified behavioral surveillance survey (BSS) methodology—BSS lite (sample size: 2,000 PWID) began in seven cities in November 2021 (data will be available in Spring 2022) to define the proportion of the population not utilizing HR and HCV services and identify approaches to improve access to and utilization of these services by PWID.
 - HCV Self-testing (HCVST) Feasibility and Acceptability Study among PWID and MSM was implemented with support of FIND in Tbilisi. A total of 200 participants (100 from each target population) took part in the study to determine the acceptability of and preferences for HCV self-testing among MSM and PWID populations and the ability to correctly perform the test and interpret results. HCVST was acceptable for more than 96% of the participants from both population groups, although more MSM (98%) were able to complete the self-test correctly than PWID (82%).
 - A randomized control trial of home-based HCV self-testing in MSM and PWID populations using an online recruitment and reporting platform—ongoing with support of FIND in Tbilisi and Batumi. A total of 750 MSM and 500 PWID are being randomly assigned to either intervention or control groups. Individuals in the intervention group will receive HCV self-tests at home through courier service or peer delivery. The individuals enrolled in the control group will be asked to follow the standard-of-care path to get anti-HCV testing at a community-based organization or a medical facility.
 - A study of risk factors for HCV re-infection among PWID was approved by the Scientific Committee and is underway. It will examine the risk factors for HCV re-infection among PWID who were treated through the Georgia Hepatitis C Elimination Program and achieved SVR.



BLOOD SAFETY

KEY ACCOMPLISHMENTS AND FINDINGS

- In January 2020, the European Union (EU) Twinning Project on Strengthening the Blood Safety System in Georgia was launched. In November 2021, as part of the Twinning Project, a draft of the Law on the Quality and Safety of Blood and Blood Components was submitted to the Government of Georgia including the following:
 - Designating a lead agency responsible for supervision of all transfusion practices at the national level.
 - Reducing the number of blood banks in Georgia to three by 2025: one National Blood Center and two additional blood banks.
 - Consolidating testing from 23 blood banks to the National Blood Center by 2025.
 - Prohibiting profit-based management by moving to only voluntary non-remunerated donations.
 - Establishing a National Hemovigilance System.
- Since January 2020, nucleic acid testing (NAT) has been performed on blood donations at the Lugar Center for the three major transfusion transmitted infections (TTIs)—HIV, HBV, and HCV; since April 2020, all donations have been screened with NAT. Serologic testing for TTIs and syphilis is performed in each blood bank. Overall, 12.3% of NAT-positive donations were serology negative (NAT yield 1:897).

- Since April 2020, all 23 blood banks participate in the State Safe Blood Program.
- In December 2020, an assessment of the existing blood banks was performed. The assessment found
 - The volume of donations varies considerably between existing blood banks (500–12,000 per year) and percentage of non-remunerated donors (from 0% to 100%).
 - The estimated total number of non-remunerated donations at all blood banks is 30,000 (33%).
 - There are no standardized quality assurance systems or universal quality standards across the 23 blood banks. Test systems are not validated, and there are no uniform confirmation testing algorithms in place.
 - The equipment used by the majority of blood banks is partially or fully non-compliant with the modern standards of blood production and testing.
 - 27% of blood banks perform serologic testing with fully automatic equipment, while 73% use semi-automatic ELISA methods.
 - A majority of blood banks perform immunohematological testing manually.
- In 2021, the Georgian government began taking steps to establish a National Blood Center for the centralization of blood services. The Center will incorporate blood processing and centralized testing facilities, including serology, molecular testing, and immunohematology laboratories, and clinical and blood component quality assurance laboratories.
- A Communication Strategy was drafted in November 2021 for the transition to 100% non-remunerated donation and will be implemented in 2022

INFECTION PREVENTION AND CONTROL

KEY ACCOMPLISHMENTS AND FINDINGS

- A new guideline, “Infection Control in Medical Facilities,” was approved by the MoDPLHSA (Decree N° 01-455/o, September 14, 2020) to ensure standardized IPC practices, including safety measures based on transmission routes, hand hygiene, disinfection and sterilization of instruments, safe injection practices and procedures, and safe blood banking and transfusion practices at all medical facilities.
- IPC regulations were updated based on a Ministerial order for prevention and management of novel SARS-CoV-2, but they also benefit populations impacted by HCV. The guidelines address
 - Confirmed or suspected cases of COVID-19 at dialysis units
 - Dental clinics
 - Infection control measures upon the death of a COVID-19-infected patient
 - Dermatology/cosmetology service providers
 - The use of personal protective equipment at a medical facility for the management of possible and confirmed cases and other safety measures



- In May 2020, the Regulation Agency for Medical and Pharmaceutical Activities implemented a monitoring system for adherence to IPC recommendations in dental clinics using a new questionnaire and check list.
 - A total of 1,048 dental clinics were evaluated, of which 989 met the requirements and could provide scheduled services. The other clinics were given an individual timeframe based on the types of adjustments needed and were shut down if they did not meet the requirements in the given timeframe.

- The Georgian Dental Association provided IPC training to more than 800 dentists, dental nurses, and staff responsible for decontamination procedures.
- With technical support from the US CDC, a tool was piloted for evaluating the IPC systems in inpatient hospitals, evaluating more than 26 medical facilities based on the supportive supervision principle.¹
- As part of a UNICEF project, IPC system assessments were conducted in 82 perinatal units based on the supportive supervision principle.
 - 24% of perinatal facilities were in full compliance with all criteria of IPC system organizational support.
 - 29% of perinatal facilities were in full compliance with all criteria for sterilization/disinfection.
 - Deficiencies were identified related to the requirements of sterilization planning and the prevention of the crossing of “dirty” and “clean” streams, especially during the stages of pre-sterilization processing and sterilization of instruments subject to sterilization.

- A total of 268 non-medical facilities (e.g., nail salons, tattoo parlors) were assessed by NCDC and regional public health centers for IPC compliance in non-healthcare settings. Of these, non-compliance was observed in 43% (n=115) of facilities, and these sites were provided with recommendations for improvement in a two-week timeframe. Upon a repeat visit, if improvements were not made, the site would be fined or closed.
- In 2021, an e-learning IPC curriculum and course was developed for physicians, personnel responsible for infection control, epidemiologists, clinical managers, and nurses.
- In-person IPC trainings have taken place in more than 60 medical facilities, with a total of 6,340 medical workers (epidemiologists, doctors, and nurses) trained.

¹Supportive supervision is a process of helping staff to improve their own work performance continuously. It is carried out in a respectful and non-authoritarian way with a focus on using supervisory visits as an opportunity to improve health staff’s knowledge and skills.

ACCOMPLISHMENTS BY STRATEGIC DIRECTION

STRATEGY 3.

IDENTIFY PERSONS INFECTED WITH HCV AND LINK THEM TO CARE

Reaching HCV elimination requires a comprehensive scale-up of high-quality HCV screening and access to treatment. Within the Georgia Hepatitis C Elimination Program, over 75,000 persons initiated treatment with a high cure rate; nevertheless, patient enrollment in treatment has declined over time and throughout the COVID-19 pandemic. The government of Georgia has prioritized developing the most optimal model for linkage to care. The program is intended to improve HCV case finding by screening the general population, conducting targeted screening of high-risk populations, and using enhanced screening in regions with known high HCV prevalence.

KEY ACCOMPLISHMENTS AND FINDINGS

- As of December 2021, 2.2 million people 18 years of age or older had been screened, and 146,778 (6.8%) were HCV antibody positive. An additional 18,586 screened anti-HCV positive using an anonymous 15-digit code, so their inclusion in the general population screening results cannot be confirmed. Overall, men aged 40–49 years had the highest rate of anti-HCV positivity at 20.8%, followed by men aged 50–59 years (17.4%) and 30–39 years (11.4%). Among women, anti-HCV prevalence was highest in those aged 50–59 years (4.6%), 60–69 years (4.3%), and over 70 years (4.5%).
- From January 2015 through December 2021, 355,905 children under 18 years of age were screened, and 971 (0.3%) were HCV antibody positive.
- An integrated TB/HIV/HCV screening program at primary healthcare centers (PHC) was piloted in the Samegrelo-Zemo Svaneti region in April 2018 with financial support from The Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM). The program has since been expanded to every region across the country. In 2020, 252,500 persons were screened, and 877 (0.3%) were positive. In 2021, 173,100 were screened, and 308 (0.2%) tested positive.
- HCV screening is available at 1,361 locations with 1,849 providers performing anti-HCV screening reported in the system during 2021. Sites and programs are presented in figure 3.2.
- As of December 31st, 2021, 20,889 people have screened positive for anti-HCV but have not had viremia testing performed. An additional 19,067 people who are HCV RNA positive have not yet started treatment. To increase identification of these individuals and their linkage to care, a previously piloted project was expanded to the entire program in 2021. The project had the following targets: conduct viremia testing on 70% (14,000 persons) who screened anti-HCV positive and engage 50% of those who are HCV RNA positive in treatment. Activities completed during 2020–2021:

- All medical facilities participating in the project were provided with updated information and material, including linkage questionnaires and methodology on how to communicate with patients lost to follow-up.
- Sixty medical facilities were included in the project:
 - ◆ Contracts were established to provide funding and ensure participation in the project.
 - ◆ Trainings on how to follow up and link people who screened HCV positive to care were conducted with 112 epidemiologists and providers from the harm reduction network and primary healthcare system.
 - ◆ An additional six PHCs were included in cities where there were more than 200 individuals in need of linkage to care.
 - ◆ Five regional coordinators were hired to facilitate connection and guide epidemiologists.
- The following activities took place to identify all persons in need of linkage to care:
 - ◆ Comprehensive lists were created from the Georgia Hepatitis C Elimination Program databases based on the following criteria: 1) screening was performed ≥ 3 months ago and no viremia testing was completed; 2) person is aged 18–75 years; 3) person cannot be found in death registry; and 4) address or telephone number is identified.
 - ◆ Based on the criteria, 18,082 persons were identified. Relevant lists were sent to the 60 medical facilities, 1 HR site, and 6 PHCs for active follow-up
- As of December 31, 2021, contact was attempted at least one time via phone or a visit by an epidemiologist for 9,989 persons. Successful contact was made with 5,397, and viremia testing was performed on 1,841 (18%). Of those, 1,023 (55.6 %) were HCV viremia positive, and 572 (55.9%) who were HCV viremia positive were enrolled in treatment.

Figure 3.1. Number of persons screened for hepatitis C per month and cumulative, and number testing positive in Georgia, 2015–2021

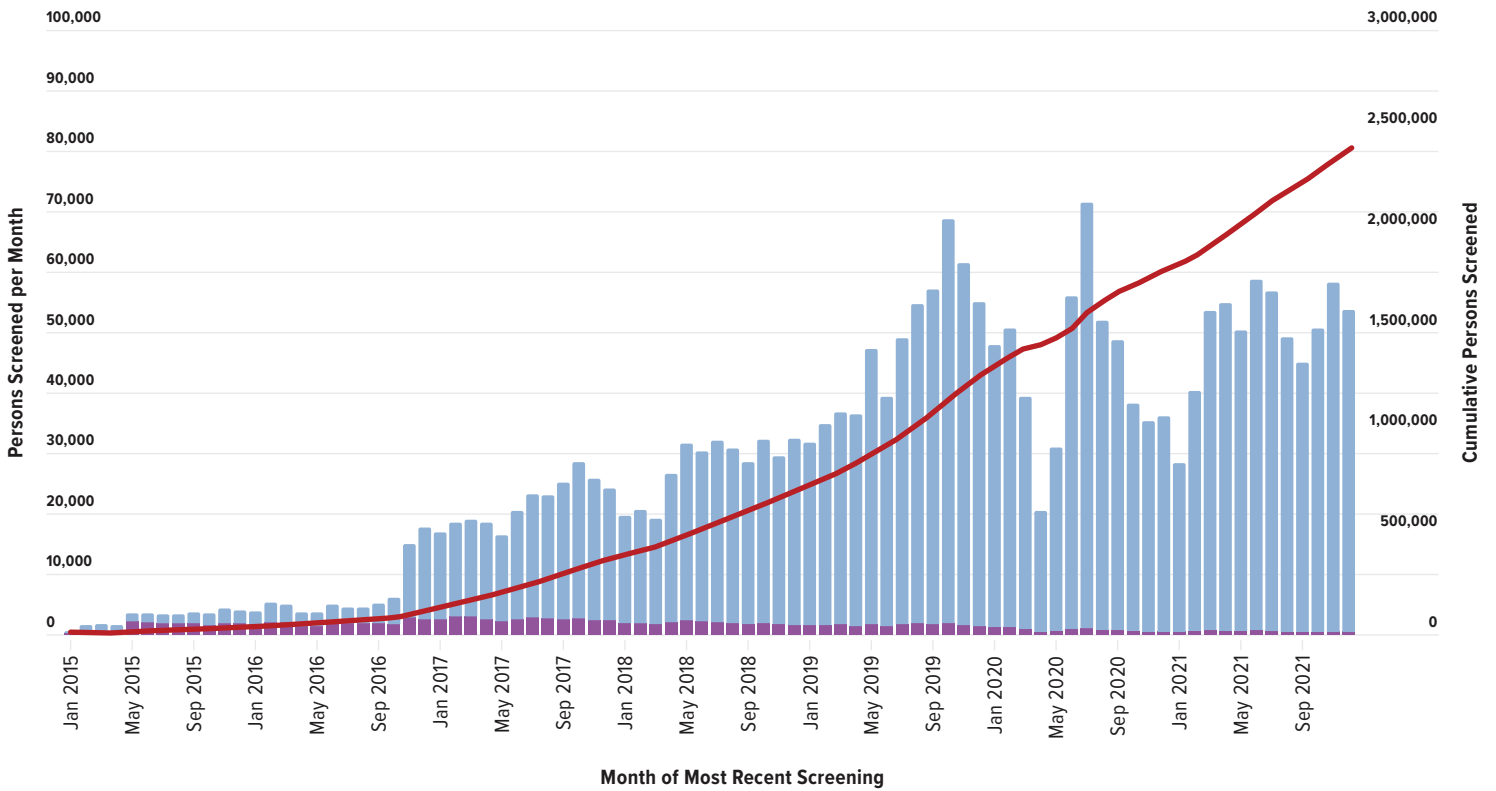
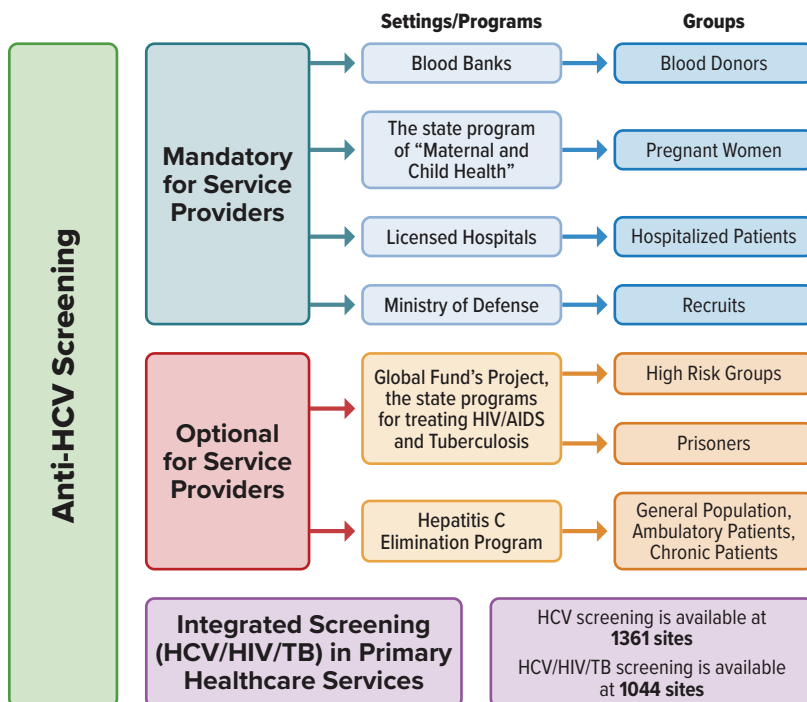


Figure 3.2. HCV Screening Sites



ACCOMPLISHMENTS BY STRATEGIC DIRECTION

STRATEGY 4.

IMPROVE HCV LABORATORY DIAGNOSTICS

Access to quality diagnostic services is crucial for surveillance, accurate and timely detection of hepatitis C infection, ensuring appropriate follow-up care for those infected with HCV, and documenting cure from infection. NCDC uses its laboratory network to improve Georgians’ access to HCV screening and to provide external quality assurance for laboratories (both public and private) licensed to perform HCV diagnostic and monitoring tests.

KEY ACCOMPLISHMENTS AND FINDINGS

- As of December 31, 2021, more than 1,000 laboratories providing hepatitis C and other diagnostic testing (including screening) were registered in the MoIDPLHSA database.²
- From 2020 through 2021, the government purchased a total of 600,000 HCV Rapid Diagnostic Test (RDT) kits from Healgen as part of the Georgia Hepatitis C Elimination Program. The performance of these RDT kits was assessed at the Lugar Center and showed 100% sensitivity and specificity.
- The number of hepatitis C screening methods, including existing and approved assays to diagnose chronic HCV infection has been expanded since the launch of the Georgia Hepatitis C Elimination Program (Table 4.1 and Table 4.2).

Table 4.1. Hepatitis C Screening (anti-HCV) Diagnostics in Georgia as of December 2021

Methods	Facility/Populations
RDTs (Procured Centrally by Government)	Outpatient clinics, NCDC lab network, HR sites/ General population, pregnant women, high-risk individuals
RDTs (Procured Centrally by Government)	Inpatient clinics/Hospitalized patients
Laboratory-Based Serology Methods (ELISA, CLIA, CMIA, etc.)	Blood banks/Donors
NAT Screening (Grifols)	Lugar Center/Donors

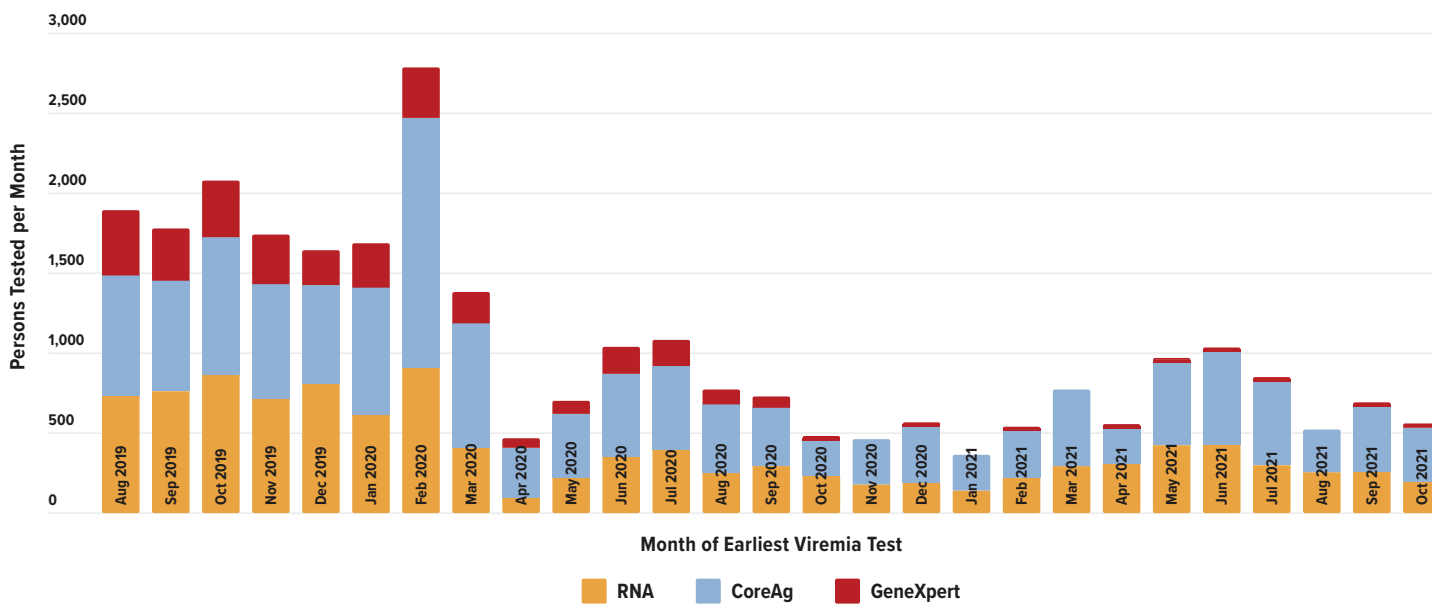
² <http://cloud.moh.gov.ge>

Table 4.2. Hepatitis C Viremia (RNA and cAg) Diagnostics in Georgia as of December 2021

Methods	Facility/Populations
Quantitative HCV RNA <ul style="list-style-type: none"> • Different Platforms • GeneXpert® HCV VL • GeneXpert® FS HCV VL 	<ul style="list-style-type: none"> • HCV treatment provider sites/Lugar Center, NCDC • HR sites/Lugar Center, NCDC • HR sites/Lugar Center, NCDC
Qualitative HCV RNA	HCV treatment provider sites
HCV cAg	Lugar Center, NCDC
NAT Discriminatory Testing	Lugar Center, NCDC

- Access to free-of-charge HCV viremia testing has allowed for continued access to HCV diagnostic tests within the Georgia Hepatitis C Elimination Program (Figure 4.1).

Figure 4.1. Number of persons tested for HCV viremia per month by test method in Georgia—August 2019–December 2021



*with CoreAG Initial Test Prioritized Over Confirmation Method

- From 2017 through 2021, 18 laboratories (including the Lugar Center [National Reference Laboratory]) were enrolled in the National External Quality Assurance (EQA) Program. From 2020 through 2021, HCV proficiency test (PT) panels were distributed five times to each laboratory.
 - A total of 13 labs in 2020 and 10 labs in 2021 participated in at least one of the scheduled PT rounds and performed HCV RNA viral load tests. Four labs performed genotyping in 2020, and none performed genotyping in 2021 (the program removed genotyping as a requirement secondary to pangenotypic regimens being in place for treatment). In 2020, 12 of the 13 laboratories performed qualitative HCV RNA tests.
 - The cumulative 2020 EQA program results for quantitative HCV RNA viral load were excellent in 73.1% of all PT specimens, good in 11.8%, acceptable in 4.2%, and not acceptable in 10.9%.
 - The cumulative 2021 EQA program results for quantitative HCV RNA viral load were excellent in 78.1% of all PT specimens, good in 14.2%, acceptable in 4.5%, and not acceptable in 3.2%. The problems identified were related to improper use of quantitative HCV PCR calibrators or non-compliance with the manufacturer’s recommendations on PCR platform-reagent combinations.
- In 2021, a new EQA program for TTI serology was introduced in the country, and 18 blood banks each received a PT panel for analysis of HCV, HBV, HIV, and syphilis three times. Two discrepancies were found in the first round related to HIV (one false negative and one false positive). All results were acceptable in the remaining rounds.
- CDC funded a project to strengthen the National Laboratory System and the national EQA Program by establishing a laboratory training hub and the ECHO Hepatitis C Diagnostics Laboratory Community. Curricula were developed and the Lugar Center held trainings on implementing quality management systems and achieving immediate, measurable improvement.
- The National EQA Program expertise and framework played a key role in the rapid scale up of COVID-19 diagnostics in Georgia.
- The second National EQA Program Workshop was held on September 10, 2021. During the meeting, the need for short- and middle-term strategies for synergistic collaboration between the participants of the HCV, COVID-19, and blood safety EQA programs was identified, and recommendations were developed for the Georgia Hepatitis C Elimination Program and the COVID-19 Emergency Response to improve laboratory capacity. Recommendations were made related to the regulatory framework of clinical laboratory technical requirements, including mandatory certification/accreditation requirements, mandatory participation in the EQA programs, and updates to diagnostic algorithms.

ACCOMPLISHMENTS BY STRATEGIC DIRECTION

STRATEGY 5.

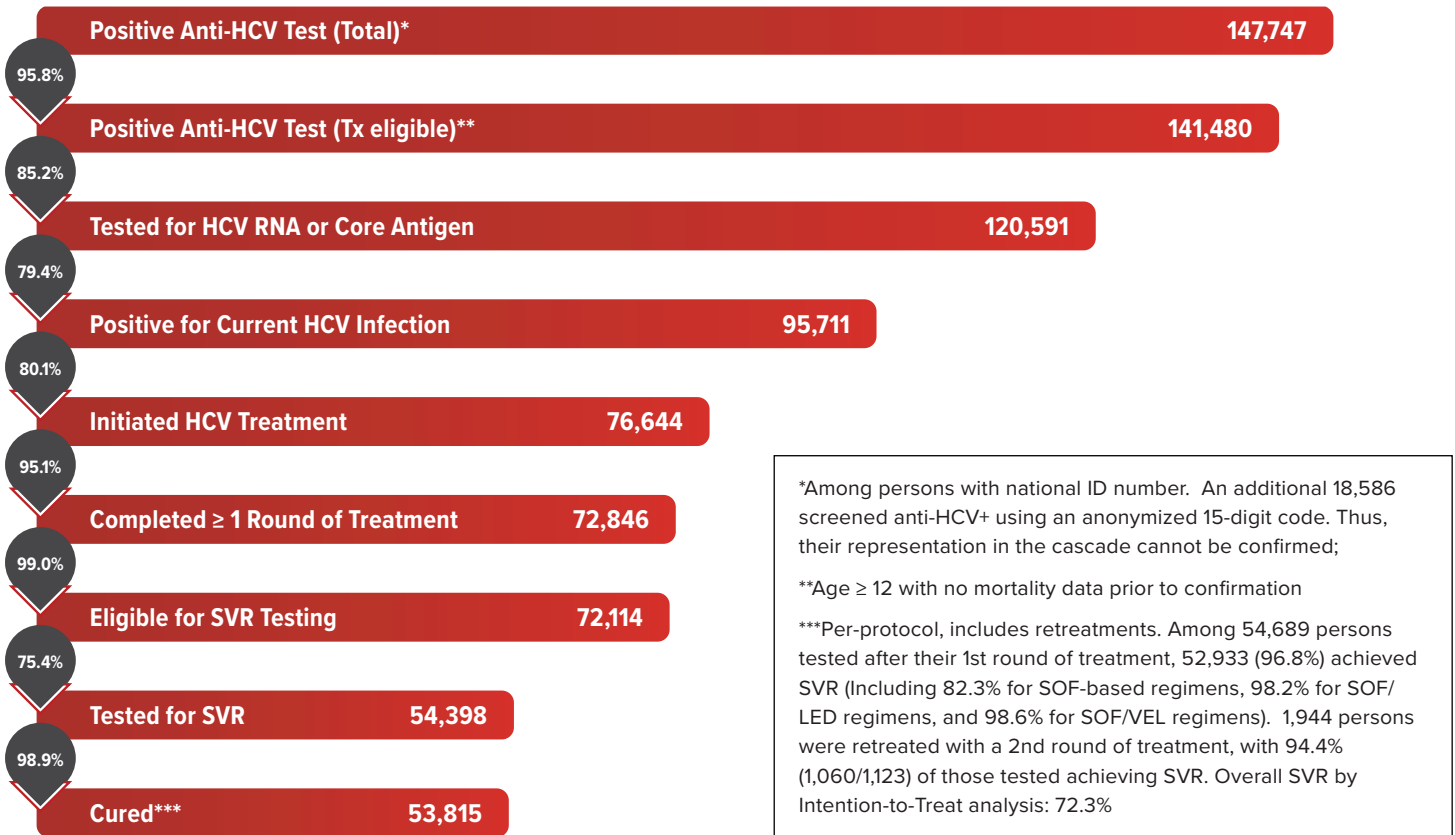
PROVIDE COMPREHENSIVE HCV CARE AND TREATMENT

Since June 2016, all HCV-infected persons have been eligible for treatment regardless of liver disease severity. Curative antiviral therapy is provided free of charge through a partnership with Gilead Sciences. Initially, all participants received sofosbuvir (SOF)-based antiviral treatment regimens, in combination with ribavirin alone or with pegylated interferon and ribavirin. Beginning in March 2016, the majority of patients began receiving sofosbuvir/ledipasvir (SOF/LED)-based regimens. From December 2018, the pangenotypic regimen Velpatasvir/Sofosbuvir (VEL/SOF) had been available for patients.

KEY ACCOMPLISHMENTS AND FINDINGS

- As of December 2021, there are 35 HCV treatment centers, including four HR sites (three NSP and one OST) and ten PHC sites.
- All HCV cases requiring treatment are reviewed by the treatment inclusion committee. Since August 1, 2018, cases are reviewed electronically in real time to reduce delay to treatment initiation. In the 6 months prior to August 1, 2018, the median time between committee review and treatment initiation was 28 days (IQR 21–38), compared to 6 days (IQR: 3–15) after the implementation of electronic committee review (August 2018–December 2021). For the period of January 2020–December 2021, the median time was 7 days (IQR 3–17).
- As of December 2021, all patients were receiving the pangenotypic regimen VEL/SOF with or without ribavirin, eliminating the need for genotyping and allowing for simplified treatment and monitoring algorithms (Appendix 2).
- The national screening registry and HCV treatment database allow for clinical monitoring and program evaluation across the care cascade. As of December 31, 2021, 147,747 persons screened positive for HCV antibodies; of those, 120,591 (81.6%) underwent HCV viremia testing. A total of 95,711 (79.4%) persons tested had active HCV infection (RNA or core antigen positive)—63.8% of the estimated 150,000 adults living with chronic HCV infection in Georgia. A total of 76,644 persons initiated treatment—59.8% of the estimated target population to be treated (128,250). Of the 54,398 patients who were evaluated for SVR, 53,815 (98.9%) tested negative for HCV by PCR, representing 44.2% of the population based on the 2020 90-95-95 goal (121,837).

Figure 5.1. Georgia Hepatitis C Elimination Program Care Cascade, April 28, 2015 – December 31, 2021



- The COVID-19 pandemic has negatively affected access to HCV screening and care services. Compared to 2019, there was about a 50% drop in HCV screening in 2020 and 2021 as well as a decline in patients initiating treatment, with an average of 505 persons initiating treatment each month in 2020 and 2021.
- SVR rates reached 98.9% (53,815 of 54,398) among patients eligible and tested for SVR, including re-treatments; the SVR rate calculated using an “intent to treat” analysis (which considered persons who discontinued treatment and those who completed treatment but did not receive SVR testing) was 72.3%.
- Treatment eligibility criteria among decentralized treatment facilities was expanded in 2020 to those with FIB-4 score between 1.45 and 3.25, while persons with advanced fibrosis and cirrhosis were referred to specialized clinics.
- Overall, from 2020 through 2021, 433 patients received direct-acting antiviral (DAA) treatment at PHC facilities, 98.5% (255 of 259) achieved SVR. Of 433 patients treated at HR facilities, 97.4% (259 of 266) achieved SVR.

ACCOMPLISHMENTS BY STRATEGIC DIRECTION

STRATEGY 6.

IMPROVE HCV SURVEILLANCE

The epidemiological surveillance system for viral hepatitis in Georgia requires urgent notification of each acute viral hepatitis (HAV, HBV, HEV) case by healthcare institutions/laboratories and PHCs. Chronic hepatitis B and acute and chronic hepatitis C are reported through a special form with aggregated monthly notifications. Acute and chronic cases of infectious diseases registered in the Electronic Integrated Diseases Surveillance System (EIDSS) are automatically collected and accumulated in the monthly report. In addition, the treatment registry and screening database was developed to allow for real-time monitoring of screening; it links with the other databases that are part of the Georgia Hepatitis C Elimination Program.

KEY ACCOMPLISHMENTS AND FINDINGS

- In 2020, acute and chronic HBV and HCV sentinel surveillance was established under the Surveillance State Program at four infectious disease hospitals (Tbilisi, Kutaisi, Zugdidi, and Batumi). Only three are currently functioning, and each is managed by a Sentinel Supervision Coordinator.
 - Within the sentinel surveillance project, a series of meetings was conducted with PHC personnel to update surveillance-related policy papers, case definitions, reporting forms, and guidelines.
 - During the project's implementation, training was conducted in three sentinel clinics (Kutaisi, Batumi and Zugdidi) and in three PHCs (Batumi, Zugdidi, Telavi) to introduce updated definitions of viral hepatitis cases and sentinel surveillance protocols to 32 doctors and epidemiologists.
- In 2020, the Lugar Center became the first regional lab to utilize Global Hepatitis Outbreak Surveillance Technology (GHOST).
 - A study evaluating re-infection and transmission networks among PWID has enrolled 100 persons from all participating study sites.
 - Transmission networks and co-infections were detected, indicating a long history of HCV infection in Georgia.
- An evaluation of the current EIDSS showed that the existing disease surveillance system has shortcomings in terms of both acute HBV case reporting and epidemiology, and the system needs to be updated and improved.
 - In 2020, 47 cases of acute hepatitis B were reported through the EIDSS. Ten cases were reported by sentinel sites, and 7 of those cases coincided with EIDSS.
 - In 2021, 19 cases of acute hepatitis B were reported in the EIDSS. Twenty-four cases were reported by the sentinel sites, and 10 of those cases coincided with EIDSS.

- A repeat nationwide serosurvey was conducted from June through October 2021 to assess the burden of hepatitis B and C among adults and children aged 5 years and older.
 - 7,237 adults and 1,473 children participated in the survey.
 - Results show 1.8% prevalence of chronic HCV infection among adults, a 67% reduction from 2015. No children were positive for anti-HCV or HCV RNA.
 - The burden of chronic HBV infection among adults is stable at 2.7% HBsAg (2.9% in 2015); anti-HBc prevalence was 21.7%.
 - The prevalence of anti-HBc in children was 0.7%, and the prevalence of HBsAg was 0.03%, exemplifying good vaccination coverage.
 - The number of people reporting risk factors associated with HCV and HBV (IDU, transfusion, past incarceration) has declined since 2015.
 - Chronic HCV infection is still apparent among PWID.

- A project to improve HCV and HBV surveillance was implemented:
 - All HCV seroconversion cases from January 2019 through November 2020 were identified in the HCV screening database and analyzed. Overall, there were 1,008 seroconversions, of which 89 died. Of the seroconversions, 803 had phone numbers available and 299 were randomly selected for follow-up.
 - Telephone interviews were conducted to collect risk factor data and understand behaviors associated with transmission of HCV and HBV. Out of 299 selected for follow-up, 73% (n=219) of respondents with an age range of 26–94 years were interviewed. Remaining findings are presented in Table 6.1.



Table 6.1. Risk factors in the period of 2-6 months before HCV diagnosis

Questions	Yes (%)
Did you undergo hemodialysis?	0.5%
Did you inject drugs?	10.2%
Did you receive a blood transfusion?	7%
Did you spend 24 hours or more in hospital?	32%
Did you have any type of surgery or invasive medical procedure?	51%
Did you get a tattoo or piercing?	2.7%
Did you get a manicure or a pedicure at beauty salons?	9.7%
Were you were incarcerated or detained in prison or jail?	3.8%
Were you treated for sexually transmitted disease(s)?	2.2%
Did you had unprotected sex (without condom) with a partner who had hepatitis C?	3.2%

- A project was implemented in 2020 and 2021 to assess hepatitis B and C testing practices and seroconversions among dialysis facilities in Georgia.
 - A total of 22 out of 27 dialysis centers (81%) participated in the survey, which included an assessment of IPC practices and screening practices for HBV and HCV. A patient satisfaction survey and a pilot chart abstraction were conducted.
 - Findings include the following:
 - ◆ HBV screening is routinely performed upon admission at 21 facilities (95.5%). Susceptible patients are routinely vaccinated with the hepatitis B vaccine at 13 study institutions (59.1%).
 - ◆ Anti-HCV screening is performed at 15 institutions (68.2%) upon admission to the center, and anti-HCV screening is performed once every six months for patients who are previously anti-HCV negative in 12 clinics (54.5%).
 - ◆ Ten of the dialysis facilities included in the study (45.5%) reported HBV and HCV seroconversions in the prior year.

- A project was initiated to estimate the risk of HCV transmission by diagnostic endoscopic procedures:
 - Monitoring visits were conducted at four selected endoscopic units, and 1,030 patients were tested between April and September 2021.
 - The project includes follow-up screening at six months to assess seroconversion rate; follow-up testing is ongoing.

- In 2020, NCDC implemented a project to develop and establish a sustainable surveillance system for children born to women with chronic HCV infection.
 - Initial data from pregnant women registered in the birth registry from 2017 through 2020 showed 707 women were anti-HCV positive, and 580 (82%) of those received viremia testing out of which 450 (78%) were confirmed having chronic HCV infection. Of those, 355 (79%) were treated, with 116 receiving treatment prior to pregnancy.
 - A study is underway to assess barriers that women who are anti-HCV positive face to seeking care in the Georgia Hepatitis C Elimination Program and to link children born to mothers with HCV infection to hepatitis C diagnostic services.



MONITORING AND EVALUATION

*Due to the fact that the 2016–2020 strategic plan was in place at the beginning of the evaluation period and the majority of activities eligible for M&E were related to HCV, the M&E matrix remains consistent with previous annual reports. An updated M&E matrix will be developed for the next annual report based on the 2021–2025 strategic plan.

STRATEGY 1. IMPROVE ADVOCACY, AWARENESS, EDUCATION, AND PARTNERSHIPS FOR HCV-ASSOCIATED RESOURCE MOBILIZATION

Objective	Indicator Name	Measurement	Data Source	Value/Result (2021)	Value/Result (2020)	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)
1.1. Educate the public and high-risk groups about viral hepatitis and the importance of testing	1. Levels of awareness among the general public regarding a) HCV Transmission b) HCV Prevention c) Testing and Diagnosis d) Treatment	High Awareness All or most participants aware Medium Awareness Some participants aware Low Awareness Few or no participants aware	* Small-scale Facebook survey ** Qualitative survey *** Serosurvey 2021	*** a) Medium b) Low c) n/a d) n/a	a) n/a b) n/a c) n/a d) n/a	** a) n/a b) n/a c) Low d) Low	* a) Medium b) Medium c) Medium d) Low	* a) High b) Medium c) High d) Medium
	2. Levels of awareness among PWID regarding a) HCV Transmission b) HCV Prevention c) Testing and Diagnosis d) Treatment	High Awareness All or most participants aware Medium Awareness Some participants aware Low Awareness Few or no participants aware	* Integrated Bio-Behavioral Surveillance Survey (IBSS) 2017 ** Qualitative study (GHRN) *** Serosurvey 2021	*** a) Medium b) Medium c) n/a d) n/a	a) n/a b) n/a c) n/a d) n/a	** a) n/a b) n/a c) Low d) Low	Data not available	* a) Medium b) Low c) Medium d) Medium
1.2. Reduce community-level stigma and discrimination associated with HCV infection	3. Level of perceived HCV-related stigma and discrimination experienced among persons with HCV in healthcare and other settings (e.g., work, housing, school, corrections)			Data not available	Data not available	Data not available	Data not available	Data not available

STRATEGY 2. PREVENT HCV TRANSMISSION THROUGH HARM REDUCTION

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)
2A. Decrease HCV incidence among PWID by promoting harm reduction	1. Number and percentage of PWID reached with defined package of services *The beneficiary is considered reached if received at least two services from the list of basic package (condom, consultation, information materials, syringe/needle) and one of them has to be syringe/needle	Numerator Number of PWID reached with preventive counseling	Database of PWID receiving HIV counseling and testing (HCT); GHRN	67.9% (N=35,650)	62.1% (N=32,607)	68.2% (N=35,811)	56.9% (N=29,891)	51.9% (N=27,250)
		Denominator Estimated number of PWID	Population size estimation (PSE) of PWID in Georgia	(N=52,500) PSE 2017	(N=52,500) PSE 2017	(N=52,500) PSE 2017	(N=52,500) PSE 2017	(N=52,500) PSE 2017
	2. Number and percentage of PWID enrolled in OST	Numerator Number of PWID enrolled in OST	Social Service Agency	Pending	71% (N=11,515)	58.7% (N= 9,552)	59.0% (N= 9,606)	45.4% (N=7,381)
		Denominator Estimated number of injection opioid users	IBSS 2017 **31% of estimated PWID	(N=16,275)** IBSS 2017	(N=16,275)** IBSS 2017	(N=16,275)** IBSS 2017	(N=16,275)** IBSS 2017	(N=16,275)** IBSS 2017
	3. Number and percentage of PWID screened for HCV infection at: a) NSP sites and outreach b) OST service centers c) Mobile ambulatories	Numerator Number of PWID screened for HCV infection	Harm reduction program records	a. 24.1% b. n/a c. 29.2% a. N=12,630 b. N=n/a c. N=15,337	a. 16.7% b. n/a c. 28.2% a. N= 8,757 b. N=n/a c. N=14,836	a. 23.0% b. 51.8% c. 27.2% a. N=12,065 b. N= 8,426** c. N= 14,259	a. 20.4% b. 47.1% c. 18.4% a. N= 10,691 b. N= 7,660** c. N= 9,659	a. 22.6% b. n/a c. 18.6% a. N= 11,885 b. N=n/a c. N= 9,745
		Denominator Estimated number of current PWID	*PSE of PWID in Georgia 2017 **IBSS	(N=52,500)* (N=16,275)**	(N=52,500)* (N=16,275)**	(N=52,500)* (N=16,275)**	(N=52,500)* (N=16,275)**	(N=52,500)* (N=16,275)**
	4. Number and percentage of PWID with presence of anti-HCV antibodies	Numerator Number of PWID with anti-HCV positivity	*Harm reduction program records	6.2%* (N=1,722) 26.9%** (N=5,711)**	9.6%* (N=2,262) 27.3%** (N=5,208)**	16.6%* (N=3,945)* 27.0%** (N= 4,479)**	22.8%* (N= 4,574)* 30.8%** (N= 3,411)**	32.1%* (N= 6,850)* 36.8%** (N= 1,941)*
		Denominator Number of PWID tested for HCV infection	**National HCV screening registry (cumulative)	(N=27,967)* (N=21,204)*	(N=23,587)* (N=19,073)**	(N=23,819)* (N=16,590)**	(N=20,067)* (N=11,085)**	(N=21,371)* (N=5,280)**

STRATEGY 2. PREVENT HCV TRANSMISSION THROUGH HARM REDUCTION *cont.*

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)
2A. Decrease HCV incidence among PWID by promoting harm reduction	5. Number and percentage of PWID testing positive on rapid tests who undergo HCV viremia testing	Numerator Cumulative number of PWID tested for HCV RNA or HCV core antigen	Elimination C	78.6% (N=4,489)	80.7% (N=4,205)	75.4% (N=3,377)	64.1% (N=2,187)	50.5% (N=981)
		Denominator Cumulative number of PWID with anti-HCV positive results	National HCV screening registry	(N= 5,711)	(N= 5,208)	(N= 4,479)	(N= 3,411)	(N=1,941)
	6. Number and percentage of PWID diagnosed with active HCV infection	Numerator Cumulative number of PWID diagnosed with active HCV infection based on HCV RNA or HCV core antigen testing	Elimination C	83.3% (N=3,741)	83.2% (N=3,500)	84.4% (N=2,850)	90.0% (N=1,968)	87.7% (N=861)
		Denominator Cumulative number of PWID who were tested for HCV RNA or HCV core antigen		(N=4,489)	(N=4,205)	(N=3,377)	(N=2,187)	(N=981)
	7. HCV prevalence among PWID by IBBS study		IBBS	N/A	N/A	N/A	N/A	63.2% Value is pooled estimate from IBBS 2017. Actual numerator unknown.
	8. Number and percentage of PWID with active HCV infection who started HCV treatment	Numerator Cumulative number of PWID started HCV treatment	Elimination C	78.6% (N= 2,942)	80.7% (N=2,825)	74.5% (N= 2,123)	68.3% (N= 1,346)	75.6% (N= 651)
		Denominator Cumulative number of PWID with diagnosed HCV infection		(N=3,741)	(N=3,500)	(N=2,850)	(N=1,968)	(N= 861)

STRATEGY 2. PREVENT HCV TRANSMISSION THROUGH HARM REDUCTION *cont.*

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)
2A. Decrease HCV incidence among PWID by promoting harm reduction	9. Number and percentage of PWID treated in the program who completed treatment	Numerator Cumulative number of PWID completed treatment	Elimination C	93.9% (N=2,764)	95.0% (N= 2,685)	89.5% (N= 1,900)	82.6% (N= 1,112)	78.5% (N= 511)
		Denominator Cumulative number of PWID initiated treatment		(N= 2,942)	(N=2,825)	(N= 2,123)	(N= 1,346)	(N= 651)
	10. Number and percentage of PWID completing treatment who achieved SVR	Numerator Cumulative number of PWID who achieved SVR	Elimination C	98.7% (N=1,932)	98.7% (N= 1,904)	98.6% (N=1,255)	97.0% (N=619)	95.8% (N=282)
		Denominator Cumulative number of PWID assessed for SVR 12-24 weeks after the end of treatment		(N=1,958)	(N= 1,929)	(N=1,273)	(N=638)	(N=294)
	11. Percentage of PWID reporting use of sterile injecting equipment the last time they injected	Numerator Number of PWID reporting use of sterile injecting equipment the last time they injected	IBBS	N/A	N/A	N/A	N/A	91.6% Value is estimate from IBBS 2017. Actual numerator unknown (N=52,500)
		Denominator Estimated number of PWID						

STRATEGY 2. PREVENT HCV TRANSMISSION THROUGH BLOOD SAFETY

Objective	Indicator Name	Measurement	Data Source	Value/Result (2021)	Value/Result (2020)	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)
2B. Prevent healthcare-related transmission of viral hepatitis by improving blood safety	1. Number and percentage of all blood banks participating and operating in the Unified Blood Donor Electronic Database (Donor Database)	Numerator Number of blood banks participating and operating in the Donor Database	Donor Database	100.0% (N=23)	100.0% (N=23)	100.0% (N=22)	100.0% (N=22)	95.5% (N=21)
		Denominator Total number of blood banks holding state license in blood production service	State Regulation Agency for Medical Activities	(N=23)	(N=23)	(N=22)	(N=22)	(N=22)
	2. Lead agency is established at central level to oversee and coordinate blood service in the country	Appropriate legislative act	MoIDPLHSA	In process	Not established	Not established	Not established	Not established
	3. Licensing regulations for blood banks are established, approved, and published	Appropriate legislative act	Legislative Department of MoIDPLHSA	In process	Not established	Not established	Not established	Not established
	4. Number and percentage of voluntary donations among all blood donations	Numerator Number of voluntary donations	Donor Database	41.2% (N=37,455)	40.6% (N=34,094)	32.7% (N=30,876)	27.5% (N=25,064)	23.1% (N=20,283)
		Denominator Total number of blood donations						
	5. Proportion of anti-HCV-reactive persons among blood donors	Numerator Number of blood donors with anti-HCV positive results	National HCV screening registry	0.6% (N=357 Cumulative: 4,750)	0.7% (N=415 Cumulative: 4,393)	0.8% (N=421 Cumulative: 3,978)	1.1% (N=547 Cumulative: 3,556)	1.6% (N=832 Cumulative: 3,022)
		Denominator Total number of unique blood donors	Donor Database	(N=59,235)	(N=56,694)	(N=55,779)	(N=51,289)	(N=51,799)

STRATEGY 2. PREVENT HCV TRANSMISSION THROUGH BLOOD SAFETY *cont.*

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)
2B. Prevent healthcare-related transmission of viral hepatitis by improving blood safety	6. Proportion of blood donors tested for HCV viremia	Numerator Cumulative number of blood donors tested for viremia after a positive serologic test	Donor Database Elimination C STOP-C databases National HCV screening registry	75.3% (N=3,575)	71.3% (N=3,134)	62.3% (N=2,506)	60.7% (N=2,226)	41.7% (N=1,193)
		Denominator Cumulative number of seroreactive blood donors		(N=4,750) Donors screened 2015-2021	(N=4,393) Donors screened 2015-2020	(N=3,978) Donors screened 2015-2019	(N=3,556) Donors screened 2015-2018	(N=3,022) Donors screened 2015-2017
	7. Proportion of blood donors diagnosed with chronic HCV infection	Numerator Cumulative number of blood donors tested positive by HCV viremia testing (Core Ag, RNA)	Donor Database Elimination C STOP-C databases National HCV screening registry	66.1% (N=2,362)	67.8% (N=2,126)	69.6% (N=1,745)	71.2% (N=1,584)	75.8% (N=904)
		Denominator Cumulative number of unique blood donors tested for viremic HCV infection		(N=3,575)	(N=3,134)	(N=2,506)	(N=2,226)	(N=1,193)
	8. Degree of the continuity of care (percentage of HCV-confirmed blood donors enrolled in the HCV treatment program)	Numerator Total number of HCV viremic donors enrolled in the treatment program	Elimination C STOP-C databases National HCV screening registry	76.5% (N=1,807)	77.9% (N=1,657)	71.9% (N=1,254)	75.2% (N=1,191)	79.9% (N=722)
		Denominator Number of blood donors tested positive by HCV viremia testing (Core Ag, RNA)	Data since the launch of the program in 2015	(N=2,362)	(N=2,126)	(N=1,745)	(N=1,584)	(N=904)

STRATEGY 2. PREVENT HCV TRANSMISSION THROUGH INFECTION PREVENTION AND CONTROL

Objective	Indicator Name	Measurement	Data Source	Value/Result (2021)	Value/Result (2020)	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)
2Ca. Prevent healthcare-associated transmission of viral hepatitis by improving infection control in healthcare facilities	1. National guidelines on IPC	Scale indicator 0 = not started 1 = under development 2 = draft complete/developed 3 = published	Published guidelines	3	3	2	2	2
	2. Number of medical universities and nursing colleges with IPC curriculum introduced into training program		Survey conducted by MoIDPLHSA/ NCDC Ministry of Education	N=4	N=4	N=4	N=2	N=2
	3. Percentage of healthcare facilities in compliance with national IPC guidelines	Numerator Number of healthcare facilities compliant with national guidelines	Survey conducted by Models / NCDC	Data not available	23.8%* (N=19)	11.0% (N=6)	11.0% (N=6)	18.2% (N=12)
		Denominator Number of healthcare facilities surveyed						
	4. Percentage of healthcare facilities with an appointed IPC focal person	Numerator Number of healthcare facilities with appointed IPC focal person	Survey conducted by MoIDPLHSA / NCDC	Data not available	83.8%* (N=67)	96.3% (N=52)	96.3% (N=52)	100.0% (N=66)
		Denominator Number of healthcare facilities surveyed						
	5. Percentage of healthcare facilities with functional IPC committees	Numerator Number of healthcare facilities with active IPC committees	Survey conducted by MoIDPLHSA / NCDC	Data not available	86.3%* (N=69)	92.6% (N=50)	92.6% (N=50)	100.0% (N=66)
		Denominator Number of healthcare facilities surveyed						

STRATEGY 2. PREVENT HCV TRANSMISSION THROUGH INFECTION PREVENTION AND CONTROL *cont.*

Objective	Indicator Name	Measurement	Data Source	Value/Result (2021)	Value/Result (2020)	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)
2Ca. Prevent healthcare-associated transmission of viral hepatitis by improving infection control in healthcare facilities	6. Percentage of healthcare facilities displaying materials on IPC awareness	Numerator Number of healthcare facilities displaying IPC-awareness materials	Survey conducted by MoIDPLHSA / NCDC	Data not available	Data not available	72.2% (N=39)	72.2% (N=39)	90.9% (N=60)
		Denominator Number of healthcare facilities surveyed				(N= 54)	(N= 54)	(N= 66)
2Cb. Prevent HCV transmission in non-traditional healthcare and other community settings	1. Percentage of non-medical facilities where SOPs are available	Numerator Number of non-medical facilities where SOPs are available	Survey conducted by NCDC and regional public health centers	100.0% (N=74)	100.0% (N=194)	75.4% (N=3,377)	89.0% (N=733)	100.0% (N=416)
		Denominator Total number of surveyed non-medical facilities				(N=74)	(N=194)	(N= 1,405)
	2. Number of non-medical facility staff trained in IPC		NCDC and regional public health centers	N=180**	N=420**	N=1,200	N=824	N=1,500

*IPC system assessment in perinatal units.

**Estimated number. Exact numbers unavailable.

STRATEGY 3. IDENTIFY PERSONS INFECTED WITH HCV AND LINK THEM TO CARE

Objective	Indicator Name	Measurement	Data Source	Value/Result (2021)	Value/Result (2020)	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)
3.1. Expand HCV testing to better reach high-risk populations	1. Number of persons tested for hepatitis C antibody 1) All locations* 2) Prisoners 3) People living with HIV/AIDS 4) Pregnant women at ANC clinics 5) TB patients 6) Hemodialysis patients 7) Inpatients 8) PWID		National HCV screening registry	1) 602,758	1) 728,381	1) 965,422	1) 702,061	1) 744,983
			State Healthcare Program	2) 62	2) 504	2) 2,628	2) 2,020	2) 4,127
				3) Pending	3) Pending	3) 4,011	3) 3,599	3) 1,220
				4) 13,875	4) 42,961	4) 34,004	4) 42,218	4) 43,097
				5) Pending	5) Pending	5) 1,994	5) 2,693	5) 414
				6) Pending	6) Pending	6) N/A	6) 2,679	6) 1,912
				7) 290,051	7) 260,816	7) 307,626	7) 287,978	7) 378,762
				8) 2,444	8) 2,235	8) 6,157	8) 5,905	8) 5,280
				2. Proportion of persons screened anti-HCV positive 1) All locations* 2) Prisoners 3) People living with HIV/AIDS 4) Pregnant women at ANC clinics 5) TB patients 6) Hemodialysis patients 7) Inpatients 8) PWID	Numerator Number of persons with HCV seropositivity	National HCV screening registry	1) 1.4% (8,205)	1) 1.5% (10,908)
	2) 100% (62)	2) 21.0% (106)				2) 12.3% (324)	2) 23.5% (474)	2) 12.6% (521)
	3) Pending	3) Pending				3) 36.0% (1,442)	3) 39.5% (1,420)	3) 30.6% (1,220)
	4) 0.6% (79)	4) 0.5% (220)				4) 0.5% (182)	4) 1.1% (481)	4) 0.6% (243)
	5) Pending	5) Pending				5) 16.6% (331)	5) 19.7% (532)	5) 18.1% (75)
	6) Pending	6) Pending				6) N/A	6) 23.8% (637)	6) 16.7% (320)
	7) 1.5% (3,828)	7) 1.6% (4,290)				7) 2.1% (6,609)	7) 3.0% (8,740)	7) 3.8% (14,521)
	8) 20.6% (503)	8) 26.6% (594)				8) 18.6% (1,144)	8) 24.9% (1,471)	8) 36.8% (1,941)
	3. Number and percentage of children screened for hepatitis C born to women positive for HCV	Numerator Number of children born to women positive for HCV and screened for hepatitis C					Data not available	Data not available
		Denominator Total number of children born to women positive for HCV during the reporting period						

*Includes outpatients, blood banks, NCDC, Public Service Halls, et al. in addition to those listed in the table.

**Individual year data are not mutually exclusive.

STRATEGY 4. IMPROVE HCV LABORATORY DIAGNOSTICS

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)	
4.1. Improve laboratory detection of HCV infection	1. Number of HCV viremia testing sites (laboratories and point of care diagnostic sites)* enrolled in the national HCV EQA program		NCDC Lugar Center *Includes the national reference laboratory	N=11	N=14	N=17	N=17	N=16	
	2. Proportion of HCV viremia testing sites that participated on all proficiency testing rounds of EQA program per year	Numerator Number of laboratories performing HCV viremia testing that participated on all proficiency testing rounds of EQA program per year	NCDC Lugar Center *Includes the national reference laboratory	81.8% (N=9)	78.6% (N=11)	76.5% (N=13)	88.2% (N=15)	75.0% (N=12)	
		Denominator Total number of laboratories performing HCV viremia testing enrolled in national EQA		(N=11)	(N=14)	(N=17)	(N=17)	(N=16)	
	3. Quality Management System (QMS) standards for certification are defined, approved, and published		Published QMS standards	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	
	4. Proportion of labs providing HCV lab services certified according to national laboratory quality management system (QMS) standards	Numerator Number of laboratories performing HCV lab services that are certified according to national QMS standards		MoIDPLHSA Not applicable until national laboratory QMS standards are approved	N/A	N/A	N/A	N/A	N/A
		Denominator Total number of laboratories performing hepatitis C laboratory services							

STRATEGY 5. PROVIDE COMPREHENSIVE HCV CARE AND TREATMENT

Objective	Indicator Name	Measurement	Data Source	Value/Result (2021)	Value/Result (2020)	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)
5.1. Promote universal access to HCV care and treatment	1. Proportion of anti-HCV positive persons assessed for chronic HCV infection	Numerator Number of anti-HCV positive persons tested for viremia (RNA, core antigen)	Elimination C STOP-C databases	85.2% (N=120,591)	84.0% (N=112,809)	80.4% (N=100,844)	74.6% (N=78,611)	63.0% (N=51,205)
		Denominator Number of anti-HCV positive persons (treatment eligible Age ≥ 12)	Data since the launch of the program in 2015	(N=141,480)	(N=134,343)	(N=124,312)	(N=105,393)	(N=81,242)
	2. Proportion of persons diagnosed with chronic HCV infection	Numerator Number of persons diagnosed with chronic HCV infection based on RNA or core antigen testing	Elimination C STOP-C databases National HCV screening registry	79.4% (N=95,711)	80.3% (N=90,578)	81.8% (N=82,486)	85.2% (N=67,001)	91.0% (N=46,573)
		Denominator Number of persons tested for viremia after a positive serological result	Data since the launch of the program in 2015	(N=120,591)	(N=112,809)	(N=100,844)	(N=78,611)	(N=51,205)
		◇ Target of identifying 90% of persons infected with HCV infection: N=135,000	National sero-prevalence survey conducted in 2015	◇70.9%	◇67.1%	◇61.1%	◇49.6%	◇34.5%
	3. Proportion of persons with chronic HCV infection who initiated antiviral therapy	Numerator Number of persons diagnosed with chronic HCV infection who initiated antiviral therapy	Elimination C STOP-C databases National HCV screening registry	80.1% (N=76,644)	80.4% (N=72,811)	78.2% (N=64,537)	78.5% (N=52,594)	91.0% (N=42,391)
		Denominator Number of persons diagnosed with chronic HCV infection	Data since the launch of the program in 2015	(N=95,711)	(N=90,578)	(N=82,486)	(N=67,001)	(N=46,573)
		◇Target of treating 95% of persons with chronic HCV infection: N=128,250	National sero-prevalence survey conducted in 2015	◇59.8%	◇56.8%	◇50.3%	◇41.0%	◇33.0%

STRATEGY 5. PROVIDE COMPREHENSIVE HCV CARE AND TREATMENT *cont.*

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)
5.1. Promote universal access to HCV care and treatment	4. Proportion of patients engaged in antiviral therapy who have completed treatment	Numerator Number of patients with chronic HCV infection who have completed treatment	Elimination C STOP-C databases	95.1% (N=72,864)	95.0% (N=69,192)	92.2% (N=59,485)	93.0% (N=48,928)	89.5% (N=37,948)
		Denominator Number of patients diagnosed with chronic HCV infection who initiated treatment	Data since the launch of the program in 2015	(N=76,644)	(N=72,811)	(N=64,537)	(N=52,594)	(N=42,391)
	5. Proportion of patients achieving SVR to HCV therapy*	Numerator Number of patients who completed treatment and achieved SVR (undetectable viral load 12-24 weeks after the end of treatment)	Elimination C STOP-C databases	98.9% (Per-protocol) 72.3% (Intention-to-treat) (N=53,815)	98.9% (Per-protocol) 73.1% (Intention-to-treat) (N=50,644)	98.7% (Per-protocol) 73.6% (Intention-to-treat) (N=42,194)	98.3% (Per-protocol) 73.9% (Intention-to-treat) (N=34,493)	98.2% (Per-protocol) 75.7% (Intention-to-treat) (N=26,692)
			Denominator Number of patients who completed antiviral therapy and were assessed for SVR 12-24 weeks post treatment	Data since the launch of the program in 2015	(N=54,398)	(N=51,208)	(N=42,734)	(N=35,106)
		◇ Target of curing 95% of persons treated for their HCV infection: N=121,838	National sero-prevalence survey conducted in 2015	◇44.2%	◇41.6%	◇34.6%	◇28.3%	◇21.9%
	6. Number of physicians providing HCV services OR provider/resident ratio	Numerator Number of physicians providing HCV services:	MoIDPLHSA	5.1 per 100,000 residents N=155	5.1 per 100,000 residents N=155	5.1 per 100,000 residents N=155	5.1 per 100,000 residents N=155	4.6 per 100,000 residents N=139
		Denominator Estimated resident population: 3,010,200						

STRATEGY 5. PROVIDE COMPREHENSIVE HCV CARE AND TREATMENT *cont.*

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)
5.1. Promote universal access to HCV care and treatment	7. Number of a) primary healthcare centers b) harm reduction sites providing HCV care and treatment		MoIDPLHSA	a) 10	a) 10	a) 7	a) 7	a) 0
				b) 4	b) 4	b) 4	b) 4	b) 0

*Per-protocol SVR rate includes retreatments and is calculated out of people who were tested for SVR. Intention-to-treat SVR rate is calculated out of a total number of patients eligible for SVR.

STRATEGY 6. IMPROVE HCV SURVEILLANCE

Objective	Indicator Name	Measurement	Data Source	Value/ Result (2021)	Value/ Result (2020)	Value/ Result (2019)	Value/ Result (2018)	Value/ Result (2017)
6.1. Estimate the national burden of chronic viral hepatitis C	1. The incidence of HCV infection among PWID and general population	Numerator Total number of new infections with HCV, defined as anti-HCV positive, per year	*Prospective cohort study of the reinfection rate among treated and cured PWID, 2015-2017 (MDM) **Prospective cohort study of the anti-HCV incidence among PWID, 2018-2019 (AIDS Center) ***Prospective cohort study of the reinfection rate among treated and cured PWID, 2019-2020 (FIND, Unitaid)	Data not available	2.67 per 100 person-years*** 60 cases out of 2284 person-years of follow-up	0.77 per 100 person-years** 7 new cases out of 906 person-years of follow-up	Data not available	1.2 per 100 person-years* 2/169 person-years of follow-up
		Denominator Total population minus people living with hepatitis C						
	2. Number of deaths attributable to HCV-associated cirrhosis or hepatocellular carcinoma (HCC)	Number of deaths from HCC and cirrhosis attributable to HCV infection	Death Registry/ Cancer registry HCC (ICD-10 code C22.0) Cirrhosis (ICD-10 codes K74.3, K74.4, K74.5, K74.6)	Data not available	Data not available	Data not available	Data not available	Data not available

RESEARCH AND SCIENCE

Established in August 2016, the Scientific Committee (SC) represents a diverse group of partners in the Georgia Hepatitis C Elimination Program, including policy makers, clinicians, and researchers. In 2020–2021, the SC continued program support by reviewing and approving research proposals focused on hepatitis C- and hepatitis B-related topics and supported researchers in securing funding, obtaining IRB approvals, study implementation, data analysis, and manuscript writing. The SC coordinated its activities with MoDPLHSA, NCDC, the Program Clinical Committee, and international organizations to increase overall efficiency of the supported research programs. Additionally, the SC served as a platform for invited speakers to disseminate research findings.

Between August 2016 and December 31, 2021, the SC reviewed a total of 80 research proposals, of which 72 were approved. Of those, 12 were approved from January 2020 through December 2021. The results of the following research projects were published and/or presented during the time period covered by this Annual Report:

PREVENTION AND AWARENESS RAISING

- **Project title:** Blood transfusion safety in Republic of Georgia: Leveraging blood centers to advance a national Hepatitis C intervention program
- **Description:** Data from the blood donor screening was analyzed from 2015 through 2017. The analysis demonstrated that prevalence of anti-HCV among blood donors declined from 2.3% in 2015 to 1.4% in 2017.
- **Publication:** Bloch EM, Kipiani E, Shadaker S, et al. Blood transfusion safety in the country of Georgia: collateral benefit from a national hepatitis C elimination program. *Transfusion*. 2020;60(6):1243-1252. doi:10.1111/trf.15815
- **Abstract/poster:** N/A

SCREENING AND LINKAGE TO CARE

- **Project title:** HCV screening and linkage to care among inpatients in Georgia, 2016-2017
- **Description:** This analysis assessed the effectiveness of the first year of the screening program to identify HCV-infected persons and link them to care. Data from Georgia’s electronic Health Management Information System and ELIMINATION-C treatment database were analyzed for patients aged ≥18 years hospitalized from November 1, 2016 to October 31, 2017. Of 291,975 adult inpatients, 252,848 (86.6%) were screened. Of them, 4.9% tested anti-HCV+, and 19.8% of them were linked to care. This study demonstrated that hospital-based screening programs can identify large numbers of anti-HCV+ persons, but low linkage-to-care rates underscore the need for screening programs to be coupled with effective linkage strategies.
- **Publication:** Shadaker S, Nasrullah M, Gamkrelidze A, et al. Screening and linkage to care for hepatitis C among inpatients in Georgia’s national hospital screening program. *Prev Med*. 2020;138:106153. doi:10.1016/j.ypmed.2020.106153
- **Abstract/poster:** N/A



- **Project title:** Integrating HCV screening and simplified treatment services in primary healthcare
- **Description:** To address the barriers in diagnosis and linkage to care, Georgia initiated service decentralization in 2018 by integrating hepatitis C virus (HCV) screening and treatment in primary healthcare centers (PHCs). This study reported a high rate of treatment initiation and cure rates in the primary healthcare setting and demonstrated the feasibility and effectiveness of integrating a simplified HCV diagnostic and treatment model in PHCs.
- **Publication:** N/A
- **Abstract/poster:**
 1. Management of hepatitis C in primary healthcare in the country of Georgia at Digital International Liver Congress, August 2020
 2. Management of hepatitis C in primary healthcare in the country of Georgia at Global Hepatitis Summit, June 2021

DIAGNOSTICS

- **Project title:** Evaluation study of rapid diagnostic tests (RDTs) detecting antibodies against hepatitis C virus
- **Description:** This retrospective multi-country study assessed performance of rapid diagnostic tests (RDTs) for detection of HCV antibodies. In HIV negative samples (n = 384), the majority of RDTs had sensitivity $\geq 98\%$ in 1 or both lots and most RDTs had specificity $\geq 99\%$. In HIV-positive samples (n = 264), specificity remained high, but sensitivity was markedly lower than in HIV-negative samples. The study also compared the performance of 2 RDTs on different samples and found that sensitivity was lower in whole blood versus plasma and serum for both RDTs. Sensitivity improved when considering only samples with detectable HCV viral load.
- **Publication:**
 1. Vetter BN, Ongarello S, Tyshkovskiy A, et al. Sensitivity and specificity of rapid hepatitis C antibody assays in freshly collected whole blood, plasma and serum samples: A multicentre prospective study. *PLoS One.* 2020;15(12):e0243040. doi:10.1371/journal.pone.0243040
 2. Vetter BN, Reipold EI, Ongarello S, et al. Sensitivity and specificity of rapid diagnostic tests for hepatitis C virus with or without HIV coinfection: a multicentre laboratory evaluation study [published online ahead of print, 2020 Jul 2]. *J Infect Dis.* 2020;jiaa389. doi:10.1093/infdis/jiaa389
- **Abstract/poster:** N/A

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- **Project title:** Prospective evaluation of the Genedrive® HCV ID Kit in Georgia
 - **Description:** This study evaluated the diagnostic accuracy of Genedrive HCV ID assay for the qualitative detection of HCV RNA in decentralized settings in Georgia and Cameroon using fresh plasma specimens from 426 participants. The Abbott RealTime HCV assay was used as the gold standard. Genedrive HCV ID assay was conducted by different users. Users also completed questionnaires to assess the usability of Genedrive. At different detection thresholds, Genedrive showed very high sensitivity (96%-100%) and specificity (99%-100%). All genotypes detected using the gold-standard assay were also detected with Genedrive. The study demonstrated that Genedrive is a simple and accurate test to confirm chronic HCV infection in decentralized, real-life, resource-limited settings.

- **Publication:** Lamoury FMJ, Njouom R, Amougou-Atsama M, et al. Diagnostic Performance and Usability of the Genedrive® HCV ID Kit in Two Decentralized Settings in Cameroon and Georgia. *Diagnostics (Basel)*. 2021;11(5):746. doi:10.3390/diagnostics11050746
- **Abstract/poster:** N/A

CARE AND TREATMENT

- **Project title:** Effectiveness of ledipasvir/sofosbuvir based regimens in patients with hepatitis C virus genotype 1, 2, 3 and 4 infection and factors associated with treatment outcomes within Georgian national hepatitis C elimination program
- **Description:** This study reported outcomes of Sofosbuvir (SOF)-based treatment regimens in patients with chronic HCV infection in Georgia. Of the 7,342 patients who initiated treatment with SOF-based regimens, 5,079 patients were tested for SVR. Total SVR rate was 82.1% in per-protocol analysis, which included only those with complete SVR data, and 74.5% in modified intention-to-treat analysis, which additionally included persons discontinuing treatment. The study provided clear evidence that SOF plus IFN and RBV for 12 weeks can be considered a treatment option for eligible patients with all three HCV genotypes.
- **Publication:** Tsertsvadze, T., Gamkrelidze, A., Nasrullah, M. et al. Treatment outcomes of patients with chronic hepatitis C receiving sofosbuvir-based combination therapy within national hepatitis C elimination program in the country of Georgia. *BMC Infect Dis* 20, 30 (2020). <https://doi.org/10.1186/s12879-019-4741-5>
- **Abstract/poster:** N/A

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- **Project title:** High sustained viral response among HCV genotype 3 patients with advanced liver fibrosis: Real-world data of HCV elimination program in Georgia
 - **Description:** This study assessed treatment outcome data from patients with HCV GEN3 and advanced liver fibrosis using sofosbuvir-based regimens. In total, 1,525 genotype 3 patients were eligible for analysis and all (100%) had advanced liver disease. Of those who received sofosbuvir/ribavirin (SOF/RBV) for 24 weeks, 79.3% achieved SVR, while 96.5% who received sofosbuvir/pegylated interferon/ribavirin (SOF/PEG/RBV) for 12 weeks achieved SVR ($p < 0.01$). Among patients with liver cirrhosis (defined as F4) overall cure rate was 85.7% as opposed to 96.4% for those with F3. While patients with HCV genotype 3 achieved a high level of overall cure rate with SOF/RBV, the inclusion of PEG led to a higher cure rate with a shorter duration of treatment.
 - **Publication:** Butsashvili M, Gvinjilia L, Kamkamidze G, et al. High sustained viral response among HCV genotype 3 patients with advanced liver fibrosis: Real-world data of HCV elimination program in Georgia. *BMC Res Notes*. 2020;13(1):332. doi:10.1186/s13104-020-05173-4
 - **Abstract/poster:** N/A

- **Project title:** Implementing HCV treatment in harm reduction centers in Georgia
- **Description:** As part of this study, 358 patients were surveyed; 48.6% received HCV treatment at specialized clinics and 51.4% at HR sites with integrated treatment. Similar proportions of surveyed patients at HR sites and clinics stated that they did not face any barriers to enrollment in the elimination program and were confident that confidentiality was completely protected during treatment. Time to treatment initiation differed significantly, with 42.9% of patients at integrated treatment sites vs 4.6% at specialized clinics receiving the first dose of medication within two weeks. The study findings suggest that integration of HCV treatment with HR services is feasible and shortens time to treatment initiation.
- **Publication:** Butsashvili M, Kamkamidze G, Kajaia M, et al. Integration of hepatitis C treatment at harm reduction centers in Georgia-Findings from a patient satisfaction survey. *Int J Drug Policy*. 2020;84:102893. doi:10.1016/j.drugpo.2020.102893
- **Abstract/poster:** N/A

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- **Project title:** Retreatment for HCV: A retrospective analysis of pooled national program data across several countries
 - **Description:** Recommended second-line treatment is limited for patients who fail initial hepatitis C virus (HCV) therapy in low- and middle-income countries. Alternative regimens and associated outcomes are not well understood. As part of this study, a pooled analysis of national program data in Egypt, Georgia, and Myanmar was conducted. The analysis observed SVR rates >90% for alternative retreatment regimens, typically based on sofosbuvir in combination with the NS5A inhibitors, such as ledipasvir.
 - **Publication:** Boeke CE, Hiebert L, Waked I, et al. Retreatment of Chronic Hepatitis C Infection: Real-World Regimens and Outcomes from National Treatment Programs in Three Low- and Middle-Income Countries. *Clin Infect Dis*. 2021;ciab461. doi:10.1093/cid/ciab461
 - **Abstract/poster:** Retreatment for HCV: Preliminary results from a Retrospective Analysis of Pooled National Program Data across Several Countries, presented at 2020 Annual Meeting of the American Association for the Study of Liver Diseases, November 13-16, 2020

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- **Project title:** The Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) project: Feasibility, acceptability, effectiveness, and cost-effectiveness of a decentralized and a centralized model of HCV viremia testing for confirmation and cure versus standard of care among harm reduction site attendees in Georgia
 - **Description:** This cluster, non-randomized intervention study assessed two novel models of viremic testing in harm reduction settings. The proportion of participants who completed each step in the HCV care cascade were compared across the three arms: 1) viremia testing (GeneXpert) on-site; 2) blood draw on site, confirmatory testing (cAg) at a centralized laboratory; 3) standard of care - patients referred for testing at the treatment centre. Confirmatory testing or blood draw on-site at HRS showed improved retention of patients in the care cascade compared to a referral of patients for blood collection. Moreover, the turnaround time to diagnosis was shortest when confirmatory testing was performed on site. Time to treatment initiation did not differ substantially.

- **Publication:** N/A
- **Abstract/poster:** The head-start project Georgia: a three-armed, cluster, non-randomised trial of the effectiveness of two novel models of HCV confirmatory testing in harm reduction sites (HRS) in Georgia at the Digital International Liver Congress, August 2020

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- **Project title:** Progress of the Georgia Hepatitis C Elimination Program
 - **Description:** This project tracks the progress towards elimination targets and reports the hepatitis C care cascade results. Ongoing analyses repeatedly demonstrates that Georgia has made substantial progress towards eliminating hepatitis C. Very high cure rates have been achieved among those who received SVR testing. Challenges remain in identifying and especially linking to care persons living with HCV in Georgia.
 - **Publication:** N/A
 - **Abstract/poster:**
 1. Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015-October 2019 at the Digital International Liver Congress, August 2020 (oral presentation)
 2. Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015-December 2020 at the International Liver Congress, June 23-26, 2021

SURVEILLANCE

- **Project title:** Evidence synthesis for real-time and retrospective evaluation of the HCV elimination program in Georgia
- **Description:** This study evaluated the cost-effectiveness of the screening and treatment undertaken in the HCV elimination program from 2015 to November 2017 compared to no treatment. Using the adapted HCV transmission and progression model calibrated to Georgian data, this study found that the first phase of the HCV elimination program was highly cost-effective in Georgia: 0.78 QALYs were gained per patient treated due to reduced disease progression, and the intervention prevented 2,673 HCV-related deaths and averted 16,225 new infections by 2030 compared to no treatment.
- **Publication:** N/A
- **Abstract/poster:** Economic evaluation of the hepatitis C virus screening and treatment program in Georgia at Digital International Liver Congress, August 2020

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- **Project title:** Impact on mortality of hepatitis C virus (HCV) treatment with direct acting anti-viral (DAA) medications, Georgia, 2015-2018
 - **Description:** This study linked data from hepatitis C screening registry, the national hepatitis C treatment database and national vital statistics using the 11-digit national personal identifier. The results demonstrated that persons with HCV infection who are cured with DAAs have an increased likelihood of survival, similar to persons never infected, compared to HCV-infected persons who did not receive treatment.
 - **Publication:** N/A
 - **Abstract/poster:** The impact on mortality of a national hepatitis C elimination program, Georgia, 2015-2019 at Digital International Liver Congress, August 2020

- **Project title:** Evaluation of alcohol use behavior among patients cured through HCV elimination program in Georgia
- **Description:** This study evaluated alcohol consumption behaviors among patients in the HCV program using an interviewer-administered questionnaire in three cities of Georgia. As of December 2020, 256 patients were enrolled in the study; the majority of them (93.7%) reported ever using alcohol in their lifetime, 10.3% considered themselves heavy drinkers, and 97.5% abstained from alcohol during treatment. In a bivariate analysis, patients who abstained from alcohol after achieving SVR were 4 times more likely to have improvement in liver fibrosis compared to those who resumed drinking. The findings present an opportunity to focus messaging and education for patients during DAA treatment to improve outcomes even after completion of treatment.
- **Publication:** N/A
- **Abstract/poster:** Evaluation of alcohol use behavior among patients cured in Georgia’s HCV elimination program (preliminary results) at Global Hepatitis Summit, June 2021

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- **Project title:** Long-term health outcome among HCV patients with advanced liver fibrosis treated through HCV Elimination Program in Georgia
 - **Description:** A total of 600 patients were included in this cohort study, which demonstrated that among patients with liver fibrosis, treatment with DAAs affords significant improvement in nearly all diagnostic markers and can lead to resolution of clinical symptoms of decompensated liver failure.
 - **Publication:** N/A
 - **Abstract/poster:** Improvement in liver fibrosis among patients with hepatitis C who achieved sustained virologic response after direct-acting antivirals treatment in Georgia (preliminary results) at the Global Hepatitis Summit, June 2021

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- **Project title:** Epidemiology of tuberculosis and hepatitis C co-infection in the Country of Georgia
 - **Description:** This study assessed the effects of HCV infection on the rate of active TB disease in a cohort of 1,778,382 adults. Active TB incidence was compared in three groups: 1) HCV antibody-negative (reference group), 2) completed HCV treatment (treated), 3) untreated HCV infection. TB was diagnosed in 2,923 (0.16%) participants. The TB incidence rate was more than 4 times higher among persons with untreated HCV infection, and 1.7 times higher among those with treated HCV compared to those without HCV infection, suggesting that integrating TB-related interventions in the hepatitis C program might be beneficial.
 - **Publication:** N/A
 - **Abstract/poster:** Association of treated and untreated chronic hepatitis C with the incidence of active tuberculosis: a population-based cohort study in the country of Georgia at the American Association for the Study of Liver Diseases, November 12-15, 2021

- **Project title:** Identification and characterization of HCV-attributable hepatocellular carcinoma among persons with hepatobiliary cancer diagnoses in Georgia: 2015-2019
- **Description:** Assessing the HCV-attributable burden of hepatocellular carcinoma (HCC) is needed to measure the impact of the elimination program and progress toward viral hepatitis elimination. This study linked the data from Georgian Cancer Registry to the Georgia Hepatitis C Elimination Program databases and found that approximately half of those with primary liver cancer (PLC) and screening data available had chronic HCV infection. This suggests that HCV contributes substantially to PLC burden in Georgia. Continuing to monitor these trends is critical to demonstrating progress towards elimination, and provides a global model for integrated surveillance of sequelae from viral hepatitis.
- **Publication:** N/A
- **Abstract/poster:** HCV-attributable liver cancer in the country of Georgia: Analysis of cases from the Georgian Cancer Registry 2015-2019 at the International Viral Hepatitis Elimination Meeting, December 2021

Other publications/abstracts/posters not related to the SC approved projects

- **Title:** HCV care cascade of PWID enrolled in methadone substitution treatment program in Georgia
- **Description:** This study examined and identified factors that affect HCV treatment uptake among PWID who received methadone substitution therapy in Georgia. HCV care cascade analysis used data from the hepatitis C program treatment registry and the MST treatment database between January 1, 2015, and December 31, 2018. The study demonstrated high rates of HCV treatment uptake and cure among MST patients with HCV infection (75.8% and 96.1%, respectively), suggesting that the MST patients could be the first microelimination target population.
- **Publication:** Stvilia K, Vepkhvadze N, Gamkrelidze A, et al. Hepatitis C treatment uptake among patients who have received methadone substitution treatment in the Republic of Georgia. Public Health. 2021;195:42-50. doi:10.1016/j.puhe.2021.03.017
- **Abstract/Poster:** HCV care cascade of PWID enrolled in methadone substitution treatment program in Georgia—Is this the first group of population in which hepatitis C will be eliminated in Georgia? at the Digital International Liver Congress, August 2020

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- **Title:** Hepatitis C core antigen test as an alternative for diagnosing HCV infection: Mathematical model and cost-effectiveness analysis
 - **Description:** This study investigated the cost effectiveness of testing strategies using antigen instead of PCR testing using a mathematical model. The results demonstrated that antigen testing, either following a positive antibody test or alone, performed almost as well as the current practice of HCV testing. The cost effectiveness of these strategies depends on the inclusion of treatment costs.
 - **Publication:** Sadeghimehr M, Bertisch B, Negro F, et al. Hepatitis C core antigen test as an alternative for diagnosing HCV infection: Mathematical model and cost-effectiveness analysis. PeerJ. 2021;9:e11895. Published 2021 Sep 10. doi:10.7717/peerj.11895
 - **Abstract/poster:** N/A



- **Title:** Innovative linkage model to re-engage lost-to-follow-up individuals in the national hepatitis C elimination program of Georgia
- **Description:** This pilot project promoted linkage to care for individuals who screened positive for HCV antibody (anti-HCV) but did not receive a viremia test. Anti-HCV-positive individuals lost to follow up residing in the 5 largest regions in Georgia were randomly selected and counselled via phone or home visit. A total of 3,859 individuals were reached, of which 77% presented for viremia testing. The project also demonstrated that individuals considered lost-to-follow-up can be re-engaged in HCV care.
- **Publication:** N/A
- **Abstract/poster:** Innovative linkage model to re-engage lost-to-follow-up individuals in the national hepatitis C elimination program of Georgia at the International Liver Congress, June 23-26, 2021

Other projects ongoing or with pending publication, abstract, or poster

PREVENTION AND AWARENESS RAISING

- **Title:** Identifying risk factors of HCV transmission in Georgia – a case-control study
- **Objective:** 1) To evaluate risk factors of HCV transmission 2) to elaborate recommendations for HCV prevention based on study findings
- **Description:** The project will build on a recently completed project that interviewed 214 people who demonstrated seroconversion for HCV to assess risk factors for recent infection. The initial study provided descriptive data on risk factors. This study will include controls to allow for statistical comparison to best understand the risk of factors associated with recent infection.



- **Title:** Study of risk factors of HCV reinfection among PWID enrolled in HCV elimination program in Georgia
- **Objective:** To evaluate risk factors of HCV re-infection among PWID treated through HCV elimination program achieving SVR.
- **Description:** This study will enroll 60 PWID who were found to be reinfected with HCV as part of a previous study conducted by FIND. All 60 will be invited to be enrolled in the study as cases, and ratio of cases and controls will be 1:3, with an overall sample size of 240.



- **Title:** Evaluation of knowledge, attitudes, and practices for HBV infection among primary healthcare doctors
- **Objective:** Evaluate knowledge, attitudes, and practices about HBV infection among primary healthcare doctors (PHDs).
- **Description:** The study will survey 500 randomly selected PHDs on their knowledge, attitudes, and practices about HBV. The findings will inform training programs and expanded testing and treatment for HBV.

SCREENING AND LINKAGE TO CARE

- **Title:** Late presentation for hepatitis C care in Georgia, 2016-2021
- **Objective:** To assess trends in late presentation for HCV care in Georgia during 2016-2021
- **Description:** This study will include all adults (age ≥ 18 years) enrolled in the elimination program during 2016-2021 in the analysis to quantify the proportion of late presenters with advanced liver disease and to identify factors associated with late presentation

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- **Title:** Eliminating HCV infection in prison settings in Georgia
 - **Objectives:** 1) To evaluate engagement in the HCV care continuum, identify gaps in HCV cascade/ service delivery and associated factors, 2) to evaluate linkage of released prisoners to HCV care providers, 3) to develop recommendations on achieving elimination of hepatitis C in prison settings
 - **Description:** This analysis will include all adult (age ≥ 18 years) individuals known to be living with chronic HCV infection while incarcerated in prisons of Georgia. The analysis will quantify HCV care cascade among prisoners, assess factors associated with engagement in the continuum, and evaluate treatment outcomes.

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- **Title:** Assessment of HCV screening and linkage to care modalities within the national Georgia Hepatitis C Elimination Program and designing the most optimal models for reaching the elimination targets
 - **Objectives:** 1) To evaluate effectiveness of various modalities in terms of diagnostic yield and engagement in HCV care (including linkage to care and treatment initiation), 2) to define the most optimal screening and linkage modalities
 - **Description:** This project will quantify screening and care cascade and conduct economic/value for money analysis for the following HCV screening models: 1) Hospital sector screening model (centralized model), 2) Hospital sector screening model (decentralized model), 3) Primary healthcare screening model, 4) HCV provider site screening model; 5) Other outpatient/outreach screening models.

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- **Title:** Learning lessons from Georgia using economic modelling to determine optimum screening and linkage-to-treatment strategies for achieving high treatment coverage in Eastern Europe and Central Asia
 - **Objective:** Use economic modelling to determine the most cost-effective strategies for improving screening and linkage to treatment for achieving HCV elimination in Georgia and elsewhere in Eastern Europe and Central Asia.
 - **Description:** This study will estimate the cost, impact and cost-effectiveness (cost/QALY saved or DALY averted) of different interventions being used in Georgia to improve screening, confirmatory testing and treatment uptake. It will also model the impact and cost of different intervention combinations.



- **Title:** Assessing the inclusion and participation of collective center internally displaced persons (IDPs) in the State HCV Elimination Program
- **Objectives:** 1) Assessing the burden of disease for HIV, hepatitis B, and hepatitis C among internally displaced persons living in collective centers, 2) understanding the extent to which the elimination program and its subsequent interventions have penetrated into these communities and with what efficacy.
- **Description:** This study will generate information about the HIV and viral hepatitis-related health status of IDPs in collective centers. Nearly half of IDPs in Georgia reside in such centers or compact settlements where their quality of life and experience differs significantly from the general population and from IDPs who live in private accommodations. Therefore, it is important to carefully examine the health status of this population, especially in terms of infectious diseases such as HIV and viral hepatitis.

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- **Title:** A controlled, observed trial of Hepatitis C self-testing in the hands of untrained users
 - **Objective:** To document if a lay person, unassisted by a healthcare worker, is able to perform a Hepatitis C Virus (HCV) test on themselves using the HCV Self-Test
 - **Description:** This multicountry controlled study (Georgia, South Africa, Spain) will evaluate the process and performance of 2 types of rapid hepatitis C self-tests (from fingerstick blood and from oral fluids) by untrained users. Self-test results will be confirmed by testing with the same test but performed by a professional user (healthcare worker). The level of agreement between the results of the investigated test obtained by a participant and those obtained by a healthcare worker will be calculated.

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- **Title:** Enhanced linkage to care for patients lost to follow up in hepatitis C elimination program
 - **Objective:** To link to care those individuals that have previously tested positive for HCV antibody but have not received viremia testing
 - **Description:** This project aims to contact 20,000 anti-HCV positive persons lost to follow-up, conduct HCV viremia testing on at least 70% (14,000) of them, and enroll 50% of the HCV RNA positive persons in the treatment program.

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- **Title:** Uptake of HCV self-testing (HCVST) among the general population in Georgia
 - **Objective:** To evaluate uptake, linkage to care, and operational considerations of different HCVST delivery models among men aged 30-59 years in Tbilisi Georgia.
 - **Description:** The study will examine two models of HCV self-test distribution: secondary distribution via female attendees at cancer screening centers in Tbilisi and pharmacy-based distribution of HCVST among male clients. It will also examine the linkage to care of persons who report positive tests using HCVST and evaluate costs associated with each HCVST model.

DIAGNOSTICS

- **Title:** Advancing blood transfusion safety using molecular detection in the country of Georgia
- **Objectives:** To evaluate the feasibility and incremental benefit of implementing NAT testing in the country of Georgia by assessing yield in seronegative samples
- **Description:** Multiplex NAT screening for HIV, HCV, and hepatitis B virus (HBV) was launched in January 2020. An analysis was conducted of serological and NAT donor/donation screening data for the first year of screening (through December 2020), with a total of 54,116 donations representing 39,164 unique donors evaluated. This program-wide implementation of NAT in Georgia demonstrates the feasibility and clinical utility of employing NAT systematically across a nationwide blood program.

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- **Title:** Implementing viral marker testing for blood products in Georgia
 - **Objective:** The main aim of the study is to understand the deficiencies in the standard methods used in Georgian blood banks to test blood donation samples for HBV, HCV, HIV, and T. pallidum, and use the findings to inform public policy on the best testing algorithm and system-wide testing of blood donations to reduce TTIs in Georgia.
 - **Description:** This study performs a comparative assessment of different assays, primarily between new ultrasensitive Abbott assays, and current assays being used by individual blood banks and through centralized NAT testing. Sample testing ran from March through June 2021. All samples received by all blood banks countrywide from March through June 2021 were included in the study and tested using the Abbott ultrasensitive assays. The samples included were all those positive for either serology or NAT and a randomly selected subset of negative samples. In total, 8,400 samples were analyzed.

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- **Title:** Analysis of HCV RNA levels of viral rebound among patients who have completed treatment for HCV to inform the limit of detection necessary to confirm SVR
 - **Objectives:** To analyze HCV RNA levels of viral rebound among patients who have completed treatment for HCV to inform the limit of detection necessary to confirm SVR
 - **Description:** This study will test factors associated with an HCV RNA in the lowest 3%, calculate summary statistics for covariates of interest and test associations between these covariates and the odds of having HCV RNA < the 97% threshold value.

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- **Title:** Strengthening HCV outbreak detection capacity within harm reduction settings in Georgia by utilizing GHOST technology
 - **Objectives:** 1) To analyze and visualize transmission patterns of HCV infection among PWID who test positive for HCV at selected HR sites located in Tbilisi (n=1) and Zugdidi (n=1), 2) To use GHOST technology to identify PWID at highest risk of transmitting HCV (high-centrality nodes with multiple molecular connections or high intra-host HCV variability or HIV coinfecting) within an injection drug use network.
 - **Description:** This study uses GHOST technology to examine the HCV transmission pattern on 100 PWID who test positive on HCV viremia testing. PWID will be enrolled in the study sites in two cities assessing networks using GHOST technology.

CARE AND TREATMENT

- **Title:** Prioritization of DAA treatment in HCV infected individuals across Europe – CARE Consortium EU project application under H2020
- **Objective:** To develop recommendations on how to rationally prioritize DAA therapy among people infected with HCV in settings with high case load and limited health budgets
- **Description:** This study is a part of CARE (Common Action against HIV, TB, and HCV across the Regions of Europe) consortium aiming to analyze and combat the HIV, TB, and HCV epidemics across Europe and Russia. The analysis will use the existing cohorts of co-infected patients from Georgia, Italy, Sweden and EuroSIDA.

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- **Title:** Comparing engagement in HCV care and treatment outcomes between persons who are HIV negative and persons who are HIV positive within the national hepatitis C elimination program
 - **Objectives:** 1) To evaluate engagement in HCV care continuum by HIV status within the Georgia Hepatitis C Elimination Program, 2) to compare SVR rates among HIV negative and HIV positive persons treated within the Georgia Hepatitis C Elimination Program
 - **Description:** This analysis will include all adult (age ≥ 18 years) persons enrolled in the elimination program and will quantify and compare engagement in HCV care cascade within the Georgia Hepatitis C Elimination Program by HIV status.

SURVEILLANCE

- **Title:** Establishing Georgian PWID cohort study to estimate incidence of HCV infection
- **Objective:** To obtain new knowledge about the epidemiology of HCV infection as well as HCV care and treatment among PWID and to move this knowledge into effective control measures towards achieving goals of the national hepatitis C elimination strategy
- **Description:** This study enrolled 1744 PWID to estimate the prevalence and incidence of HCV infection in this population. Of them, 563 were found to be anti-HCV positive. The remaining study participants were followed for a median of 11 months, and anti-HCV seroconversion was documented in 7 of them.

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- **Title:** Surveillance and risk of transmission of HCV and HBV in renal dialysis, Georgia
 - **Objectives:** 1) To describe the infection control practices in dialysis units in Georgia (in general and specific to hepatitis B and hepatitis C virus), 2) to determine the prevalence of HBV and HCV among those receiving dialysis, 3) to determine the seroconversion rate in dialysis units/clinics
 - **Description:** This project collected information from dialysis clinics about type of services at the unit, number of patients served, availability of infection control service at the unit, HCV and HBV testing and laboratory methods, prevalence and seroconversion of HBV and HCV among dialysis patients, and treatment coverage of HBV and HCV patients. A total of 23 facilities throughout country participated.

- **Title:** Evaluation of HCV transmission through endoscopy procedures
- **Objectives:** 1) To evaluate the adherence to standard safety measures during diagnostic endoscopic procedures in Georgian hospitals and outpatient clinics, 2) to train staff serving at endoscopic units on safety precautions for the prevention of healthcare associated infections, 3) to estimate HCV incidence among patients undergoing gastroscopy, colonoscopy, and bronchoscopy.
- **Description:** As part of this study, IPC assessment questionnaires were administered to 4 endoscopic units (3 in Tbilisi and 1 in Kutaisi) to assess infection control practices in the facility. 500 patients were enrolled from each hospital for a total of 2,000 patients; all were screened for anti-HCV at time zero and will be followed-up at 6 months. Patient-level HCV risk-factors data will be collected using a standardized data collection instrument.

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- **Title:** Rates and risk factors for HCV reinfection within the national hepatitis C elimination program: Implications for program success
 - **Objectives:** 1) To determine rate of HCV reinfection among persons successfully treated within the Georgia Hepatitis C Elimination Program, 2) to identify risk factors associated with HCV reinfection
 - **Description:** This analysis will be limited to persons who achieved SVR within the elimination program. The study team will conduct probability sampling stratified by geographic location and age group. Selected subjects will be enrolled to obtain plasma specimens and administer survey questionnaire. Among those positive for HCV RNA, the study will use HCV genotype data to determine whether this is reinfection or late relapse.

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- **Title:** Epidemiology of HBV infection among HCV patients treated with DAAs
 - **Objective:** To evaluate epidemiology of HBV infection among HCV infected patients treated within elimination program in Georgia
 - **Description:** This study evaluates the rate of HCV/HBV co-infection (presence of HBsAg among patients with positive HCV RNA), the rate of HBV exposure among HCV-infected patients (presence of anti-HBc among patients with positive HCV RNA), and the HCV cure rate among HBV-infected patients. It also examines the role of HBV/HCV co-infection on liver fibrosis level and factors associated with HBsAg clearance among HCV-infected patients.

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- **Title:** A population-based serosurvey of prevalence and risk factors for SARS-CoV-2, Hepatitis C and Hepatitis B virus infection in Georgia, 2021
 - **Objective:** To estimate prevalence of serological evidence of past or present HCV and HBV infection and prevalence of chronic HCV and HBV infection among adults and children aged >5 years
 - **Description:** This study provided updated prevalence estimates and risk factors for HCV and HBV infection in Georgia, geographic distribution, and other behavioral risk factors (e.g., alcohol consumption) associated with infection. It also characterized circulating genotypes of HCV and HBV in different population sub-groups and provided updated information on current knowledge and perceptions towards viral hepatitis. (full summary on page 7).

- **Title:** MTCT for children born to mothers with chronic HCV infection
- **Objective:** Develop and establish a sustainable surveillance system on children born to women with chronic HCV infection
- **Description:** This study aims to identify, follow-up, and link to HCV care all eligible (at or after 18 months of age) children born to women with chronic HCV infection, and to assess HCV burden and obstacles to linkage-to-care among the women of reproductive age. By linking the data from the Georgian birth registry and the HCV treatment registry, the study conducted 185 interviews among anti-HCV positive mothers.

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- **Title:** Viral hepatitis B and C surveillance capacity building (study of HCV seroconversions; acute HCV and HBV sentinel surveillance project)
 - **Objective:** To enhance viral hepatitis surveillance through policy development and surveillance capacity building in the country
 - **Description:** This project involves utilizing existing HCV screening systems to 1) identify serconversions and conducting investigations, 2) establishing enhanced surveillance activities among young persons (<18 years old) who screen positive, 3) enhancing/expanding current sentinel surveillance pilot at infectious diseases hospitals by utilizing standard case detection and laboratory testing.



TECHNICAL ADVISORY GROUP RECOMMENDATIONS

5TH HEPATITIS TECHNICAL ADVISORY GROUP (TAG) RECOMMENDATIONS FOR THE GEORGIA HEPATITIS C ELIMINATION PROGRAM

On November 19-20, 2019, the Georgian Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs (MoIDPLHSA), together with experts from the U.S. Centers for Disease Control and Prevention’s (CDC) Division of Viral Hepatitis (DVH), the World Health Organization (WHO), and other international partners, convened Georgia’s fifth external Hepatitis C Technical Advisory Group (TAG) meeting. A total of twelve experts in the field of viral hepatitis prevention and control served as TAG members. The two-day meeting was opened with remarks from the First Deputy Minister of MoIDPLHSA, the US Embassy Charge d’Affaires, the Director of CDC’s DVH, a representative from Gilead Sciences, and the Head of the WHO Georgia office. The program began with introduction of the TAG members and review of last year’s recommendations followed by an overview of the progress of the HCV Elimination Program since its launch in April 2015, including the activities on decentralization and integration of HCV services in primary healthcare centers, hospitals and harm reduction settings in Georgia. The TAG then explored progress of the HCV elimination program on topics including: promote advocacy, awareness, education, and partnerships for HCV-associated resource mobilization; prevent HCV transmission: harm reduction, blood safety, and infection control; identify and link to care persons infected with HCV; improve HCV laboratory diagnostics; provide HCV care and treatment; and improve HCV surveillance. Sessions to explore these topics included presentations from Georgian public health officials and clinicians. For each session, two TAG members moderated, and specific discussants were invited on stage to lead the discussion and answer questions. On the final day, following a time for deliberation, the TAG presented draft recommendations for review and comment.

First and foremost, the TAG would like to congratulate Georgia on the remarkable progress in all aspects of the Hepatitis C Elimination Program since the last TAG meeting. The TAG appreciates the sustained commitment of the Georgian government to improve the Program, the commitment of Georgian staff and clinical partners working on the Program, and the efforts to implement or revise activities in response to the recommendations of the 2018 TAG. The TAG also appreciates the open and transparent presentation of data. The quality of evaluation data and the discussions of Program strengths and challenges facilitated the work of the TAG. Based on the presented information and discussions, the TAG developed the following recommendations to resolve key challenges for the Program and assist the country of Georgia in successful achievement of country goals for HCV elimination.

THE TAG MEMBERS INCLUDED

Dr. Carolyn Wester (co-chair)

U.S. Centers for Disease Control and Prevention

Dr. Margaret Hellard (co-chair)

Burnet Institute, Australia

Dr. Evan Bloch

The Johns Hopkins University, USA

Dr. Carlos del Rio

Emory University, USA

Dr. Graham Foster

Queen Marys, University of London, UK

Dr. Sharon Hutchison

Glasgow Caledonian University, UK

Dr. Jeffrey Lazarus

Barcelona Institute for Global Health, Spain

Dr. Jorge Mera

Cherokee Nation Health Services, USA

Dr. Antons Mozalevskis

World Health Organization, Denmark

Dr. Priti Patel

U.S. Centers for Disease Control and Prevention

Dr. Tatjana Reic

European Liver Patients Association, Belgium

Dr. Anders Widell

Lund University, Sweden

OVERARCHING CONSIDERATIONS

- Recommend developing an updated 2021–2025 National Strategic Plan for the Elimination of Hepatitis C Virus in Georgia
 - Should be integrated into Georgia’s Universal Health Care response
 - Consider including HBV

SECTION 1. PROMOTE ADVOCACY, AWARENESS, EDUCATION, AND PARTNERSHIPS FOR HCV-ASSOCIATED RESOURCE MOBILIZATION

- Prioritize increased engagement of HCV cured patients to assist with increasing broader community awareness about hepatitis C and hepatitis C cure:
 - Create paid opportunities for individuals with lived hepatitis experience to participate in the elimination program (e.g. patient navigators, media campaigns)
- Involve peers in all aspects of HCV elimination, including those cured of HCV, key populations such as people who inject drugs (PWID), and from both liver patient associations and related associations, such as haemophilia
- Continue to explore ways to minimize the impact of the criminal justice system on harm reduction efforts:
 - Modify laws regarding the carrying of injecting paraphernalia for drug users and syringe service providers, including safe disposal of syringes
- Continue dialogue with other stakeholders (Ministry of Justice, Police, Government) about the public health approaches in drug policies
- Initiate campaigns to reach marginalized populations, including ethnic minorities, immigrants, and internally displaced persons including the use of outreach workers/peers.

SECTION 2. PREVENT HCV TRANSMISSION: HARM REDUCTION

- Ensure HCV testing, care, and treatment services are available at all harm reduction sites.
 - Ensure that all necessary HCV diagnostics are accessible at all harm reduction sites.
 - Eliminate delays in government approval for implementation of HCV services
 - Allow opioid substitution treatment (OST) physicians and narcologists to provide HCV services
 - ◆ Ensure adequate supervision, training, and support for OST physicians and harm reduction physicians providing HCV testing, care, and treatment services [e.g. utilizing the ECHO model (Extension of Community Healthcare Outcomes)]
 - Improve synergies with harm reduction and existing HCV testing, diagnostics, and treatment services
- Ensure all harm reduction related mobile van services have the capacity to provide needle and syringe services, OST, and hepatitis C testing, diagnostics, and treatment for remote areas
- Eliminate regulatory barriers (e.g. cameras, on-site doctor, physical space requirements, safes) to facilitate rapid integration of HCV services into harm reduction
- Pilot integration of HCV services and primary healthcare services into harm reduction sites consistent with Universal Health Coverage
- Develop a strategy to ensure that harm reduction funding is maintained going forward

SECTION 3. PREVENT HCV TRANSMISSION: BLOOD SAFETY

- Mandate participation of all blood collection sites in Georgia’s State Safe Blood Program
- Perform phased implementation of NAT testing with a view to testing of all donor specimens for the major transfusion transmitted viruses (i.e. HIV, HCV and HBV)
 - Maintain a trial period with limited implementation (e.g. restrict to limited numbers of centers) to evaluate workflow; identify challenges, particularly with respect to turn around time, logistical considerations (e.g. transportation of samples) and the impact on regional blood supply (i.e. shortages in blood products); and evaluate the costs of implementation as well as measures to improve efficiency of testing (e.g. pooling)
- Implement standardization and quality assurance of serological testing and algorithms within Georgia State Program
- Assess feasibility of centralized testing for all blood screening
- Develop an accreditation framework:
 - State Safe Blood Program evaluation of blood services to determine adherence to standard practice
- Develop a look-back system including sample archiving to identify recipients of blood products from positive donors and ensure positive donors are linked to care
- Continue efforts to increase proportion of voluntary blood donors

SECTION 4. PREVENT HCV TRANSMISSION: INFECTION CONTROL IN HEALTHCARE, NON-TRADITIONAL HEALTHCARE, AND COMMUNITY SETTINGS

- Utilize epidemiologic and molecular data on acute cases to determine contribution of healthcare to new HCV cases:
 - Conduct a special study of cases without recognized risk factors to identify healthcare exposures and healthcare-related outbreaks
 - Investigate clusters of healthcare transmission to identify risk factors and prevent additional cases
 - Determine the relative contributions of different healthcare settings to new HCV infections, including nontraditional healthcare
- Complete the national infection prevention and control (IPC) guidance
 - Develop a dissemination plan and implementation guidance with standard protocols
 - Dedicate resources to support implementation of the national guidance
- Strengthen IPC training and engagement of clinical staff in healthcare settings; perform ongoing IPC quality assessments in healthcare settings with risk of bloodborne pathogen transmission
- Consider a pilot study to assess critical infection control practices (e.g. injection safety, instrument sterilization) in select healthcare setting considered high-risk (e.g. dental and endoscopy) to inform prevention needs
- Implement and assess routine monitoring for HCV in special populations (e.g. CDC recommends maintenance hemodialysis patients be screened upon outpatient dialysis initiation and every 6 months thereafter for susceptible patients)

SECTION 5. IDENTIFY AND LINK TO CARE PERSONS INFECTED WITH HCV

- Integration of testing for HCV with:
 - Primary care screening for non-communicable diseases (NCDs)
 - HIV and TB
- Assess testing uptake and proportion positive
- Assess the role of migration and internally displaced populations contributing to the lost to follow-up tested HCV-positive (labor migrants to the European Union, Turkey, Russia, and other locations) and consider tailored campaigns (e.g. inform Georgian citizens leaving the country to work/returning from abroad about the HCV elimination program)
- Focus testing efforts towards high-yield populations using evidence-based approaches:
 - Geographically (e.g. Tbilisi)
 - High burden settings (e.g. emergency departments and correctional facilities)
 - Men age 30 and above with special attention to war veterans
 - Persons with a history of incarceration
 - Limit pediatric HCV testing to exposed infants (eliminate routine testing for hospitalized children <12 years of age)



- Explore the feasibility of innovative strategies for testing:
 - ◆ PWID (e.g. respondent-driven sampling, bring in a friend/family/household/ high-risk contact for screening)
 - ◆ Expanding community-based testing among populations with limited access to healthcare services
 - ◆ Targeted outreach efforts (e.g. lost to follow-up following positive anti-HCV screening)
- Improving linkage to care:
 - Increase number of people tested and treated by community providers (harm reduction and primary health care) so that a substantial proportion of treatment is delivered where client is tested
 - Eliminate barriers to care (e.g. cameras, taxation of commodities, regulations that prohibit specialized providers such as narcologists, dentists, pharmacists)
 - Explore role of patient incentives for linkage
 - Explore the role of provider incentives for linkage and treatment
 - Implement peer navigator strategies where appropriate (e.g. high-volume screening locations)
 - Additional strategies to be considered:
 - ◆ Treatment services should be available where testing is conducted
 - ◆ Provide training for primary care physician and harm reduction physicians in counseling patients with HCV to increase linkage to care
 - ◆ Minimize turnaround time and notification to patients of viremia testing results
 - ◆ Pilot innovative test and treat strategies (e.g. allow patients to change providers once treatment is initiated if necessary)
 - ◆ Navigation of released prisoners from screening, viremia testing, treatment initiation, and treatment completion should be initiated

SECTION 6. IMPROVE HCV LABORATORY DIAGNOSTICS

- Continue quality controls and proficiency monitoring and make these standard operating procedures
- Use the quality data generated on 13 rapid diagnostic tests at Lugar to select those with the highest sensitivity and specificity for procurement for the HCV elimination program
- Continue to study the utility of dried blood spot (DBS) for inclusion in the HCV elimination program
- Continue support for archiving of key blood samples for future use (outbreak investigations, DAA resistance appearance, and research)
- Explore cost-effective approaches for confirming core antigen negative results (e.g. pool testing)
- Develop and implement strategies for expanded and shared use of GeneXpert machines in the HCV elimination program

SECTION 7. PROVIDE HCV CARE AND TREATMENT

- To facilitate access to treatment, remove unnecessary barriers preventing “one-window” testing and treatment, such as centralized approval process for treatment, and camera recording of patients taking the first dose of medication for each bottle dispensed
- Introduce pangenotypic DAA regimens as soon as feasible; this will eliminate the need for genotype testing, simplifying the workup and patient care pathway, and reducing costs
- Implement the use of both branded and licensed generic versions of medications for treatment of hepatitis C and hepatitis B in Georgia
- Minimize on-treatment monitoring utilizing best practices from WHO, EASL, and AASLD guidelines (see attached)
- Expand patient eligibility for treatment at primary healthcare centers, harm reduction sites and other non-specialist sites to include all HCV infected patients except when decompensated cirrhosis or other serious co-morbidities are present. Ensure expert consultation is available for all providers (e.g. via ECHO, phone hotline, academic detailing) providing care and treatment
 - Patients with possible compensated cirrhosis (FIB-4 score > 3.25; platelets < 150,000 mm³; APRI >2.0; or fibroscan stiffness >12.5 kPa) following completion of treatment at primary healthcare sites, harm reduction sites, and other sites, should be referred to a specialist for post-treatment cirrhosis evaluation and care
- Following confirmation of viremia, treatment should be initiated immediately, prior to staging or other testing
- SOF/VEL should be used for end-stage renal disease HCV infected patients (FDA approved and AASLD recommended)
 - Consider HCV micro-elimination within dialysis patient population
- Expand the list of providers, such as primary healthcare providers, narcologists, TB specialists, etc., that are eligible to treat HCV infected patients so that patients are treated where diagnosed
- Implement micro-elimination of HCV in the prison population:
 - Eliminate barriers to treatment (e.g. minimum sentence requirement, care navigators)
- Engage key stakeholders (e.g. hospital administrators, mayors, prison wardens, nephrologists, hematologists, etc.) to implement targeted micro-elimination efforts
- Re-testing (including RNA testing for those previously treated) in high risk groups should be implemented on a regular basis and documented
- Re-testing and re-treatment for potential reinfection should be encouraged in key populations and made free of charge for all patients
- Consider incorporating comprehensive care and treatment of NCDs for HCV patients engaged in treatment

SECTION 8. IMPROVE HCV SURVEILLANCE

- Develop, implement, and strengthen surveillance for acute/incident HCV infections:
 - Include sentinel sites with high volume emergency departments; persons with suspected hepatitis should be tested for acute hepatitis A, B, and C
 - Identify and investigate new HCV infections among repeat blood donors and blood donors who test antiHCV-NAT positive
 - Establish surveillance for acute infections and re-infections at select settings serving at-risk populations (e.g. persons who inject drugs (PWID), prisoners, dialysis patients, and persons who receive blood products)
 - ◆ Perform screening with NAT in immunocompromised persons
- Utilize GHOST (Global Hepatitis Outbreak Surveillance Technology) program to detect and intervene on transmission networks
- Assess HCV cascade of care by region and key populations
- Establish hepatocellular carcinoma (HCC) surveillance among cirrhotic patients treated in the program:
 - HCC treatment should be linked to the elimination program
 - If resources are limited, consider identifying a high-risk cohort for prioritized screening

6TH HEPATITIS TECHNICAL ADVISORY GROUP (TAG) RECOMMENDATIONS FOR THE GEORGIA HEPATITIS C ELIMINATION PROGRAM

On March 15–16, 2021, the Georgian Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs (MoIDPLHSA), together with experts from the U.S. Centers for Disease Control and Prevention’s (CDC) Division of Viral Hepatitis (DVH), the World Health Organization (WHO), and other international partners, convened Georgia’s sixth external Viral Hepatitis Technical Advisory Group (TAG) meeting virtually. The TAG consists of twelve international experts in viral hepatitis prevention and control, and is co-chaired by the Director of CDC’s DVH.

The two-day meeting opened with remarks from the First Deputy Minister of MoIDPLHSA, the US Embassy Charge d’Affaires, the Director of CDC’s DVH, a representative from Gilead Sciences, and the Head of the WHO Georgia office. The meeting began with introduction of the TAG members, then presented progress on the HCV Elimination Program since its launch in 2015. Attention was also paid to the development of the 2021–2025 National Strategic Plan on Viral Hepatitis Elimination, which will be finalized and published later this year.

Presentations highlighted the accomplishments of the HCV Elimination Program through January 2021, including: 2.2 million people screened, 140,216 anti-HCV positive individuals identified, 113,151 persons testing positive for HCV RNA or core antigen, and 73,045 initiating treatment with direct acting antivirals.

The TAG explored progress of the HCV elimination program by reviewing the 2019 TAG recommendations, accomplishments, and ongoing challenges for each strategy in the 2016–2020 strategic plan: 1) advocacy and education, 2) prevention of transmission (including harm reduction, blood safety, and infection control), 3) linkage to care, 4) laboratory diagnostics, 5) care and treatment, and 6) surveillance. Two TAG members moderated each session, and provided an overview of pre-recorded scientific presentations pertinent to the strategy. On the second day, the TAG presented draft recommendations for review and comment.

The TAG would like to congratulate Georgia on the remarkable progress toward hepatitis C elimination, especially in light of the COVID-19 pandemic and its impact on all aspects of care. The TAG appreciates the sustained commitment of the Georgian government, Georgian staff and clinical partners working on the Program, and the efforts to implement 2019 TAG recommendations, while simultaneously developing a strategic plan for the next 5 years of the program. In particular, the TAG would like to recognize the efforts to incorporate hepatitis B in the program and next strategic plan. The TAG also appreciates the collegial and open sharing of data, and the valuable discussion and expertise demonstrated by Georgian colleagues. Based on the presentations and discussion, the TAG developed the recommendations listed below to aide the program in achieving the goal of hepatitis elimination.

THE TAG MEMBERS INCLUDED

Dr. Carolyn Wester (co-chair)

U.S. Centers for Disease Control and Prevention

Dr. Jeffrey Lazarus

Barcelona Institute for Global Health, Spain

Dr. Margaret Hellard (co-chair)

Burnet Institute, Australia

Dr. Jorge Mera

Cherokee Nation Health Services, USA

Dr. Evan Bloch

The Johns Hopkins University, USA

Dr. Antons Mozalevskis

World Health Organization, Denmark

Dr. Carlos del Rio

Emory University, USA

Dr. Priti Patel

U.S. Centers for Disease Control and Prevention

Dr. Graham Foster

Queen Mary University of London, UK

Dr. Tatjana Reic

Croatian Society for liver Disease “Hepatos”, Croatia

Dr. Sharon Hutchinson

Glasgow Caledonian University, UK

Dr. Anders Widell

Lund University, Sweden

OVERARCHING CONSIDERATIONS

- The COVID-19 Pandemic has created barriers and opportunities for the HCV Elimination Program
 - Barriers: reduced in-person encounters resulted in decreased numbers tested and treated
 - Opportunities: able to leverage COVID-19 serosurvey to obtain data on HCV and HBV; expanded diagnostic testing provides opportunities for novel models for both HBV vaccine delivery and HCV testing in hard-to-reach populations; and increased attention to infection prevention and control (IPC)

STRATEGY 1. PROMOTE ADVOCACY, AWARENESS, EDUCATION, AND PARTNERSHIPS FOR HCV-ASSOCIATED RESOURCE MOBILIZATION

- Implement evidence-based education and communication campaigns to increase broader community awareness about hepatitis B and C and hepatitis C cure:
 - Prioritize the inclusion of people with lived experience to assist with campaign messaging and to serve as peer navigators (including creation of paid opportunities)
 - Build capacity for newly formed patients' advocacy groups
 - Ensure use of person-first language in communication and education materials
 - Use information collected around knowledge, attitudes, and practices related to hepatitis from the upcoming 2021 hepatitis serosurvey questionnaire to inform HCV and HBV communication campaigns and materials
 - Ensure that individuals with liver disease from chronic hepatitis B and C are prioritized for COVID-19 vaccination
- Continue advocacy for and improvement of policies to reduce barriers to access to care for viral hepatitis
 - Continue efforts to support the legal environment and modification of laws related to the possession of drug injection paraphernalia
 - Explore options for allowing Harm Reduction (HR) sites to be certified to provide hepatitis treatment

STRATEGY 2. PREVENT HCV TRANSMISSION: HARM REDUCTION

- Expand HR services and network of care provided
 - Maintain support of Harm Reduction Sites/Needle-syringe programs (HR/NSPs) as an integral component of national health service delivery, and continue to provide government funding for HR/NSPs
 - Expand capacity at all HR/NSPs (including mobile sites) to provide HCV screening, viremia testing, and pursue certification to provide treatment
 - ◆ Ensure that HCV and HBV testing is provided free of charge to all, including HR/NSPs beneficiaries
 - Integrate HBV vaccination into HR/NSP service sites, and explore opportunities to include HBV testing and treatment in HR/NSP sites
 - Expand the number of HR/NSP sites that provide integrated HCV treatment (currently 4 sites)
- Reduce loss to follow-up and improve linkage to care at HR sites
 - Reduce time from receipt of positive HCV RNA/Core Ag result to treatment initiation to ≤ 2 weeks
 - Expand qualitative analysis to identify barriers to seeking care, pursuing viremia testing, and completing treatment; implement targeted interventions to address identified barriers



- Ensure continuous monitoring of high-risk populations to enhance detection of HCV infection and re-infection
 - Implement repeat HCV testing among PWID, including HCV RNA/Core Ag testing among persons who inject drugs (PWID) who continue to be at risk for infection after achieving SVR; utilize data from repeated HCV RNA/Core Ag testing to inform surveillance for re-infection
- Continue to support Opioid Substitution Therapy (OST) Programs through state-based funding as a recognized integral part of harm reduction
 - Integrate OST into certain high-risk settings (e.g., prisons)
 - Ensure that changes to OST program introduced during the COVID-19 pandemic (e.g., allowing for more “take-away” doses) are maintained



STRATEGY 2. PREVENT HCV TRANSMISSION: BLOOD SAFETY

- Infectious risk specific
 - Standardize testing approach, including serological markers
 - ◆ Transition to automated testing
 - ◆ Standardize testing algorithms across sites; incorporate repeat and confirmatory testing
 - ◆ Assess mini-pool Nucleic Acid Testing (NAT)
 - Complete re-assessment of all blood bank collection facilities
 - Conduct surveillance for any donor who tests positive for HCV and HBV and follow to link-to-care
 - ◆ Develop national database or tracking mechanism to prevent subsequent donation by those who test positive for a given marker
 - ◆ Conduct look-back (e.g., with follow-up testing) of all individuals who were transfused with blood from a donor who subsequently tests positive; the look-back period should be defined to balance yield with logistical feasibility (e.g. 6-12 months beyond last negative donation)
 - ◆ Consider following blood transfusion recipients prospectively to estimate seroconversion rates
 - Refine donor selection with reduced proportion of remunerated and first-time blood donors
 - ◆ Conduct an impact study ahead of transition to exclusive voluntary donors (VNRBDs)
 - ◆ Conduct a qualitative assessment of motivators for and deterrents against donation
- General Blood Safety
 - Align with European Union (EU) standards
 - Conduct assessment of infrastructure (coordinate with blood bank assessments)
 - Bolster immunohematology capabilities (collateral benefit to oncology services)
 - Impose regulatory controls on procurement: restrict to tests that have been adequately validated (e.g. CE marked)

STRATEGY 2. PREVENT HCV TRANSMISSION: INFECTION CONTROL IN HEALTHCARE, NON-TRADITIONAL HEALTHCARE, AND COMMUNITY SETTINGS

- Infection Prevention and Control (IPC) Guidance and Implementation
 - Ensure that IPC guidance is disseminated and implemented nationwide
 - ◆ Leverage COVID-19 IPC trainings to improve provider knowledge and adherence to injection safety and other basic practices to prevent HCV and HBV transmission in the healthcare setting
 - ◆ Perform IPC assessments in healthcare settings with risk of bloodborne pathogen transmission
 - ◆ Develop standard protocols and other tools to support implementation of national guidance

- Collect Evidence to inform IPC Activities
 - Utilize epidemiologic and molecular data on acute cases (e.g., from sentinel surveillance sites) to determine contribution of healthcare to new HCV and HBV cases:
 - ◆ Conduct a special study of cases without recognized risk factors to identify healthcare exposures and healthcare-related outbreaks
 - ◆ Investigate clusters in healthcare settings to identify risk factors and prevent additional cases
 - ◆ Determine the relative contributions of different healthcare settings to new HCV infections, including non-traditional healthcare settings
 - Conduct assessment of critical infection control practices (e.g., injection safety and instrument sterilization) in select healthcare settings considered high-risk (e.g., dental and endoscopy) to inform prevention needs
 - Conduct a study to assess the general population’s knowledge and understanding of the risk of HCV and HBV from injection practices in healthcare and non-traditional settings; use findings to inform education and communication campaigns
 - Implement and assess routine monitoring for HCV and HBV infection in maintenance hemodialysis patients
 - Utilize ongoing IPC assessment and research results to improve setting-specific IPC recommendations to prevent HCV and HBV transmission

STRATEGY 3. IDENTIFY AND LINK TO CARE PERSONS WITH HCV

- Evaluate Hepatitis C Elimination Program data to ensure understanding of demographic and geographic distribution of those screened and not linked to care
- Focus testing efforts and improve linkage to care in populations in most need of targeted outreach efforts, including:
 - Geographic (e.g., Tbilisi)
 - High-burden settings (e.g., emergency departments and correctional facilities)
 - Men age 30 years and older with special attention to war veterans or persons with a history of incarceration
 - PWID



- Expand community-based testing among populations with limited access to healthcare services (e.g., door-to-door program)
- Continue to expand the number and type of sites that integrate HCV testing
 - Primary care clinics
 - HIV clinics and TB clinics
 - Diabetes clinics
 - OST Clinics
 - Mental Health services
 - COVID-19 clinics or testing sites
- Decrease the rate of advanced stage diagnosis through focusing efforts on increased screening of individuals with diabetes, high BMI, alcohol use disorder, and incarceration
 - Increase the HCV screening education of medical personnel who take care of these populations
- Expand reflex testing to improve the viremia confirmation gap
 - Develop strategies for ensuring individuals screened for HCV antibodies in all sites where testing is performed are linked to viremia testing and care (not just referred), either through onsite viremia testing, screening/linkage project model, or for patients screened in door-to-door Rapid Diagnostic Tests (RDTs); consider obtaining Dried Blood Spots (DBS) as well to send to the Lugar Center
- Continue to evaluate the role of HCV self-testing with RDTs among different populations [e.g., PWID, men who have sex with men (MSM), and other groups]
- Expand peer navigator programs and strategies in high-volume screening locations and other areas as appropriate
- Expand the role of provider incentives for linkage and treatment



STRATEGY 4. IMPROVE HCV LABORATORY DIAGNOSTICS

- Continue sending proficiency panels from the Lugar Center to labs and blood banks (3 times/year) to ensure quality control
 - Provide guidelines on actions to be taken when panels/laboratories fail
- Continue decentralization of RNA testing to stand alone instruments (e.g., GeneXpert and Genedrive)
 - Follow the rapid development of new, simple isothermal RNA detecting tests for inclusion in the program when available
- Rapid Diagnostic Tests (RDTs) for anti-HCV antibodies
 - Explore use of oral swab based RDTs



- Recommend use of RDTs that have been validated for use in decentralized settings (e.g., HCV One Step Rapid test, Healgen anti-HCV) and define acceptance criteria for use of other state procured RDTs
- Explore implementation of HCV self-testing
- Dried blood spot (DBS) testing for RNA
 - Introduce DBS (preferably from plasma or serum) in RDT positive patients for shipment to the Lugar Center for RNA testing
 - Monitor turnaround time from RDT taken via DBS to patient contact with conclusive viremia result for treatment
- Explore use of Plasma Separation Cards (PSC), including molecular epidemiology, GHOST, outbreak analyses, and resistance mutations
- Consider pilot study in HR sites to test all anti-HCV positive and negative samples for HCV Core Ag to determine rate of window phase infections
- Explore strategies to conduct HDV testing at least once for every person with chronic HBV infection



STRATEGY 5. PROVIDE HCV CARE AND TREATMENT

- Expand Primary Care sites and providers offering HCV screening, viremia testing, and treatment
 - Expand scope of treatment in non-specialist sites to include treatment of patients with non-decompensated cirrhosis
- Pilot HCV test-and-treat strategies in range of settings including point of care RNA testing, pre-treatment evaluation, and DAAs on the shelf to reduce time from testing to treatment
 - Develop timeline goals from testing to treatment (e.g. patients should start DAA no later than 2 weeks after RNA tests are resulted)
- Alter treatment protocols nationwide to ensure simplified, more accessible treatment, including:
 - Eliminate routine on-treatment lab tests
 - Give full course of medication on initiation
 - Minimize on-treatment follow-up appointments in person; conduct via alternate mechanisms (e.g., telephone)
- Disseminate information on HCV and HBV screening recommendations, safety of treatment and medication in persons with renal insufficiency, and determine opportunities for dialysis clinicians to provide HCV treatment to patients
 - Engage nephrologists and other kidney care providers to identify and treat HCV infection among dialysis patients

- Implement more comprehensive treatment programs in high-impact populations (e.g., dialysis and prison)
- Design innovative strategies to engage HCV RNA positive individuals in care with particular focus on those with lowest treatment initiation rates, including:
 - Individuals 70 years of age or older
 - Individuals on hemodialysis
 - Individuals with hemophilia

STRATEGY 6. IMPROVE HCV SURVEILLANCE

Surveillance

- Continue to strengthen surveillance for acute/incident HCV and HBV infections, including through sentinel surveillance sites
- Establish surveillance for acute infections and re-infections at select settings serving at-risk populations (e.g., PWID, prisoners, hemodialysis patients, and persons who receive blood products)
 - Adopt AASLD/EASL/WHO recommendations to test high-risk individuals (e.g., PWID and MSM), at least annually, including testing for viremia in those previously diagnosed and treated (and thus seropositive)
 - Identify and investigate new HCV infections among repeat blood donors and blood donors who test anti-HCV-negative/NAT-positive to identify the risks for recent HCV infection
 - Continue efforts to apply GHOST (Global Hepatitis Outbreak Surveillance Technology) to detect and intervene on transmission networks
- Assess existing surveillance capacity for hepatitis B and build upon existing HCV systems (e.g., screening registry, treatment registry) to include HBV
- Expand surveillance system to identify and track pregnant women with HCV infection and children born to mothers with HCV infection

Program Effectiveness

- Develop stratified iterations of the national HCV treatment cascade, including stratifications by geography, patient characteristics, facility type, and other pertinent factors
- Establish hepatocellular carcinoma (HCC) surveillance among patients with cirrhosis, including after achieving the SVR, within HCV Elimination Program or national healthcare system
- Engage with WHO to pilot the WHO Guidance for Validation of Elimination of Viral Hepatitis

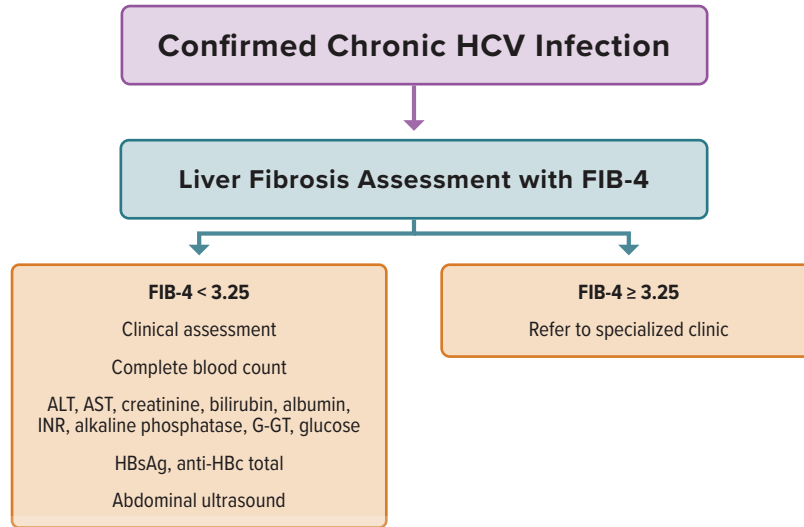
APPENDIX 1.

HEPATITIS C DIAGNOSTIC METHODS AND KITS AVAILABLE IN GEORGIA

PCR Equipment	HCV RNA Viral Load Kits	HCV Qualitative Kits
Abbott m2000rt	Abbott RealTime HCV kit	HCV Real Time TmQual (Sacache) ref# TVI-100 FRT
COBAS Taqman 48 ROCHE	Cobas TaqMan HCV Quantitative Test V2.0, Roche	Cobas TaqMan HCV Quantitative Test V2.0, Roche
Quantstudio Dx, Applied Biosystems	Robrogene, HCV RNA Quantification Kit 3.0. Germany	Robrosene, HCV RNA Quantification Kit 3.0. Germany
Quantstudio 5 RT PCR, Applied Biosystems	HCV Real TM Quant Dx V1, Sacace Biotechnologies	HCV Real TM Quant Dx V1, Sacace Biotechnologies
DTlite, DNA-Technology	RT-GEPATOGEN-C Quant PCR Amplif Kit, DNA Technology	RT-GEPATOGEN-C Quant PCR Amplif Kit, DNA Technology

APPENDIX 2.

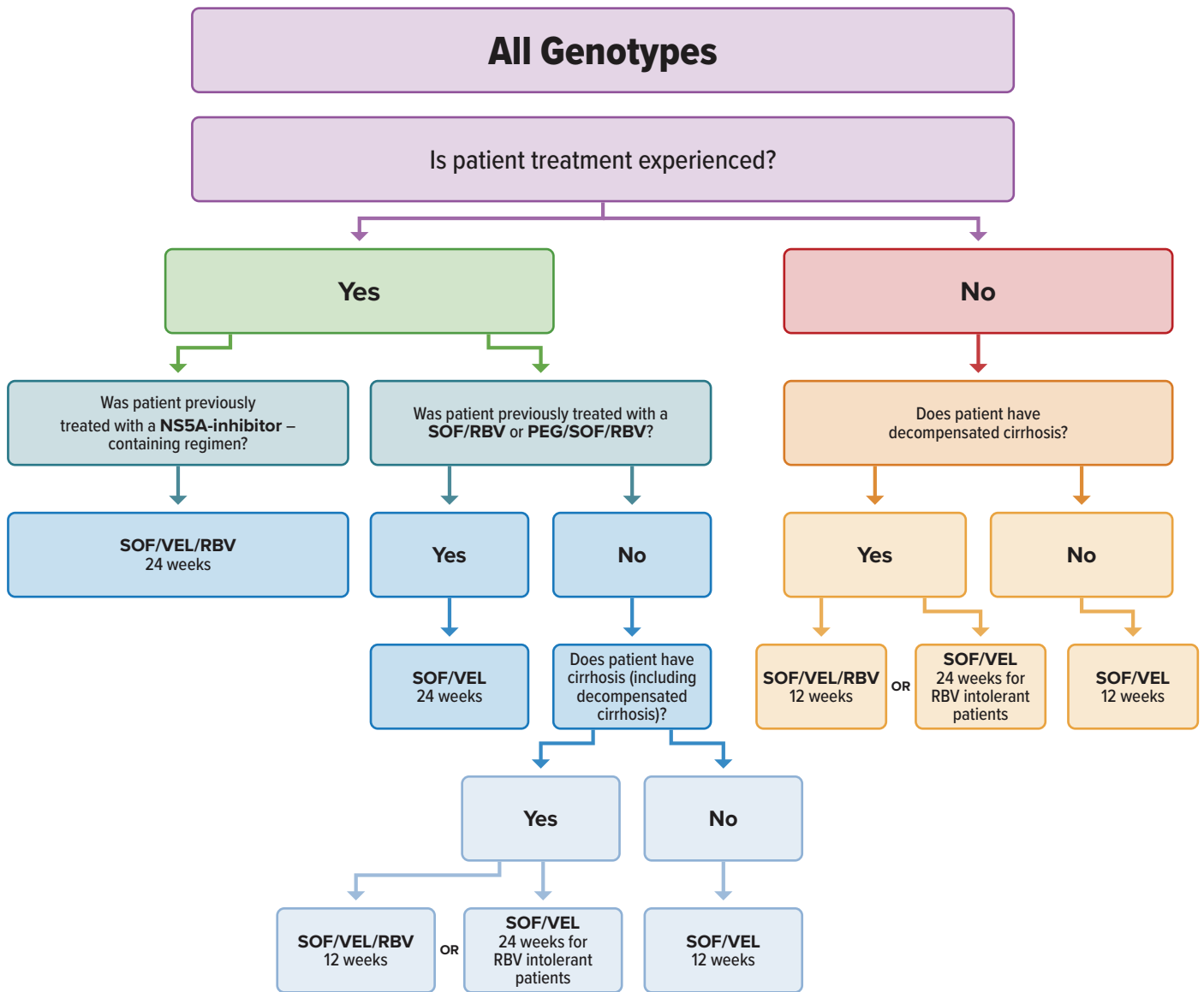
TREATMENT ALGORITHMS



Measurements	During Treatment (weeks)			After Treatment Completion (weeks)
	4	8	12	12 or 24
Clinical Assessment	X	X	X	X
HCV RNA Quantitative				X
Complete Blood Count	X*	X*	X*	
ALT	X	X	X	

*Only for patients receiving Ribavirin containing regimens

ALGORITHMS *cont.*



NOTE: All decompensated cirrhotics should receive 600mg RBV, all others should receive weight based ribavirin (RBV) dosage. Patients with weight <75kg receive 1000mg RBV daily and ≥75kg receive 1200mg RBV daily.

APPENDIX 3.

SCIENTIFIC MEETING PRESENTATIONS OF THE GEORGIA HEPATITIS C ELIMINATION PROGRAM

i. ABSTRACTS

1. The head-start project Georgia: a three-armed, cluster, nonrandomized trial of the effectiveness of two novel models of HCV confirmatory testing in harm reduction sites (HRS) in Georgia

Abstract Presented at EASL International Liver Congress, 2020; Virtual Event

Authors: Maia Japaridze¹, Jessica Markby², Irma Khonelidze³, Maia Butsashvili⁴, Maia Alkhazashvili³, Sonjelle Shilton².

¹Foundation for Innovative New Diagnostics, Georgia, ²Foundation for Innovative New Diagnostics, Geneva, Switzerland, ³Georgia National Centers for Disease Control, Georgia, ⁴Health Research Union, Georgia

Background and Aims: Georgia, a middle-income country with an estimated population of 3.7 million people, is among the world's highest-burden countries, with an HCV prevalence of 6.7% in the general population and a higher burden of disease in high-risk populations especially PWID. In 2015, Georgia embarked on an elimination program, however, significant gaps remain in case finding and linkage to care. In particular, although screening programs have largely been decentralized for high-risk groups, viremic testing remains a bottleneck for PWID accessing care. Here we describe two novel models of viremic testing that aim to address these weaknesses in the care cascade.

Method: A cluster, non-randomized intervention study where HRS are assigned to one of three arms Arm1: 4 HRS, viremia testing (GeneXpert) on-site, Arm 2: 2 HRS, blood draw on site, confirmatory testing (cAg) at a centralized laboratory, Arm 3 2 HRS, standard of care patients referred for testing at the treatment center. Participants are eligible for the study if they tested anti-HCV positive on the same day and did not have prior confirmed diagnosis. The proportion of participants who completed each step in the HCV care cascade was compared across the three arms as well as the turn-around time of test results.

Results: Between May 2018 and November 2019, 1671 participants were enrolled (621 in Arm 1, 486 in Arm 2; 565 in Arm 3). Participants were predominantly male (95.4%), mean age was 44.0 (19–88) years and 79.1% were currently injecting drugs. 95% of participants reported having taken an HIV test and of these 14 (0.84%) self-reported being HIV-positive. To date, 1517 participants have had a confirmatory viremia test done: 621 (100%) in Arm 1, 483 (99.4%) in Arm 2; 438 (77.5%) in Arm 3. Of those confirmed positive, treatment was initiated for 450 (87.0%) in Arm 1, 273 (70.9%) in Arm 2 and 345 (98.0%) in Arm 3. On average participants received their results the same day (<3 hours) in Arm 1, 21.5 days in Arm 2 and 18.6 days in Arm 3 from the time they had blood drawn for testing.

Conclusion: Confirmatory testing or blood draw on-site at HRS showed improved retention of patients in the care cascade compared to the referral of patients for blood collection. Moreover, the turnaround time was shortest when confirmatory testing was performed on-site. These findings will facilitate the scale-up of decentralized HCV care for PWID in Georgia and globally

2. Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015–October 2019

Abstract Presented at EASL International Liver Congress, 2020; Virtual Event

Authors: Tengiz Tsertsvadze^{1,2}, Amiran Gamkrelidze³, Nikoloz Chkhartishvili¹, Akaki Abutidze^{1,2}, Lali Sharvadze^{2,4}, Vakhtang Kerashvili¹, Maia Butsashvili⁵, David Metreveli⁶, Lia Gvinjilia⁷, Shaun Shadaker⁸, Muazzam Nasrullah⁸, Tamar Gabunia⁹, Ekaterine Adamia⁹, Stefan Zeuzem¹⁰, Nezam Afdhal¹¹, Sanjeev Arora¹², Karla Thornton¹², Francisco Averhoff⁸

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Background and Aims: In April 2015 with the technical assistance of U.S. CDC and commitment from Gilead Sciences to donate direct-acting antivirals (DAAs), Georgia launched the world’s first HCV elimination program. A key strategy of the program is nationwide HCV screening, active case finding, linkage to care, provision of treatment for all HCV-infected persons and effective prevention interventions. The elimination program aims at achieving 90–95–95 targets by 2020: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated. We report progress towards elimination targets 4 years into the elimination program.

Method: A hepatitis C care cascade was constructed using data from the national HCV treatment program (Figure). A national serosurvey in 2015 estimated that 150,000 over 18 years of age were infected with HCV in the country. The program collects data on all persons registered with the treatment program. Treatment was provided with Sofosbuvir, Ledipasvir/Sofosbuvir or Velpatasvir/Sofosbuvir-based regimens. Data on persons tested for chronic HCV infection through sustained virologic response (SVR) were extracted as of October 31, 2019.

Results: Overall 121,043 persons tested positive for HCV antibodies and of those 97,348 (80.4%) underwent HCV confirmatory testing. Chronic HCV infection was confirmed in 79,955 (82.1%) persons, representing 53.3% of the estimated 150,000 adults living with HCV. A total of 62,927 (78.7%) patients initiated treatment – 49.1% of the estimated target population to be treated (128,250). Of the 41,220 patients who were evaluated for SVR, 40,693 (98.7%) tested negative for HCV by PCR, representing 33.4% of the estimated target population to be cured (121,837). Very high cure rates were achieved for all HCV genotypes: 98.9% in genotype 1, 98.9% in genotype 2 and 98.3% in most challenging to treat genotype 3. Treatment effectiveness was comparable among persons with advanced fibrosis (F3 and F4) with 98.2% achieving SVR, and among patients with mild or no liver fibrosis (\leq F2), SVR = 99.0%.

Conclusion: Georgia has made substantial progress towards eliminating hepatitis C, with more than half of persons with HCV infection identified and registered for treatment. Very high cure rates have been achieved among those who received SVR testing. Challenges remain in identifying and especially linking to care persons living with HCV in Georgia. A nationwide integrated, decentralized model of HCV treatment, which is already implemented, will be critical to improving linkage to care and close the gaps in the HCV cascade.

3. The impact on mortality of a national hepatitis C elimination program, Georgia, 2015–2019

Abstract Presented at EASL International Liver Congress, 2020; Virtual Event

Authors: Lia Gvinjilia¹, Shaun Shadaker², Amiran Gamkrelidze³, Tengiz Tsertsvadze^{4,5}, Nikoloz Chkhartishvili^{4,6}, Maia Butsashvili⁷, David Metreveli⁸, Maia Kereselidze³, Vladimer Getia³, Alexander Turdziladze³, Irina Tskhomelidze¹, Tinatin Kuchuloria¹, Philip Spradling⁹, Jian Xing⁹, Muazzam Nasrullah⁹, Francisco Averhoff⁹.

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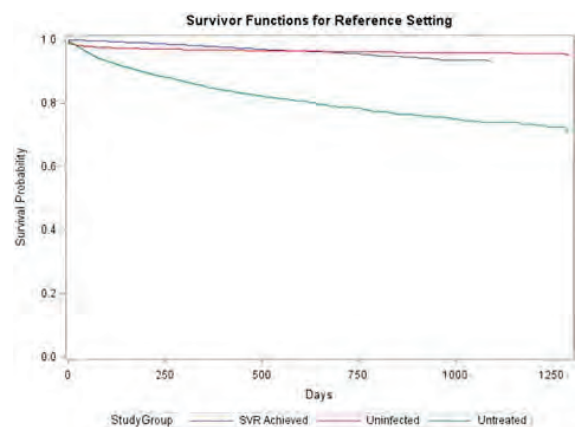
Background and Aims: Georgia embarked on a national hepatitis C elimination program in April 2015, which provided direct-acting antiviral (DAA) medications free of charge to all hepatitis C virus (HCV) infected persons. We aimed to evaluate the impact of the program on all-cause mortality.

Method: We identified adults (≥18 years) registered in the national hepatitis C screening registry from April 2015 through May 2018 and linked these data to the national hepatitis C treatment database and national vital statistics using the 11-digit national personal identifier. We used vital statistics data to identify deaths through December 2018. Kaplan-Meier survival plots were generated to determine and compare survival among three groups: HCV-uninfected persons (screened negative for anti-HCV), persons HCV-infected (confirmed by viremia testing) who were not treated, and persons with HCV infection confirmed by viremia testing who were treated and cured (i. e. achieved sustained virologic response; SVR). We calculated adjusted hazard ratios (aHR) using Cox proportional hazards regression models for the three groups after controlling for sex, age, and hospitalization-regardless of the admission diagnosis.

Results: We identified 1,002,229 HCV-uninfected persons, 14,234 HCV-infected persons who were not treated, and 32,485 patients who were HCV infected and cured of their infection (achieved SVR). Untreated HCV-infected persons, as well as those who were infected and achieved SVR, were mostly men (73.4% and 79.8% respectively), while 57.7% of uninfected persons were females. Uninfected persons were slightly younger than those infected and not treated, and those who were cured (median ages: 43, 49 and 45, respectively) ($p < 0.0001$). The Kaplan-Meier analysis revealed that a greater proportion of untreated HCV-infected persons died during the study period compared to both uninfected and HCV cured persons (Figure). Overall, untreated persons had the highest proportion of deaths (8.0%; $n = 1140$), followed by uninfected (4.4%; $n = 44, 047$) and cured persons (1.8%; $n = 575$). In adjusted models, untreated HCV-infected persons were more likely to die compared with uninfected persons (aHR 2.34; 95%CI 2.20–2.48) and those who achieved SVR (aHR 3.12; 95%CI 2.82–3.45).

Conclusion: Our findings demonstrate that persons with HCV infection who are cured with DAAs have an increased likelihood of survival, similar to persons never infected when compared to HCV-infected persons who did not receive treatment.

Figure. Comparison of Kaplan-Meier survival curves between study groups, adjusted for sex, age and hospitalization events.



4. Progress in hepatitis C testing as a part of the hepatitis C elimination program in Georgia

Abstract Presented at EASL International Liver Congress, 2020; Virtual Event

Authors: Amiran Gamkrelidze¹, Tamar Gabunia², Alexander Turdziladze¹, Irma Khonelidze¹, Maia Tsereteli¹, Vladimer Getia¹, Ekaterine Adamia², Tinatin Kuchuloria³, Irina Tskhomelidze³, Muazzam Nasrullah⁴, Shaun Shadaker⁴, Lia Gvinjilia³, Francisco Averhoff⁴.

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Background and Aims: The country of Georgia, with a population of 3.7 million and an estimated 150,000 adults with chronic hepatitis C virus (HCV) infection, initiated the world's first national hepatitis C elimination program in April 2015. Through the elimination program, screening for hepatitis C is available to all citizens free of charge. The aim of this analysis is to describe progress in hepatitis C testing as part of the hepatitis C elimination program.

Method: This analysis utilizes data from the national screening registry and treatment databases linked by national ID, and 2014 general population census. An information system was created to collect data from the elimination program utilizing the national ID to monitor and evaluate program performance and surveillance.

Results: As of November 10, 2019, 1,628,452 adults have been tested for hepatitis C (56.9% of the adult population), of whom 125,016 (7.7%) were anti-HCV positive. In 2015 the positivity rate averaged 27.0%, but has fallen to 4.4% in the first half of 2019. Overall, 98,134 individuals received viremia testing, of whom 80,074 (81.6%) were found to have chronic HCV. Screening rates are similar for men and women (55.9% vs. 57.9%, respectively). Among men screening rates are highest among those aged ≥ 60 (64.2%) and lowest among those aged 18–29 (51.7%). The overall positivity rate for adult males is 12.4%. The highest positivity rate is seen in men aged 30–59 (18.6%). Among women screening rates are highest among those (60.7%) aged 18–29 (60.7%) and lowest among those aged 30–59 (56.4%). The overall positivity rate for adult females is 3.7%. The highest positivity rate is seen in women aged ≥ 60 (5.3%).

Conclusion: The overall anti-HCV prevalence was higher in males and among those aged 30–59 years. The anti-HCV positivity rate has been declining since the launch of the HCV elimination program in April 2015. Although significant progress has been made, a substantial proportion of infected people need to be identified, confirmed, and linked to care.

5. Economic evaluation of the hepatitis C virus screening and treatment program in Georgia

Abstract Presented at EASL International Liver Congress, 2020; Virtual Event

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Background and Aims: In spring 2015, the country of Georgia initiated an HCV elimination program with directly acting antivirals (DAA) donated by Gilead, alongside outstanding political commitment, and allocation of resources for a comprehensive program. We evaluated the cost-effectiveness of the screening and treatment undertaken in the HCV elimination program from 2015 to November 2017 compared to if no treatment had been done, from the perspective of the Ministry of Health (MoH) and patients.

Method: We adapted an HCV transmission and progression model calibrated to Georgian data on HCV prevalence and demographics of the general population and people who inject drugs (PWID) to project the impact of treatment of 41,483 patients during the study period. Quality adjusted life year (QALY) weights for liver disease stages including pre-cirrhosis, compensated and decompensated cirrhosis were estimated from EQ-5D-5L data collected from a subset of HCV-infected patients enrolled in the elimination program. Unit costs were gathered from the financial module of the MoH on reimbursement schemes for healthcare providers. Cost of screening tests, diagnostics and monitoring during treatment, and the annual cost of care for patients with advanced liver disease, were then calculated per patient treated. Indirect costs of public awareness campaigns, infrastructure investment, administrative costs, and logistics were included as fixed costs. Case-finding costs were estimated based on the cascade of care. Estimated economic costs of DAA drugs (sofosbuvir and sofosbuvir/ledipasvir) were included in sensitivity analysis. The incremental cost-effectiveness ratio (ICER) in terms of cost per QALY gained was calculated in 2015 US dollars accounting for all costs and outcomes from 2015–2030 with a discount rate of 3% for both costs and outcomes, and compared to a willingness-to-pay threshold of \$3765 per QALY gained (1x GDP per capita in 2015).

Results: The total cost of screening and treatment per patient was \$555. The average cost of liver disease care per patient was \$416 with no treatment or \$311 under the treatment scenario, with 0.78 QALYs gained per patient treated due to reduced disease progression. The intervention also prevented 2,673 HCV-related deaths and averted 16,225 new infections by 2030 compared to no treatment. The ICER of the intervention excluding DAA costs was \$959/QALY, while including the cost of DAAs at a minimal generic cost of \$143 per patient results in an ICER of \$1,244.

Conclusion: The first phase of the HCV elimination program was highly cost-effective in Georgia. This provides valuable data on efficiency of national programs for scaling up HCV treatment for achieving HCV elimination.

6. HCV care cascade of PWID enrolled in methadone substitution treatment program in Georgia - is this the first group of population in which hepatitis C will be eliminated in Georgia?

Abstract Presented at EASL International Liver Congress, 2020; Virtual Event

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Background and Aims: Since April 2015 Georgia has started the hepatitis C elimination program with elimination goals by 2020. PWIDs enrolled in the Methadone Substitution Treatment (MST) Program are also included in the large-scale screening program aimed to accelerate active HCV case detection. There are a total of 22 MST sites providing long-term substitution treatment to PWIDs in Georgia. HCV antibody screening is provided to patients at enrollment in the MST program. The aim is to describe the HCV care cascade among MST program beneficiaries.

Method: HCV care cascade was generated for the period of January, 2018 through October, 2019. The data linkage between MST database and the national screening registry was done by matching the national personal ID number. Cascade of care was generated using the matched data.

Results: Overall 9,552 PWIDs registered in MST database by November 1, 2019. A total of 8,265 (87%) MST patients had HCV screening of whom 7,041 (85%) tested positive and 5,998 (85%) were tested for viremia with the positivity rate of 85% (n = 5073). A total of 4,237 (83%) initiated treatment. By the date of the analysis 3,956 (93%) have already completed treatment of whom 3,808 (97%) were eligible for SVR. The cure rate among SVR tested was 96% (2,531/ 2,622).

Conclusion: The analysis of the HCV care cascade for MST program beneficiaries shows high rates for screening and viremia testing uptake, treatment initiation, and SVR rates. Meeting HCV elimination goals by 2020 are feasible, however, requires more effort.

7. Management of hepatitis C in primary healthcare in the country of Georgia

Abstract Presented at EASL International Liver Congress, 2020; Virtual Event

Authors: Tengiz Tsertsvadze^{1,2}, Akaki Abutidze^{1,2}, Lali Sharvadze^{2,3}, Nikoloz Chkhartishvili¹, Amiran Gamkrelidze⁴, Lia Gvinjilia⁵, Maia Butashvili⁶, David Metreveli⁷, Vakhtang Kerashvili¹, Shaun Shadaker⁸, Muazzam Nasrullah⁸, Tamar Gabunia⁹, Ekaterine Adamia⁹, Stefan Zeuzem¹⁰, Nezam Afdhal¹¹, Sanjeev Arora¹², Karla Thornton¹², Francisco Averhoff⁸.

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Background and Aims: In April 2015, with a partnership with Gilead Sciences and technical assistance from U.S. CDC, Georgia launched the world’s first hepatitis C elimination program. By August 30, 2019, more than 60 thousand persons initiated treatment, achieving >98% cure rates. Broad access to direct acting antivirals (DAAs) resulted in rapid increase in treatment uptake in 2016, which has since declined due to barriers in diagnosis and linkage to care. To address this issue Georgia initiated service decentralization in 2018 by integrating hepatitis C virus (HCV) screening and treatment in primary healthcare centers (PHCs). We report preliminary results of an integrated model of HCV care in PHCs from August 2018 through August 2019.

Method: By August 31 2019, a total of 10 PHCs provided HCV care services throughout the country. The integrated model was based on a “one-stop shop” approach, by which patients received all HCV screening, treatment and care services at the PHCs. PHCs provided care to HCV treatment-naïve patients with no or mild fibrosis (FIB-4 score<1.45) using simplified diagnostics and a treatment monitoring approach, while persons with advanced liver fibrosis/cirrhosis were referred to specialized clinics. Patients received Sofosbuvir/ Ledipasvir and/or Sofosbuvir/Velpatasvir for 12 weeks. Sustained virological response (SVR) was defined as undetectable HCV RNA 12– 24 weeks after the end of therapy. The Extension for Community Healthcare Outcomes (ECHO) telemedicine model was utilized to train and support primary healthcare providers. Regular teleECHO video conferencing was conducted to provide primary care providers with advice and clinical mentoring.



Results: Among persons diagnosed with active HCV infection, 639 were evaluated for FIB-4 score. Of these, 436 (68.2%) had FIB4 score <1.45; of them 355 (81.4%) initiated treatment. A total of 241 patients completed treatment. Of 146 patients within the 12–24 week window of SVR eligibility, 108 had been tested at the time of analysis, and 107 achieved SVR (99.1% cure rate).

Conclusion: Our study reported the feasibility and effectiveness of integrating a simplified HCV diagnostic and treatment model in PHCs. Countrywide expansion of this model is warranted to bridge the gaps in the HCV care continuum and ensure high rates of treatment uptake towards achieving elimination targets.

8. Novel approach to near POC testing for HCV RNA; integration of HCV RNA testing into existing near POC machines used in National TB program

Abstract Presented at the International Congress on Infectious Diseases, 2020; Kuala Lumpur, Malaysia

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Background and Aims: Georgia embarked on a hepatitis C (HCV) elimination program in 2015, the program started in a centralized manner and is evolving to providing decentralized HCV care. To facilitate decentralization, the Foundation for Innovative New Diagnostics (FIND) in collaboration with the Georgian government, has introduced and implemented integration of HCV RNA testing on near point of care (POC) nucleic acid testing (NAT) machines currently used for tuberculosis (TB), under the Unitaid-funded, HEAD (Hepatitis Elimination through Access to Diagnostics) Start program.

Method: In order not to interrupt existing service delivery for TB, selection criteria for the integration sites were jointly decided by stakeholders from the Georgian MoH, NCDC, National TB program. Baseline data on TB testing prior to the intervention was collected and at project end the TB testing numbers during the project will be compared with the baseline to assess if the integration of HCV impacted the already established TB testing. Training on the use of the HCV assay was provided to 8 Georgian labs and the testing is monitored via on-line real-time database as well as site support visits.

Results: From March to October 2019 2293 HCV tests were run, of these 2116 tests resulted in a valid result and 177 tests resulted in no result/error/invalid. During the same time period 6, 630 TB tests were run that resulted in a valid result, and 163 TB test run resulted in no result/error/invalid.

Conclusion: Integration of HCV RNA testing using near POC testing in Georgia is feasible and does not appear to negatively impact already established TB testing using those same machines. Multisectoral stakeholder engagement is key to creating an enabling environment for the integration of multi-disease testing to take place. In the Georgian context, as the laboratory technicians were primarily used to conducting testing using the sample type of sputum, additional training for the laboratory technicians on how to correctly handle samples types such as plasma and whole blood is needed to ensure quality testing and low error rates. Integration of HCV testing onto existing machines for TB should be closely monitored in rollout to identify spot training and opportunities for quality improvement.

9. Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015–June 2020

Abstract Presented at International Viral Hepatitis Elimination Meeting, 2020; Virtual Event

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Background and Aims: In April 2015 with the technical assistance of U.S. CDC and commitment from Gilead Sciences to donate direct-acting antivirals (DAAs), Georgia launched the world's first HCV elimination program. Key strategies include nationwide HCV screening, active case finding, linkage to care, decentralized care, provision of treatment for all HCV persons and effective prevention interventions. The elimination program aims at achieving 90-95-95 targets by 2020: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated. We report progress towards elimination targets 5 years into the elimination program.

Method: The estimated number of persons living with HCV infection was based on the 2015 population-based national seroprevalence survey, which showed that 5.4% of the adult general population has chronic HCV infection (approximately 150,000 persons). The program collects data on all persons registered with the treatment program. Treatment was provided with Sofosbuvir, Ledipasvir/Sofosbuvir or Velpatasvir/Sofosbuvir-based regimens. Data on persons tested for chronic HCV infection through sustained virologic response (SVR) were extracted as of June 2020. Advanced fibrosis was defined as F_{≥3} by METAVIR score based on elastography and/or FIB-4 score >3.25.

Results: As of June 30, 2020, a total of 87,626 persons were diagnosed with chronic active HCV infection, representing 58.4% of the estimated 150,000 adults living with HCV. A total of 70,032 (79, 9%) patients initiated treatment – 54.6% of the estimated target population to be treated (128,250). Of the 47,207 patients who were evaluated for SVR, 46,648 (98.8%) tested negative for HCV by PCR, representing 38.3% of the estimated target population to be cured (121,837). Very high cure rates were achieved for all HCV genotypes: 98.9% in genotype 1, 98.9% in genotype 2 and 98.3% in most challenging to treat genotype 3. Treatment effectiveness was comparable among persons with advanced fibrosis (F₃ and F₄) with 98.2% achieving SVR, and among patients with mild or no liver fibrosis (≤ F₂), SVR= 99.1%.

Conclusions: Georgia has made substantial progress towards eliminating hepatitis C, with more than half of persons with HCV infection identified and registered for treatment. Very high cure rates have been achieved among those who received SVR testing. Challenges remain in identifying and especially linking to care persons living with HCV in Georgia. A nationwide integrated, decentralized model of HCV treatment, which is already implemented, will be critical to improving linkage to care and close the gaps in the HCV cascade.

10. Simplified HCV treatment model in primary healthcare in the country of Georgia

Abstract Presented at International Viral Hepatitis Elimination Meeting, 2020; Virtual Event

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Background and Aims: In April 2015, Georgia in partnership with U.S CDC and Gilead Sciences launched the world's first hepatitis C elimination program. By June 2020, more than 70 thousand persons initiated treatment, achieving >98% cure rates. Patient enrollment in HCV treatment sharply increased in 2016, but since it has been slowing down due to deficiencies in HCV testing and linkage to care. To overcome existing challenges Georgia initiated service decentralization in 2018 by integrating HCV screening and treatment in primary healthcare centers (PHCs).

Method: By June 30, 2020, a total of 11 PHCs provided HCV care services throughout the country. The integrated model was based on a “one-stop shop” approach, by which patients received all HCV screening and care services in selected PHCs. Treatment naïve patients with no or mild fibrosis (FIB-4 score < 1.45) received care at PHCs and underwent examinations as per simplified diagnostic and treatment monitoring algorithm, while persons with FIB-4 score > 1.45 were referred to specialized clinics. Patients received Sofosbuvir/Ledipasvir or Sofosbuvir/Velpatasvir for 12 weeks. Sustained virological response (SVR) was defined as undetectable HCV RNA 12-24 weeks after the end of therapy. The Extension for Community Healthcare Outcomes (ECHO) telemedicine model was utilized to train and support primary healthcare providers. Regular teleECHO videoconferencing was conducted to provide primary care providers with advice and clinical mentoring.

Results: Among persons diagnosed with active HCV infection, 1223 were evaluated for FIB-4 score. Of these, 819 (67%) had FIB-4 score < 1.45; of them 798 (97.4%) initiated treatment. A total of 674 patients completed treatment. Of 536 patients eligible for SVR testing, 438 had been tested at the time of analysis, and 430 achieved SVR (98.2% cure rate).

Conclusion: Our study reported that a simplified HCV diagnostic and treatment model in PHCs significantly enhanced diagnosis and linkage to care for treatment services without compromising the quality. Countrywide expansion of this model will further improve treatment uptake ensuring high cure rates within the national hepatitis C elimination program.

11. The Effect of COVID-19 on the Hepatitis C Screening in Georgia

Abstract Presented at International Viral Hepatitis Elimination Meeting, 2020; Virtual Event

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Background and Aims: Georgia, a country with a population of 3.7 million, has an estimated 150,000 adults living with chronic hepatitis C (HCV) infection. In April 2015, the country initiated the world’s first National Hepatitis C Elimination Program. Within the state elimination program, all HCV-related services, including screening, are covered by the Georgian government and are available to all citizens free of charge. To achieve the 2020 target of diagnosing 90% of HCV-infected persons, the government of Georgia has prioritized resources to increase uptake of screening and diagnosis. The first COVID-19 case was registered on the 26th of February 2020. A number of non-pharmaceutical interventions, including full lockdown throughout the country, were implemented through May 2020. The aim of this analysis is to describe the impact of COVID-19 on the uptake of HCV screening as part of the Georgian Hepatitis C Elimination Program.

Method: This descriptive analysis utilizes data from the national screening registry and treatment databases linked by a unique 11-digit national ID, and the 2020 general population census.

Results: As of July 31, 2020, 1,884,141 adults have been tested for hepatitis C (66.5% of the adult population), of whom 135,206 (7.2%) were anti-HCV positive. Overall, 108,813 individuals received viremia testing, of whom 88,475 (81.3%) were found to have chronic HCV. Screening rates are similar for men and women (65.1% vs. 67.6%, respectively) and are highest among those aged ≥60, 78.6% and 60.7% for men and women, accordingly. This may be explained with the high proportion of hospitalized patients, who are screened for hepatitis C on admission (29.1% of total screenings). Screening rates are lowest among those aged 18-29 (56.1% and 63.1% for men and women, respectively). The overall positivity rate for adult males is 11.5%. The highest positivity rate is seen in men aged 30-59 (16.9%). Among women, the overall positivity rate for adult females is 3.5%. The highest positivity rate is observed in women aged ≥60 (5.1%). In 2019, 38,030-64,613 (mean 49,219) newly screened individuals were registered per month. Monthly rates of newly screened individuals decreased to 12,304-34,647 (mean 26,606) in March – July 2020.

Conclusions: The overall anti-HCV prevalence was highest in males and among those aged 30-59 years. Monthly rates of HCV-screened individuals dropped significantly in 2020 compared to 2019. Observed COVID-19 related reduction in HCV screening uptake will delay progress towards delivery of the Georgian program elimination goals.



12. Self-testing for HCV: Multicountry evidence on usability and acceptability

Abstract Presented at Conference on Retroviruses and Opportunistic Infections, 2021; Virtual Event

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Background and Aims: Globally, ≤ 20% of all persons with hepatitis C (HCV) infection have been tested and only one-quarter of diagnosed persons have been treated. Self-testing for HCV antibodies (HCVST) may be an additional strategy to expand access to HCV testing and support elimination efforts. We undertook studies to assess the usability and acceptability of HCVST in the general population as well as key populations: men who have sex with men (MSM) and people who inject drugs (PWID).

Method: Observational studies were conducted in five countries: Egypt (general population); China (MSM); Kenya (PWID); Vietnam and Georgia (PWID and MSM). Oral fluid OraQuick[®] HCV Rapid Antibody Test with Instructions for Use (IFU) adapted for ST was used as a prototype HCVST kit. Participants were provided written and pictorial IFU and then conducted ST in a private room with a trained observer. In Egypt, in addition to IFU, study personnel provided a one-to-one demonstration on how to use the test. Usability was evaluated through observer assessment of errors and difficulties during ST using a standardized checklist; and acceptability using a semistructured questionnaire. HCVST results were read and interpreted by participants and then re-read by the observer. All participants were re-tested with a professional use OraQuick[®] HCV Test performed by a trained provider.

Results: A total of 775 participants were enrolled across five studies. Participants completing all testing steps without any mistakes were greatest in Egypt and Georgia (>70%), and lowest in PWID from Kenya (30%) and Vietnam (46%). The most common error was incorrect sample collection. Inter-reader agreement ranged from 86% to 99%, and inter-operator agreement from 85% to 99%. The majority of PWID from Vietnam and Kenya required assistance in performing HCVST. The proportion of participants who found the kit very easy or easy to conduct ranged from 55% in Egypt and 66% in Kenya, to more than 80% in other countries. Acceptability was high with > 90% of participants in four countries willing to use HCVST again and who would recommend it to family and friends.

Conclusion: These are the first studies globally to demonstrate high usability and acceptability of HCVST in both general and key populations. While most users self-tested with ease, assisted self-testing models are needed for some populations such as PWID. HCVST is an important strategy for further consideration as it may be a promising tool for increasing coverage and achieving elimination goals.

13. Innovative linkage model to re-engage lost-to-follow-up individuals in The National Hepatitis C Elimination Program of Georgia

Abstract Presented at EASL International Liver Congress, 2021; Virtual Event

Authors: Amiran Gamkrelidze¹, Alexander Turdziladze¹, Maia Tsreteli¹, Vladimer Getia¹, Ana Aslanikashvili¹, Lia Gvinjilia², Tinatin Kuchuloria², Irina Tskhomelidze², Shaun Shadaker³, Paige A. Armstrong³, Maia Japaridze⁴, Sonjelle Shilton⁴

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Background and Aims: In 2015, Georgia launched a national hepatitis C virus (HCV) elimination program with the goal of reducing the country's HCV prevalence by 90%. By implementing systematic screening, and expanding harm reduction services and diagnostic capacity, 72% of the adult population had been screened for HCV by the end of 2020. However, referral of anti-HCV positive individuals for viremia testing, and subsequent enrollment in the treatment program, remains a challenge. In 2019, the National Center for Disease Control and Public Health partnered with the Foundation for Innovative New Diagnostics (FIND) to pilot a project to promote linkage to care for individuals who screened positive for HCV antibody (anti-HCV) but did not receive a viremia test.



Method: Anti-HCV-positive individuals lost-to-follow-up residing in the 5 largest regions in Georgia were included in the pilot. Individuals with no documented viremia test results were randomly selected from the national database. Selected individuals were located and counseled via phone or home visit by trained epidemiologists and primary healthcare physicians and referred to an HCV care and treatment facility. If the first attempt was unsuccessful, one repeat attempt was made to contact the individual. Incentives were provided to the regional health personnel for each patient that was successfully linked to care, defined as anyone who presented for viremia testing.

Results: In December 2019, out of 7,130 antibody-positive persons without viremia testing, a total of 5,313 (75%) were followed-up, of which 3,859 (73%) were reached. The remaining could not be reached, had moved, or emigrated. Of those contacted, 2,972 (77%) presented for viremia testing, of whom 1,685 (57%) were positive for HCV RNA or core antigen. Overall, 887 (53%) persons with chronic HCV infection were linked to care and enrolled in the HCV treatment program, which differed geographically; 46% of persons from urban areas were enrolled, compared to 57% of those in rural areas.

Conclusion: As Georgia nears elimination goals, ensuring all patients who screen positive for anti-HCV are linked to care is increasingly important. This pilot demonstrates the effectiveness of incentive-based active case follow-up. The project also demonstrates that individuals considered lost-to-follow-up can be re-engaged in HCV care. Lessons learned from this project are particularly relevant during the COVID-19 pandemic, when disruptions of care can compromise progress toward hepatitis elimination.

14. Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015–December 2020

Abstract Presented at EASL International Liver Congress, 2021; Virtual Event

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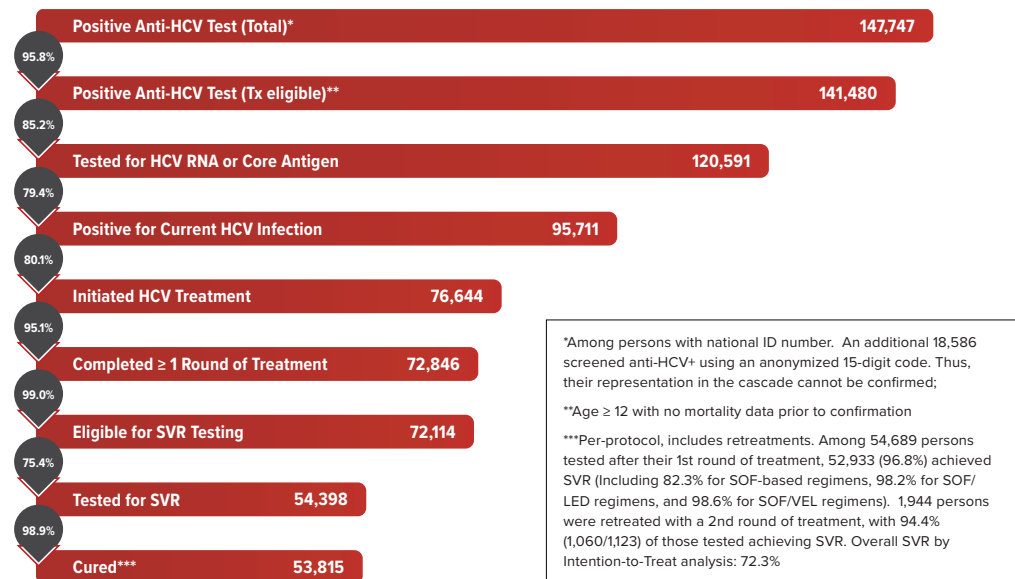
Background and Aims: In April 2015, with the technical assistance of the U.S. CDC and commitment from Gilead Sciences to donate direct-acting antivirals (DAAs), Georgia launched the world's first HCV elimination program. Key strategies include nationwide HCV screening, active case finding, linkage to care, decentralized care, provision of treatment for all HCV persons, and effective prevention interventions. The initial goal of the program was to achieve the following targets by 2020: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated. We report progress towards elimination targets 5 years into the elimination program.

Method: The program collects data on all persons registered with the treatment program. Treatment was provided with Sofosbuvir, Ledipasvir/Sofosbuvir, or Velpatasvir/Sofosbuvir-based regimens. Data on persons tested for chronic HCV infection, and those deemed cured by sustained virologic response (SVR) were extracted as of December 2020.

Results: As of December 31, 2020, a total of 90,578 persons were diagnosed with chronic HCV infection, representing 60.4% of the estimated 150,000 adults living with HCV in Georgia. A total of 72,811 (80.4%) patients initiated treatment – 56.8% of the estimated target population to be treated (128,250). Of the 51,208 patients who were evaluated for SVR, 50,644 (98.9%) tested negative for HCV by PCR, representing 41.6% of the estimated target population cured (121,837). High cure rates were achieved for all HCV genotypes: 98.9% in genotype 1, 98.9% in genotype 2 and 98.3% in genotype 3, typically the most challenging to treat. Treatment effectiveness was comparable among persons with advanced fibrosis (F3 and F4) with 98.2% achieving SVR, and among patients with mild or no liver fibrosis (\leq F2), SVR= 99.1%.

Conclusions: Georgia has made substantial progress towards eliminating hepatitis C, with over 40% of persons with chronic HCV infection identified and cured. Efforts to identify and link to care persons with HCV infection, ensure SVR testing and implement prevention interventions are needed to achieve the elimination goals.

Figure. Georgia Hepatitis C Elimination Program Care Cascade, April 28, 2015 – December 31, 2021



15. The effect of COVID-19 on the progress of the hepatitis C elimination program in Georgia

Abstract Presented at EASL International Liver Congress, 2021; Virtual Event

Authors: Amiran Gamkrelidze¹, Alexander Turdziladze¹, Maia Tsereteli¹, Vladimer Getia¹, Ana Aslanikashvili¹, Sophia Surguladze¹, Lia Gvinjilia², Tinatin Kuchuloria², Irina Tskhomelidze², Shaun Shadaker³, Paige A. Armstrong³

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Background and Aims: Georgia, with a population of 3.7 million, has an estimated 150,000 adults living with chronic hepatitis C virus (HCV) infection. The country initiated the world's first national HCV elimination program in 2015, with free screening and treatment available to all citizens. Despite great progress,

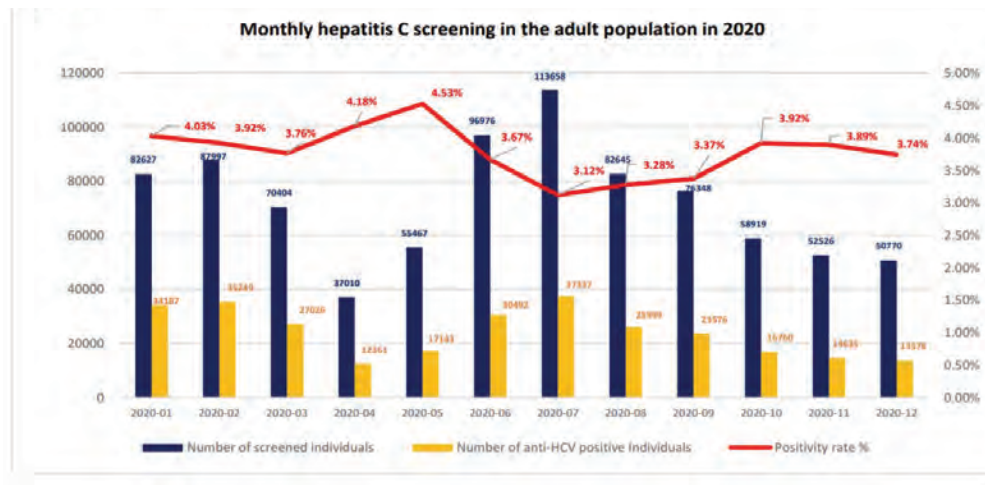
the COVID-19 pandemic has created new challenges for the program. This analysis describes the progress made in HCV screening since program initiation and the impact of the COVID19 pandemic on testing.

Methods: A national database was created to collect screening data for the HVC program, for the purpose of surveillance and program monitoring and evaluation. This analysis uses data from the national HCV screening registry and treatment databases linked by individuals’ national IDs, and the 2014 general population census.

Results: As of January 23, 2021, 2,100,693 adults have been tested for antibody to HCV (anti-HCV) (73.4% of the adult population), of whom 157,515 (7.5%) were anti-HCV positive. Overall, 113,315 (71.9%) of anti-HCV-positive individuals received follow-up viremia testing, and 90,498 (79.8%) were found to have chronic HCV infection. The COVID-19 pandemic has led to a decline in testing in the national HCV elimination program. Screening rates dropped after restrictions were imposed in March 2020, from as high as 87,997 in February, to just 37,010 in April. Testing briefly increased in the summer, with 113,658 tests performed in July, due in part to relaxed restrictions and intensified integrated screening programs (HCV, tuberculosis, and HIV). Overall, the number of individuals tested in 2020 decreased by 51% (288,343) compared to 2019 (584,987).

Conclusion: Although the program has made significant progress toward HCV elimination, the ongoing pandemic has led to a decline in testing rates. In response, Georgia intends to increase integrated screening, and seek active approaches to link patients to care. The lessons learned and impact on the program demonstrate how a pandemic can prove challenging for public health programs and highlights the need to employ innovative strategies to avoid loss of progress.

Figure.



16. Feasibility and effectiveness of models of HCV viraemia testing at harm reduction sites in Georgia: A prospective 3 arm study

Abstract Presented at EASL International Liver Congress, 2021; Virtual Event

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Background and Aims: In 2015, Georgia began a hepatitis C virus (HCV) elimination programme. Although screening programmes have largely been decentralised for high-risk groups, viraemia testing remains a limiting factor for people who inject drugs (PWID). As part of HEAD-Start (Hepatitis C Elimination through Access to Diagnostics) Georgia, Foundation for Innovative New Diagnostics (FIND) in partnership with Georgia’s National Centers for Disease Control and Public Health conducted a cluster, non-randomized interventional study to describe two models of viraemia testing that aim to address this gap and compare them to the current standard of care (SOC).

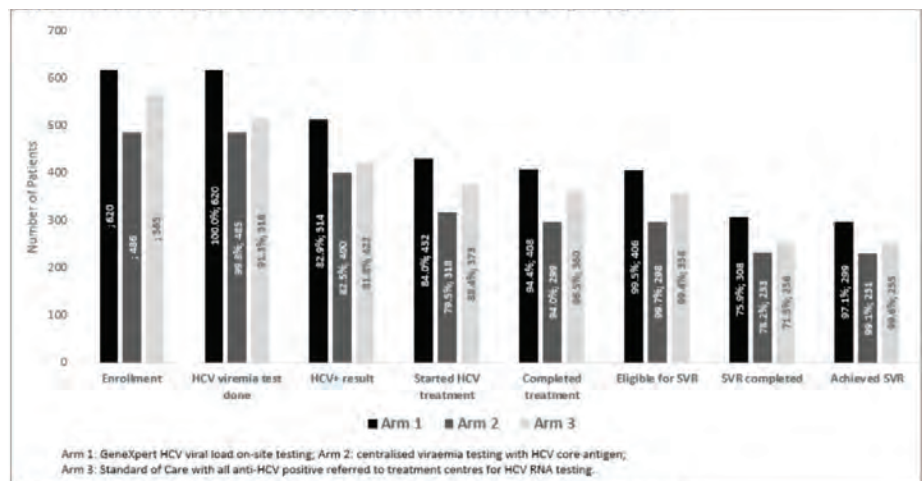
Method: We assigned 8 harm reduction sites (HRS) to one of three arms. Arm 1: GeneXpert HCV viral load on-site testing, Arm 2: centralised viraemia testing with HCV core antigen (centralised HCVcAg), or Arm 3: SOC with all anti-HCV positive referred to treatment centres for HCV RNA testing.

Results: Between May 2018 and September 2019, 1671 HCV-seropositive participants were enrolled (Arm 1, 620; Arm 2, 486; Arm 3, 565). Participants were predominantly male (95.4%), with a median age of 43 years (interquartile range [IQR]: 37, 50), and 1290 (77.2%) were currently injecting drugs. Significantly higher proportions of participants in Arms 1 (100.0%) and 2 (99.8%) had viraemia testing performed compared with Arm 3 (91.3%) (Arm 1 vs Arm 3; P<.001, Arm 2 vs Arm 3; P<.001) (Figure). Among viraemic participants, treatment uptake was similar across all arms (Arm 1, 84.0%; Arm 2, 79.5%; Arm 3, 88.4%). The time between screening and sample collection for viraemia testing was significantly longer in Arm 3 (median 1 [0, 4] days) compared with both Arm 1 (P<.001) and Arm 2 (P<.001) (median 0 [0, 0] days for both), and the overall time between screening to treatment initiation was longer for Arm 3 (67 [45, 94] days) compared with Arm 1 (57 [39, 87] days; P<.001) and Arm 2 (50 [38, 80] days; P<.001).

Conclusion: Point-of-care viraemia testing and blood drawn on-site for HCVcAg testing resulted in more HCV seropositive patients receiving viraemic testing within a shorter timeframe compared with referral for blood collection using SOC. However, proportions of viraemic patients who were referred to treatment centres and subsequently initiated treatment were similar across all arms. These findings underscore the benefits of fully decentralised HCV care.

Figure. Retention of patients in the hepatitis C care cascade by study arm

Abbreviations: HCV = hepatitis C virus; SVR = sustained virologic response



17. Evaluation of alcohol use behavior among patients cured in Georgia's HCV elimination program (preliminary results)

Abstract Presented at Global Hepatitis Summit, 2021; Taipei, Taiwan

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Background and Aims: Georgia has one of the highest rates of wine consumption in the world. Combined with a high prevalence of chronic HCV infection, the synergistic effects can lead to worse liver-related outcomes. There is no data on the role of alcohol consumption on progression of liver disease among hepatitis C virus (HCV) patients in the country. This study evaluates alcohol consumption behaviors among patients in the HCV program.

Method: An interviewer-administered questionnaire was used to collect data on demographic, clinical, and drinking behavior. Patients were enrolled from three clinics, one in Tbilisi and two in other large cities in Georgia. Participants were then randomly selected from the list of patients treated with direct-acting antivirals (DAAs), and who subsequently achieved SVR. Data on baseline and post-treatment fibrosis levels (measured by FIB4 score or liver elastography) were abstracted to evaluate the association of alcohol use with liver fibrosis progression.

Results: As of December 2020, 256 patients were enrolled in the study. Of those, 11.1% were ≤35 years old, 81.7% were male, 98.4% were Georgian, 69.8% were married, 38.9% had a university degree, and 61.5% were employed. The majority of participants (93.7%) report ever using alcohol in their lifetime, and 10.3% consider themselves heavy drinkers. Nearly all (94.1%) people knew that heavy alcohol consumption can accelerate the development of liver fibrosis, and 97.5% abstained from alcohol during treatment. Among those, 75.7% resumed drinking after achieving SVR. More than half (52.1%) of the patients felt moderate alcohol intake is normal for those with low fibrosis scores. And only 12.8% of patients thought drinking is unacceptable among people with HCV infection. In a bivariate analysis, patients who abstained from alcohol after achieving SVR were 4 times more likely to have improvement in liver fibrosis compared to those who resumed drinking (29.5% vs 7.4%, respectively; $p < 0.02$).

Conclusion: Drinking alcohol is common in Georgia, and a high proportion of people in the HCV treatment program consume alcohol. Abstaining from alcohol is advantageous to improvement in fibrosis, even after SVR has been achieved. However, a majority of patients with HCV infection do not drink alcohol during treatment, but resume drinking after achieving SVR. The findings present an opportunity to focus messaging and education for patients during DAA treatment to improve outcomes even after completion of treatment.

18. Improvement in liver fibrosis among patients with Hepatitis C who achieved sustained virologic response after direct acting antivirals treatment in Georgia (preliminary results)

Abstract Presented at Global Hepatitis Summit, 2021; Taipei, Taiwan

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Background and Aim: In 2015, Georgia launched a national HCV elimination program. This study assesses changes in liver stiffness, biochemical, and clinical parameters in a cohort of HCV-infected patients with advanced liver fibrosis who were enrolled in the HCV elimination program and achieved SVR after treatment with DAAs.

Method: The study cohort included patients ≥ 18 years with advanced liver fibrosis level by elastography ($\geq F3$) or FIB4 score > 3.25 , who were treated with DAAs and achieved SVR at 12–24 weeks post-treatment. A random sample was selected from clinics providing care and treatment to HCV patients. Baseline data (prior to initiating treatment) were abstracted from patients' medical records. Follow-up laboratory and clinical measures were collected at 4 years posttreatment.

Results: A total of 600 patients were included in the study. At 4 years post-treatment, mean liver stiffness decreased from 23.7 kPa to 11.3 kPa ($p < .0001$). Mean difference in FIB-4 score was 1.6 (from 3.52 to 1.92) ($p < .0001$). Mean ALT level decreased from 111.9 to 28.2 ($p < .0001$) and mean AST level from 89.6 to 26.7 ($p < .0001$). Platelet count increased from 159,200 to 190,500/ μL ($p < .0001$). Hemoglobin levels increased by a mean of 0.3 g/dL ($p = .039$), and spleen length and width decreased by mean of 4.3 mm ($p = .004$) and 3.1 mm ($p < .0001$), respectively. Among patients with ascites at baseline ($n = 17$), 11 (64.7%) experienced resolution; for the majority ($n = 583$) without ascites at baseline, 10 (1.7%) developed ascites during follow-up period. Four patients developed HCC between baseline and 4-year follow up visit.

Conclusion: Among patients with liver fibrosis, treatment with DAAs affords significant improvement in nearly all diagnostic markers, and can lead to resolution of clinical symptoms of decompensated liver failure.

19. Management of hepatitis C in primary healthcare in the country of Georgia

Abstract Presented at Global Hepatitis Summit, 2021; Taipei, Taiwan

Authors: Tengiz Tsertsvadze^{1,2}, Amiran Gamkrelidze³, Nikoloz Chkhartishvili¹, Akaki Abutidze^{1,2}, Lali Sharvadze^{2,4}, Vakhtang Kerashvili¹, Maia Butshashvili⁵, David Metreveli⁶, Tinatin Kuchuloria⁷, Lia Gvinjilia⁷, Shaun Shadaker⁸, Tamar Gabunia⁹, Ekaterine Adamia⁹, Stefan Zeuzem¹⁰, Nezam Afdhal¹¹, Sanjeev Arora¹², Karla Thornton¹², Francisco Averhoff⁸, Paige A. Armstrong⁸

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Background and Aims: In April 2015, through a partnership with Gilead Sciences and technical assistance from U.S. CDC, Georgia launched the world's first hepatitis C elimination program. By December 31, 2020, more than 72,000 persons initiated treatment with >98% reporting sustained virologic response (SVR) cure. Broad access to direct acting antivirals (DAAs) resulted in rapid increase in treatment uptake in 2016, which has since declined due to barriers in diagnosis and linkage to care. To address this issue Georgia initiated service decentralization in 2018 by integrating hepatitis C virus (HCV) screening and treatment in primary healthcare centers (PHCs). We report preliminary results of an integrated model of HCV care in PHCs from August 2018 through June 2020.

Method: By June 30 2020, a total of 10 PHCs provided HCV care services throughout the country. The integrated model was based on a single-location delivery model, by which patients received all HCV screening, treatment and care services at a PHC. PHCs provided care to HCV treatment-naïve patients with no or mild fibrosis (FIB-4 score<1.45) using simplified diagnostics and a treatment monitoring approach, while persons with advanced liver fibrosis/cirrhosis were referred to specialized clinics. Patients received Sofosbuvir/Ledipasvir and/or Sofosbuvir/Velpatasvir for 12 weeks. SVR was defined as undetectable HCV RNA 12-24 weeks after end of therapy. The Extension for Community Healthcare Outcomes (ECHO) telemedicine model was utilized to train and support primary healthcare providers. Regular teleECHO videoconferencing was conducted to provide primary care providers with advice and clinical mentoring.

Results: Among persons diagnosed with active HCV infection, 1,223 were evaluated for FIB-4 score. Of these, 819 (66.9%) had FIB4 score<1.45 and qualified for treatment at a PHC; of them 798 (97.4%) initiated treatment, and 674 (85%) of those who initiated treatment completed it. Of 536 patients within the 12-24 week window of SVR eligibility, 438 had been tested at the time of analysis, and 427 achieved SVR (97.5% cure rate).

Conclusion: Our study reported the feasibility and effectiveness of integrating a simplified HCV diagnostic and treatment model in PHCs. Countrywide expansion of this model is warranted to bridge the gaps in the HCV care continuum and ensure high rates of treatment uptake towards achieving elimination targets.

20. Association of treated and untreated chronic hepatitis C with the incidence of tuberculosis: A population-based cohort study in the country of Georgia

Abstract Presented at The Liver Meeting- American Association for the Study of Liver Diseases, 2021; Virtual Event

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Background and Aims: Hepatitis C virus (HCV) infection causes dysregulation and suppression of immune pathways involved in the response against and control of tuberculosis (TB) infection. However, research on the role of HCV as a risk factor for active TB disease is lacking. The country of Georgia’s novel program for hepatitis C elimination and national databases for both HCV and TB presents a unique opportunity to explore the incidence of TB disease among HCV-infected persons. This study assessed the effects of HCV infection on the rate of TB disease.

Method: We conducted a cohort study among adult citizens of Georgia tested for HCV antibodies between January 1, 2015 and September 30, 2020. Data were obtained from the Georgian hepatitis C elimination program, National TB Program, and national death registry electronic databases and linked using a unique national ID. The exposure of interest was the status of HCV infection, with three categories: (1) HCV antibody-negative (reference group); (2) completed HCV treatment (treated); (3) untreated HCV infection. The outcome was newly diagnosed TB. Follow-up started at HCV antibody testing and ended at first TB diagnosis, death, or end of the study period. Crude incidence rates and 95% confidence intervals (CI) were calculated. To calculate adjusted hazards ratios (aHR) and 95% CIs, we used a stratified Cox model with HCV status treated as a time-varying covariate, adjusted for sex, incarceration, and region of residence, stratified by birth cohort.

Results: A total of 1,778,382 adults were included, with a median follow-up time of 27 months (interquartile range: 26 months). TB was diagnosed in 2,923 (0.16%) participants. The TB incidence rate was 66 cases per 100,000 person-years (PY) among HCV negative persons, 109 cases per 100,000 PY among those treated for HCV, and 295 cases per 100,000 PY among persons with untreated HCV infection. In multivariable analysis, those with untreated (aHR=2.8, 95%CI: 2.4, 3.2) or treated (aHR=1.4, 95%CI: 1.2, 1.7) HCV infection had significantly higher rates of TB compared to HCV negative persons.

Conclusion: Those with HCV infection were at higher risk of being diagnosed with incident TB disease. Our findings suggest that screening for latent TB infection and TB disease could be considered in the process of clinical evaluation of people with HCV infection; this could improve early detection of TB disease, which is one of the priorities of World Health Organization’s End TB strategies.

Table. Rate of active TB in population with known hepatitis C status.

*Number of people who completed HCV treatment is also counted in the untreated group since they **contributed person-time to both groups;

Adjusted for sex, incarceration, and region of residence, using age as time-scale.

Abbreviations: HCV, hepatitis C virus; TB, tuberculosis; IR, incidence rate; PY, person-year; aHR, adjusted hazards ratio.

HCV status	Total N*	Incident TB cases	IR per 100,000 PY	aHR** (95%CI)
HCV antibody negative	1,708,041	2,522	66	1
Untreated HCV infection	70,341	253	295	2.8 (2.4, 3.2)
Completed HCV treatment	53,456	148	109	1.4 (1.2, 1.7)

21. The effect of COVID-19 on the progress of the hepatitis C elimination program in Georgia

Abstract Presented at International Viral Hepatitis Elimination Meeting, 2021; Virtual Event

Authors: Amiran Gamkrelidze¹, Alexander Turdziladze¹, Maia Tsreteli¹, Vladimer Getia¹, Ana Aslanikashvili¹, Sophia Surguladze¹, Lia Gvinjilia², Tinatin Kuchuloria², Irina Tskhomelidze², Shaun Shadaker³, Paige A Armstrong³

¹National Center for Disease Control and Public Health Georgia, Tbilisi, Georgia; ²The Task Force for Global Health, Tbilisi, Georgia; ³National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, CDC, Division of Viral Hepatitis, Atlanta, United States

Background and Aims: Georgia, with a population of 3.7 million, has an estimated 150,000 adults living with chronic hepatitis C virus (HCV) infection. The country initiated the world's first national HCV elimination program in 2015, with free screening and treatment available to all citizens. Despite great progress, the COVID-19 pandemic has created new challenges for the program. This analysis describes the progress made in HCV screening since program initiation and the impact of the COVID-19 pandemic on testing.

Method: A national database was created to collect screening data for the HCV program, for the purpose of surveillance and program monitoring and evaluation. This analysis uses data from the national HCV screening registry and treatment databases linked by individuals' national IDs, and the 2014 general population census.

Results: As of August 30, 2021, 2,220,000 adults have been tested for antibody to HCV (anti-HCV) (77.6% of the adult population), of whom 162,657 (7.3%) were anti-HCV positive. Overall, 118,400 (72.8%) of anti-HCV-positive individuals received follow-up viremia testing, and 93,839 (79.3%) were found to have chronic HCV infection. The COVID-19 pandemic led to a decline in testing in the national HCV elimination program. Screening rates dropped after restrictions were imposed in March 2020, from as high as 87,997 in February, to just 37,010 in April. Testing briefly increased in the summer, with 113,658 tests performed in July, due in part to relaxed restrictions and intensified integrated screening programs (HCV, tuberculosis, and HIV). Overall, the number of individuals tested in 2020 decreased by 51% (288,343) compared to 2019 (584,987). During January–August 2021, total number of persons screened is lower than the same eight-month period in 2020 (433,907 versus 552,593).

Conclusion: Although the program has made significant progress toward HCV elimination, the ongoing pandemic has led to a decline in testing rates, with numbers continuing to decline in 2021. In response, Georgia intends to increase integrated screening, and seek active approaches to link patients to care. The lessons learned and impact on the program demonstrate how a pandemic can prove challenging for public health programs, and highlights the need to employ innovative strategies to avoid loss of progress.

22. HCV-Attributable liver cancer in the country of Georgia: Analysis of cases from the Georgian Cancer Registry, 2015-2019

Abstract Presented at International Viral Hepatitis Elimination Meeting, 2021; Virtual Event

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Background and Aims: Georgia has a high national prevalence of hepatitis C virus (HCV) infection, with 5.4% of adults chronically infected based on a 2015 serosurvey. In response, a national Hepatitis C Elimination program was launched in 2015 to provide widespread testing and treatment with direct-acting antiviral agents (DAAs). By the end of 2020, 73% of the adult population had been screened for anti-HCV and >70,000 had been treated. Chronic HCV infection is a leading cause of hepatocellular carcinoma (HCC), which has a 5-year survival of 10-20%.

The Georgia Hepatitis C Elimination Program maintains high-quality registries, providing data for HCV screening, testing and treatment. These data can be linked to other health registries; analyses of case-level data from the HCV registries linked to the recently-inaugurated (2015) Georgian Cancer registry (GCR) may facilitate a better understanding of the HCV-attributable burden of HCC in Georgia. Assessing the attributable disease burden of chronic viral hepatitis (CVH) is needed to measure the impact of the program and progress toward viral hepatitis elimination.

Method: We extracted data for all cases in the GCR classified as C22 (Primary Liver Cancer [PCL]) using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) during 2015-2019. Data on demographics (date of birth, sex, residence), date of diagnosis, and death (if applicable), and clinical information were abstracted. Using Georgia's unique National ID, cases were matched to the HCV Screening and HCV Treatment Registries (anti-HCV and RNA test results, fibrosis scores, genotype, HBsAg results, and data on treatment (initiation, completion, and cure).

Results: Among 869 case-patients, 72% were male and median age at diagnosis was 62 years (IQR 55-71); males were younger than females at diagnosis. Overall, 698 (84%) case-patients died as of April 2021, and 288 (33%) survived > 1 year from date of diagnosis.

One-third (275, 32%) of cases were classified as HCC (C22.0), 96 (11%) as intrahepatic cholangiocarcinoma (ICC, C22.1), and most cases (490, 56%) were not classified to a specific cancer subtype (NSCT, C22.7/C22.9). A minority of cases (253, 29%) were diagnosed histologically.

Most cases (588, 68%) were screened for anti-HCV, and the proportions screened increased from 27% in 2015 to 93% in 2019. Of these, 351 (60%) were anti-HCV positive, and 283 (80%) were confirmed to be viremic. Among viremic cases, 209 (74%) had fibrosis assessment, and 190 (91%) were classified as Metavir F3-F4. Chronic HCV infection was strongly associated with both younger age ($p < .0001$) and male sex (OR=3.6 [95% CI 2.4-5.5]).

Conclusion: Georgia has a comprehensive Hepatitis C Elimination program, with surveillance systems that can link testing, treatment, and cancer registry data. Still, only two-thirds of cases of PLC had data on HCV status; however, the proportion screened increased substantially during the study period. Approximately half of those with PLC and screening data available had chronic HCV infection, suggesting HCV contributes substantially to PLC burden in Georgia. Continuing to monitor these trends is critical to demonstrating progress towards elimination, and provides a model globally for integrated surveillance of sequelae from viral hepatitis.



ii. POSTERS

DECENTRALIZING HCV TESTING TO HARM REDUCTION SITES; HEAD-START GEORGIA

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Introduction

Georgia, a middle-income country with an estimated population of 3.7 million people, is among the world's highest hepatitis C virus (HCV)-burden countries, with an HCV prevalence of 7.7% in the general population and a higher disease burden in high risk populations, such as people who inject drugs (PWID). In 2015, Georgia embarked on an elimination programme, yet significant gaps remain in case finding and linkage to care. In particular, although screening programmes have largely been decentralized for high risk groups, viremic testing remains a bottleneck for PWIDs wishing to access care. Here we describe two novel models of viremic testing that aim to address these weaknesses in the care cascade.

Methods

A cluster, non-randomized intervention study where harm reduction sites (HRS) are assigned one of three approaches in the HCV care cascade that we have called "arms" – Arm 1: at 4 HRS, on site viremia testing (GeneXpert); Arm 2: at 2 HRS, on site blood draw, with confirmatory testing (cAG) at a centralized laboratory; and Arm 3: at 2 HRS, standard of care patients are referred for testing at the treatment centre. Participants are eligible for the study if they tested HCV positive on the same day and did not have a prior confirmed diagnosis. The proportion of participants who completed each step in the HCV care cascade were compared across the three arms as well as the turnaround time of test results.

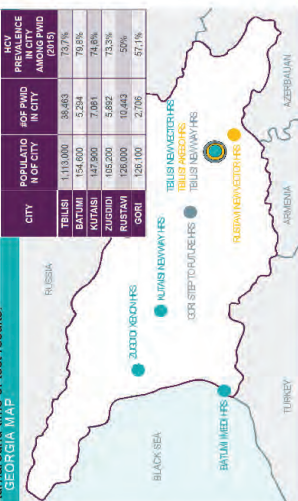


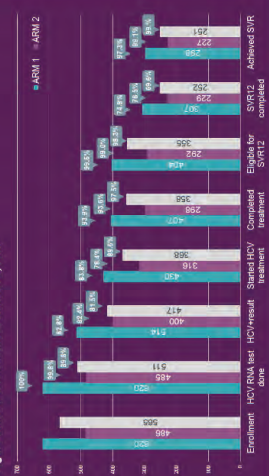
Figure 1. Geographic distribution of study sites in Georgia
 FINDdx logo: Because diagnosis matters
 HEAD-start logo: Harms to Eliminate, Aids to Reduce

Table 1: Patient characteristics

Mean (SD)	range	%	n	%	n	%
Male	43.8	95.4	1671	95.4	1671	95.4
Female	8.8	9.7	93	9.7	93	9.7
Age	38.0	10.0	1671	100.0	1671	100.0
Median	35.0	10.0	1671	100.0	1671	100.0
Range	18-74	100.0	1671	100.0	1671	100.0
Median	35.0	10.0	1671	100.0	1671	100.0
Range	18-74	100.0	1671	100.0	1671	100.0
Median	35.0	10.0	1671	100.0	1671	100.0
Range	18-74	100.0	1671	100.0	1671	100.0
Median	35.0	10.0	1671	100.0	1671	100.0
Range	18-74	100.0	1671	100.0	1671	100.0

Results

Between May 2018 and May 2020, 1,671 participants were enrolled (620 in Arm 1, 486 in Arm 2, and 565 in Arm 3). Participants were predominantly male (95.4%); the median age was 35.0 (IQR 28-43) years, and 77% were PWID. 95% participants reported having taken an HIV test, and of these 14 (0.84%) self-reported being HIV-positive. To date, 1,616 participants have had a confirmatory viremia test done: 620 (100%) in Arm 1; 485 (99.8%) in Arm 2, and 511 (89.8%) in Arm 3 (Arm 1 v 2 p=0.942, Arm 1 v 3 p=0.171, Arm 2 v 3 p=0.223). Of those who were confirmed positive, treatment was initiated for 430 (83.8%) in Arm 1, 316 (78.4%) in Arm 2, and 368 (88.6%) in Arm 3.



On average, participants received their results the same day (<3.2 hours) in Arm 1, after 10 days in Arm 2, and after 6.9 days in Arm 3, from the time they had blood drawn for testing.

Table 2: Turnaround time across the HCV care cascade

Time between (range) for each Arm	HCV screening confirmation test	Sample testing completion for confirmation test	Completion of sample testing and result entered into national database	Result to patient and result to national database	Total time
Arm 1	Same day (0-4 days) n=613	1 hr 55 min (1-2 hrs) n=613	16 hr 24 min (0-1 days) n=613	24 minutes (0-1 hrs) n=613	81.6 days (median) n=613
Arm 2	Same day (0-4 days) n=477	6.3 days** (1-85 days) n=477	4.0 days (0-4 days) n=477	10.0 days (0-18 days) n=477	63.7 days (median) n=477
Arm 3	6.9 days (0-49 days) n=489	5.6 days (0-83 days) n=489	4.5 days (0-35 days) n=489	6.9 days (0-27 days) n=489	63.1 days (median) n=489

**Time between completion of sample testing and result delivered back to the patient
 ***Includes the time spent for repeated test of PCR if cAg test result is negative or in grey zone

Conclusion

The introduction of decentralized HCV confirmatory testing catalysed the decentralization of HCV treatment in the HRS. On-location based approaches to blood sample collection resulted in a larger proportion of participants receiving their confirmatory test results. The turnaround time for confirmatory testing was shortest where point-of-care service was performed.

Acknowledgements

We would like to thank our partners: National Center for Disease Control and Public Health (NCDC), Ministry of Health Georgia, Health Research Union (HRU), Georgian Harm Reduction Network (GHRN), harm reduction sites, U.S. Centers for Disease Control and Prevention and the participants for their involvement in the project. This project is funded by Unitaid.



A project funded by Unitaid
 Innovation in Global Health

ii. POSTERS cont.

Randomized control trial of home-based hepatitis C self-testing in key populations in Georgia

27

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Introduction

Georgia, a middle-income country with an estimated population of 3.7 million people, is among the world's highest-burden countries for HCV, with an estimated seroprevalence of 7.7% in the general population and a higher burden of disease in high-risk populations such as persons who inject drugs. In 2015, Georgia embarked on an elimination program for HCV, which includes the expansion of HCV testing, linkage to care and treatment. Although, the country made a substantial progress in HCV testing, but the gap still remains that needs to be addressed through testing of different screening modalities to reach marginalized groups of the population.

Following the WHO recommendation on the use of HCV self-test (HCVST) in July 2021, this study aims to evaluate the impact of an online self-testing program enabling home delivery of HCV self-tests (HCVST) to people who inject drugs (PWID) and men who have sex with men (MSM) in Georgia.

PRIMARY OUTCOME

- To assess the impact of HCV self-testing home delivery on HCV antibody testing rates in PWID and MSM

SECONDARY OUTCOMES

- To assess the impact of HCV self-testing on linkage and completion of HCV RNA confirmatory testing in HCV antibody positive individuals
- To assess the impact of HCV self-testing on treatment initiation in HCV RNA positive individuals eligible to start treatment
- To assess the acceptability and feasibility of HCV self-testing at baseline and after study participation. Information about knowledge, attitudes, and practices related to HCV and risk taking behaviours will be collected
- To assess the cost of the proposed HCV self-testing model

Methods

A randomized controlled trial with a total 1250 study participants equally distributed among five arms. (n=250 per arm). Participants will be recruited using an existing online HIV self-testing platform, selftest.ge (figure 1). All study participants will complete a baseline survey collecting demographics, knowledge and attitudes towards HCV testing through the online platform. Randomization to intervention or control will be done among participants who primarily identify as MSM (arm 1, 2 and 3) and among those who primarily identify as PWID (arm 4 and 5).

Arm 1, 2 and 4 participants receive a home delivered HCV ST. Arm 1 participants get the HCV ST by courier delivery and Arm 2 and 4 by peer delivery. Arm 3 and 5 participants will receive information about where they can get the HCV testing as a part of the standard of care for PWID and MSM communities (figure 2). All participants will enter the results into the online platform. All participants will be offered two follow-up surveys in 1 to 4 weeks and 6 to 8 weeks after enrollment to collect information on their risk behaviors relating to sexual practices and injecting equipment sharing (figure 3).



Figure 1. Online platform selftest.ge

RECRUITMENT	INTERVENTION AND CONTROL GROUPS	DELIVERY METHOD	TESTING PLATFORM
Equality Movement (Tbilisi & Batumi)	GROUP 1 INTERVENTION (Tbilisi & Batumi)	MSM (n=250)	Participant performs HCVST
Imedi Batumi	GROUP 2 INTERVENTION (Tbilisi & Batumi)	MSM (n=250)	Participant performs HCVST
	GROUP 3 CONTROL (Tbilisi & Batumi)	MSM (n=250)	Information where to get HCV test
	GROUP 4 INTERVENTION (New Way HRS)	PWID (n=250)	Peer Delivery
	GROUP 5 CONTROL (New Way HRS)	PWID (n=250)	Information where to get HCV test

Figure 2. Study Arms



Figure 3. Follow-up Surveys

Supportive Tools Provided

- Peer support
- Video and Printed instructions
- Educational leaflets
- Hotline available to answer questions and concerns
- Information for referral for follow up diagnostics and treatment

Expected results

Completed study participant surveys will be collected through the online platform www.selftest.ge, and clinical data will be obtained from National data base. Descriptive and bivariate analyses will be conducted to evaluate the impact of the HCV ST. The study is powered to detect at least a 20% between-group difference in uptake of HCV antibody self-testing, based on 80% statistical power and an alpha level of 0.05. The study is not powered to detect significant differences in the impact related objectives, given an estimated HCV prevalence of less than 10%. Community stakeholders group representing both key populations, MSM and PWID, HCV converted to monitor for any potential social harms arising from HCV ST and knowledge of test results.

Conclusion

The study is designed to generate valuable information regarding the acceptability and impact of home-based HCVST on HCV testing uptake and follow up care among the marginalized population groups such as MSM and PWID. The participants enrollment will start in October through November 2021 and preliminary data will be available in Dec 2021.

Acknowledgements

We would like to thank our partners: National Center for Disease Control and Public Health (NCDC), Ministry of Health Georgia, Tanadgoma organization, Equality Movement organization, Tbilisi New Way HRS, Batumi Imedi HRS, and World Health Organization. This project is funded by the Government of the Netherlands



ii. POSTERS cont.

PORTFOLIO OF FIRST-EVER RANDOMIZED CONTROL TRIALS TO MEASURE IMPACT OF HEPATITIS C SELF-TESTING IN GEORGIA, MALAYSIA, AND PAKISTAN

#64

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Introduction

Globally, only 21% of the estimated 58 million people living with hepatitis C virus (HCV) know their status. As a result, there is a significant need to scale up HCV testing if the WHO 2030 hepatitis elimination goals are to be achieved. HCV self-testing (HCVST), which was recently recommended by WHO as an additional approach to HCV testing, may help close this gap but there are currently no data on the real-world impact of HCVST. In these three studies, we aim to evaluate the acceptability and impact of 3 different HCVST models in Georgia, Malaysia, and Pakistan.

Methods

Georgia is a 5-arm project design, with intervention and control arms for 1,250 participants made up of people who inject drugs (PWID) and men who have sex with men (MSM), in Batumi and Tbilisi (Figure 1). Malaysia is a 2-arm project design for a total of 750 participants made up of anyone residing in the country who identifies as a key population. In both studies, participants will be randomized for an intervention group receiving HCVST (either oral-fluid or blood-based) or receiving information on the nearest facility-based HCV testing service (Figure 2). In Georgia, participants are randomized to courier delivery of HCVST, peer-delivery of HCVST, or control, while in Malaysia, participants are randomized either for courier delivery of HCVST or control. Participants will enter their test results into an online platform and will complete knowledge attitude and practices (KAP) surveys and follow-up surveys in 1-4 weeks and 6-8 weeks post-enrollment to collect information on risk behaviors. Pakistan is a cluster, randomized trial comparing secondary distribution of information for HCV screening. The clusters, consisting of neighborhoods in 2 union pamphlets encouraging visits to a testing facility for HCV screening. The clusters, consisting of neighborhoods in 2 union pamphlets encouraging visits to a testing facility for HCV screening of HCVST via study staff or for control clusters councils in Karachi, Pakistan, are randomized either for home distribution of HCVST or control (Figure 3) where information on HCV and a request to attend the local hospital for HCV screening (Figure 3) are handed out.

Expected results

For Georgia and Malaysia, completed study participant surveys will be collected through the online platform selftest.ge and selftest.com. In Georgia, linkage data will be retrieved from the national hepatitis C database. In Malaysia, peer navigators will verify participant self-reported linkage data. In Pakistan, data will be collected by the study staff and entered in the OpenClinica data capture platform. Descriptive and bivariate analyses will be conducted to evaluate the impact of HCVST. In each country, a community stakeholder group will be convened to monitor for any potential social harms arising from HCVST and test results. The group will include members from the study population (MSM and PWIDs [Georgia and Malaysia]), and the general population (Pakistan). Each study is powered to detect at least a 20% between-group difference in HCV antibody testing based on 80% statistical power and an alpha level of 0.05. Ethical approval has been received by each relevant country body. Enrollment started on 7 September 2021 in Malaysia and in November in Pakistan and December in Georgia. Preliminary data sharing is expected in January 2022.

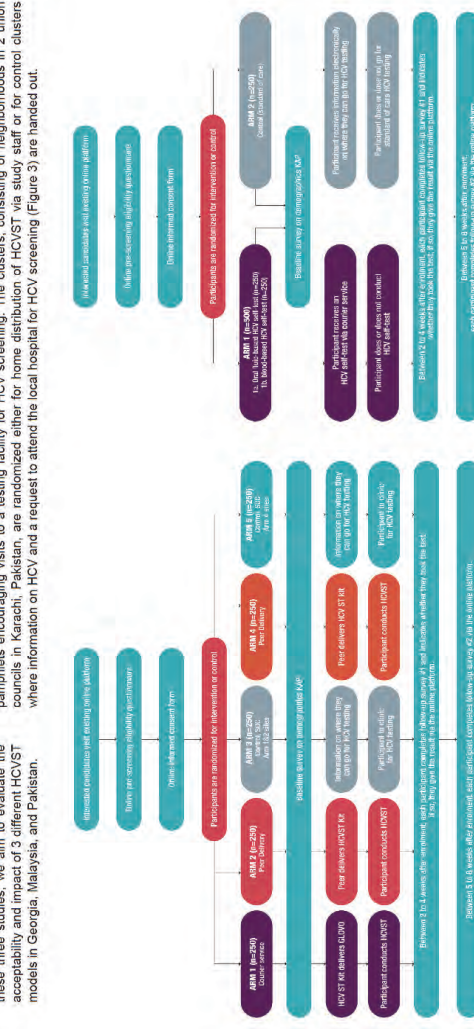


Figure 1. Georgia study flow

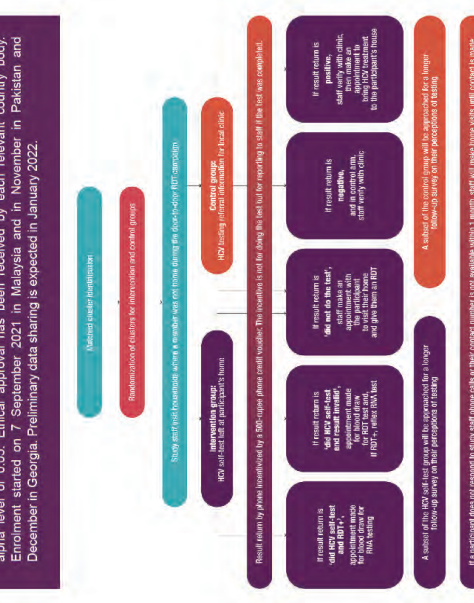


Figure 2. Malaysia study flow



Figure 3. Pakistan study flow



iii. ORAL PRESENTATIONS

1. Georgia HCV Elimination Program: Successes and Challenges during COVID-19, Amiran Gamkrelidze

Presented at the Virtual International Liver Congress, 2021

2. The effect of COVID-19 on the progress of the hepatitis C elimination program in Georgia, Amiran Gamkrelidze

Presented at the Virtual International Liver Congress, 2021

3. The Georgian Model for Hepatitis C Elimination, Tengiz Tsertsvadze

Presented at the Virtual Central and Eastern European Meeting on Viral Hepatitis and HIV 2021

4. Three-armed, cluster intervention study of hepatitis C viremia testing for people who inject drugs in Georgia

Presented at the Virtual International Network on Hepatitis in Substance Users Conference, 2021

APPENDIX 4.

PUBLICATIONS OF THE GEORGIA HEPATITIS C ELIMINATION PROGRAM

RESEARCH ARTICLE

Open Access



Treatment outcomes of patients with chronic hepatitis C receiving sofosbuvir-based combination therapy within national hepatitis C elimination program in the country of Georgia

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Abstract

Background: Georgia has one of the highest HCV prevalence in the world and launched the world's first national HCV elimination programs in 2015. Georgia set the ambitious target of diagnosing 90% of people living with HCV, treating 95% of those diagnosed and curing 95% of treated patients by 2020. We report outcomes of Sofosbuvir (SOF) based treatment regimens in patients with chronic HCV infection in Georgia.

Methods: Patients with cirrhosis, advanced liver fibrosis and severe extrahepatic manifestations were enrolled in the treatment program. Initial treatment consisted of SOF plus ribavirin (RBV) with or without pegylated interferon (INF). Sustained virologic response (SVR) was defined as undetectable HCV RNA at least 12 weeks after the end of treatment. SVR were calculated using both per-protocol and modified intent-to-treat (mITT) analysis. Results for patients who completed treatment through 31 October 2018 were analyzed.

Results: Of the 7342 patients who initiated treatment with SOF-based regimens, 5079 patients were tested for SVR. Total SVR rate was 82.1% in per-protocol analysis and 74.5% in mITT analysis. The lowest response rate was observed among genotype 1 patients (69.5%), intermediate response rate was achieved in genotype 2 patients (81.4%), while the highest response rate was among genotype 3 patients (91.8%). Overall, SOF/RBV regimens achieved lower response rates than IFN/SOF/RBV regimen (72.1% vs 91.3%, $P < 0.0001$).

In multivariate analysis being infected with HCV genotype 2 (RR = 1.10, CI [1.05–1.15]) and genotype 3 (RR = 1.14, CI [1.11–1.18]) were associated with higher SVR. Patients with cirrhosis (RR = 0.95, CI [0.93–0.98]), receiving treatment regimens of SOF/RBV 12 weeks, SOF/RBV 20 weeks, SOF/RBV 24 weeks and SOF/RBV 48 weeks (RR = 0.85, CI [0.81–0.91]; RR = 0.86, CI [0.82–0.92]; RR = 0.88, CI [0.85–0.91] and RR = 0.92, CI [0.87–0.98], respectively) were less likely to achieve SVR.

Conclusions: Georgia's real world experience resulted in high overall response rates given that most patients had severe liver damage. Our results provide clear evidence that SOF plus IFN and RBV for 12 weeks can be considered a treatment option for eligible patients with all three HCV genotypes. With introduction of next generation DAAs, significantly improved response rates are expected, paving the way for Georgia to achieve HCV elimination goals.

Keywords: HCV, Elimination, DAAs, SVR, Georgia

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Background

Globally, an estimated 71 million people are chronically infected with hepatitis C virus (HCV), and 400,000 die annually from hepatitis C-related liver diseases [1]. Management of HCV infection has been revolutionized after the availability of direct acting antivirals (DAAs), and Sofosbuvir (SOF) was the first widely introduced DAA [2, 3]. Clinical trials have demonstrated high efficacy of SOF-based regimens in patients infected with genotypes 1–6 [4–8].

Georgia has one of the highest HCV prevalence rates among general population in the world [9], and launched the world's first national HCV elimination program in 2015 [10]. The elimination program has adopted a comprehensive strategy that addresses both prevention and treatment of HCV infection. A key component of the program is the provision of DAAs free of charge to all Georgian citizens; this was made possible through an agreement with Gilead Sciences to donate DAAs. Georgia has set itself the ambitious target of diagnosing 90% (135,000 persons) of people living with HCV, treating 95% (128,000 persons) of those diagnosed and curing 95% (121,000) of treated patients by 2020 [9]. We report outcomes of SOF-based treatment regimens in patients with chronic HCV infection in the country of Georgia.

Methods

All Georgians aged 18 years or older that are infected with HCV are eligible for the free of charge treatment program. The hepatitis C elimination program was launched on 28 April 2015. All patients treated from launch through 31 October 2018 are included in the analysis. Treatment-naïve and experienced patients with cirrhosis (including decompensated cirrhosis), advanced liver fibrosis, severe extrahepatic manifestations, HCV re-infection after liver transplantation and HIV-coinfection were prioritized for enrollment in the treatment program. Initially, DAA treatment was exclusively SOF based and included ribavirin (RBV) with or without pegylated interferon, depending on the HCV genotype, per national guidelines. From February 2016, more effective, interferon free DAA combination - sofosbuvir and ledipasvir (SOF/LDV) was introduced, and treatment regimens were revised. Beginning in June 2016, treatment criteria were relaxed allowing enrollment of all HCV infected persons regardless of level of liver fibrosis, to be treated. Treatment guidelines were established by a committee composed of treatment experts from Georgia in consultation with international experts. Based on eligibility of interferon therapy all HCV genotype 1 and 3 patients received SOF plus, Pegylated interferon (IFN) and RBV for 12 weeks or SOF plus RBV for 24 weeks.

HCV genotype 2 treatment naïve patients without cirrhosis were treated with the 12-week combination of SOF plus RBV, while cirrhotic patients and those with prior treatment failure received the 12-week regimen of SOF plus IFN and RBV or the 20-week regimen of SOF plus RBV based on eligibility of interferon. Patients with decompensated cirrhosis received SOF plus RBV for 48 weeks.

Treatment was initially limited to four sites in Tbilisi, and later expanded with sites from other cities within Georgia; by October 2018, 31 sites were providing HCV treatment in the country. The HCV treatment program providers also participated in Project ECHO (Extension for Community Healthcare Outcomes).

A national HCV treatment database was established, which collected standard data for each patient enrolled in treatment program. Each treatment site was responsible for data entry for each enrolled patient. Data were de-identified and sociodemographic, clinical and laboratory data were extracted from national HCV treatment database. Characteristics measured included: age, gender, HCV RNA, FIB-4 test score, METAVIR score, HBsAg, treatment regimen, HCV genotype and city where treatment was provided. Sustained virologic response (SVR) was defined as undetectable HCV RNA at least 12 weeks after the end of treatment. The presence of cirrhosis was confirmed by vibration-controlled transient elastography or acoustic radiation force impulse elastography (ARFI) compatible with stage F4 fibrosis (≥ 14.5 kpa)_by METAVIR. Decompensated cirrhosis was defined as the presence of current or past ascites, hepatic encephalopathy and variceal haemorrhage etc. SVRs were calculated using both per-protocol and modified intent-to-treat (mITT) analysis. Per-protocol approach included only those with complete SVR data, while in mITT analysis persons discontinuing treatment were also included. Persons who died or had no SVR test > 24 weeks after completing treatment were excluded from analysis.

Statistical analysis

All analyses were performed with SAS version 9.3 software (SAS Institute, Inc., Cary, NC, USA). Variables were categorized as follows: age category: 18–44, 45–60, and > 60; HCV RNA category: < 800,000 IU/mL vs. $\geq 800,000$ IU/mL; FIB-4 test: <1.45, 1.45–3.25 and > 3.25; METAVIR score: <F4 and F4. We used the chi-square or Fisher's exact to compare differences in categorical variables with SVR. We performed a multivariate logistic-regression analysis involving baseline demographic, clinical and laboratory characteristics to identify independent predictors of SVR. A *p*-value < 0.05 was considered significant. The final model included

variables associated ($p < 0.05$) with SVR in the bivariate analysis. The results are presented with a Risk ratio (RR) and 95% Confidence intervals (CIs). Results for patients who completed treatment and tested for SVR through 31 October 2018 were analyzed. The study was approved by the Institutional review board of the Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi.

Results

A total of 7342 patients with chronic HCV infection received SOF-based therapy from April 28, 2015 until October 31, 2018 and 5079 had complete SVR data.

The pretreatment demographics, clinical and laboratory characteristics of patients with complete SVR data are described in Table 1. Most patients, 2838 (55.9%) were age 45–60 years, 4381 (86.3%) were males and 2783 (57.9%) had stage F4 fibrosis (by METAVIR). Overall, 1724 (33.9%) of the patients had HCV genotype 1, followed by HCV genotype 3, 2305 (45.4%) and HCV genotype 2, 1047 (20.6%). Only 3 patients were infected with HCV genotype 4. Majority of patients were treated with IFN/SOF/RBV for 12 weeks (52.1%), followed by SOF/RBV for 24 weeks (27.9%), SOF/RBV for 20 weeks (7.8%), SOF/RBV for 12 weeks (7.2%), and SOF/RBV for 48 weeks (5.0%).

A total of 521 persons discontinued treatment, with the most common causes for not completing treatment being death (48.8%; $n = 254$), self-discontinuation (19.6%; $n = 102$), and loss to follow up (15.9%; $n = 83$). Among those who died during treatment, the majority 299/521 (57.4%) had severe liver disease (METAVIR scores of F3 or F4).

A total of 5079 persons with complete SVR data and 521 persons who discontinued treatment, were included in treatment efficacy analysis (total 5600 persons). Total SVR rate was 82.1% (4170/5079) in per-protocol analysis and 74.5% (4170/5600) in mITT analysis.

Of those with an SVR12, the lowest response rate was observed among genotype 1 patients (1198/1724; 69.5%), intermediate response rate was achieved in genotype 2 patients (852/1047; 81.4%), while the highest response rate was among genotype 3 patients (2117/2305; 91.8%). There were only 3 patients with genotype 4 and all were cured.

Overall, SOF/RBV regimens achieved lower response rates than IFN/SOF/RBV regimen (72.1% vs 91.3%, $P < 0.0001$). This difference was seen in all genotypes (57.0% vs 80.8%, $P < 0.0001$ for genotype 1; 76.9% vs 96.3%, $P < 0.0001$ for genotype 2 and 82.5% vs 96.9%, $P < 0.0001$ for genotype 3 respectively) (Fig. 1).

Multivariate analysis (Table 2) showed that when controlling those factors which were significantly associated with SVR in bivariate analysis, being infected with HCV genotype 2 (RR = 1.10, CI [1.05–1.15], $P = 0.001$) and

genotype 3 (RR = 1.14, CI [1.11–1.18], $P < 0.0001$) were associated with higher SVR. Patients with cirrhosis (RR = 0.95, CI [0.93–0.98], $P < 0.0001$), receiving treatment regimens of SOF/RBV 12 weeks, SOF/RBV 20 weeks, SOF/RBV 24 weeks and SOF/RBV 48 weeks (RR = 0.85, CI [0.81–0.91], $P < 0.0001$; RR = 0.86, CI [0.82–0.92], $P < 0.0001$; RR = 0.88, CI [0.85–0.91], $P < 0.0001$ and RR = 0.92, CI [0.87–0.98], $P = 0.005$, respectively) were less likely to achieve SVR.

Discussion

This study from Georgia is one of the largest real-world cohorts examining outcomes of HCV treatment with SOF based regimens, among patients with severe liver disease. We assessed real-world efficacy of SOF plus RBV with or without IFN in these difficult-to-treat patients with chronic hepatitis C. Our study demonstrated that SOF-based regimens can result in high overall SVR rates, similar to SVR rates achieved in clinical trials [11, 12]. While newer combination DAAs are now available, SOF is now one of the most readily available DAAs worldwide, at affordable prices in many low middle income countries, and as such, these findings have relevance today. In particular, the acceptable SOF plus RBV outcomes among the most severely ill patients, regardless of genotype are highly relevant.

In our study response rates among patients with HCV genotype 2 were lower than reported in clinical trials and real-life studies which showed high efficacy of SOF plus RBV combination treatment among HCV genotype 2 patients including those with cirrhosis and/or treatment experience [8, 12–15]. Lower efficacy of treatment in genotype 2 patients may have been associated with a reported high prevalence of HCV recombinant form 2 k/1b among Georgian HCV genotype 2 patients [16]; these patients do not respond well to standard treatment for genotype 2 and regimens used for genotype 1 seem to be more effective [17]. Therefore there is a need for reassessing existing modalities for the management of HCV genotype 2 infection, especially in areas with high prevalence of HCV recombinant form 2 k/1b [18].

We observed high cure rates in HCV genotype 3 patients that are one of the most challenging subpopulations to treat [19]. IFN-based regimens were superior to SOF/RBV alone. The results of clinical trials showed that HCV genotype 3 patients achieved higher SVR12 rates with a 12 week SOF and RBV in combination with IFN that patients who were treated with SOF and RBV alone [12].

Our findings support use of a 12 week regimen of SOF plus RBV in combination with IFN as a treatment option for eligible HCV genotype 3 patients in settings, where

Table 1 Baseline characteristics of adult persons with complete SVR data treated with SOF-based regimens by HCV genotypes within the national hepatitis C elimination program, April 28, 2015 – October 31, 2018

Characteristic	TOTAL		Genotype 1		Genotype 2		Genotype 3		Genotype 4	
	n	%	n	%	n	%	n	%	n	%
Age category, n (%)										
18–45	1635	32.2	386	22.4	299	28.6	948	41.1	2	66.7
45–60	2838	55.9	944	54.8	630	60.2	1264	54.8	.	.
60+	606	11.9	394	22.9	118	11.3	93	4.0	1	33.3
Gender, n (%)										
Female	698	13.7	486	28.2	101	9.6	110	4.8	1	33.3
Male	4381	86.3	1238	71.8	946	90.4	2195	95.2	2	66.7
HCV RNA categories, n (%)										
< 800,000 IU/mL	2922	57.7	901	52.5	625	59.8	1393	60.5	3	100.0
≥ 800,000 IU/mL	2145	42.3	816	47.5	420	40.2	909	39.5	.	.
FIB-4 Test										
< 1.45	200	5.7	65	6.0	51	7.0	84	5.0	.	.
1.45–3.25	1763	50.2	491	45.0	403	55.1	868	51.5	1	50.0
> 3.25	1546	44.1	535	49.0	277	37.9	733	43.5	1	50.0
Metavir score										
< F4	2021	42.1	676	39.8	516	50.9	827	39.6	2	66.7
F4	2783	57.9	1021	60.2	497	49.1	1264	60.4	1	33.3
Liver function tests, n (%)										
ALT >2 X ULN	2585	51.0	731	42.5	466	44.6	1385	60.2	3	100.0
AST >2 X ULN	2604	51.4	783	45.6	442	42.3	1376	59.8	3	100.0
Billirubin >1.1 mg/dL	4423	87.3	1520	88.5	928	88.8	1972	85.7	3	100.0
Albumin < 35 g/L	2001	39.5	670	39.0	469	44.9	862	37.4	.	.
INR >1.49	687	13.6	260	15.1	132	12.6	295	12.8	.	.
Co-infections, n (%)										
HBsAg+	108	2.2	28	1.7	19	1.9	61	2.8	.	.
HBsAg-	4777	97.8	1666	98.3	985	98.1	2123	97.2	3	100.0
Treatment regimen, n (%)										
IFN/SOF/RBV (12 wk)	2646	52.1	905	52.5	240	22.9	1500	65.1	1	33.3
SOF/RBV (12 wk)	364	7.2	3	0.2	360	34.4	1	0	.	.
SOF/RBV (20 wk)	395	7.8	3	0.2	392	37.4
SOF/RBV (24 wk)	1418	27.9	695	40.3	7	0.7	714	31	2	66.7
SOF/RBV (48 wk)	256	5	118	6.8	48	4.6	90	3.9	.	.
City of treatment site, n (%)										
Tbilisi	3800	74.8	1294	75.1	819	78.2	1684	73.1	3	100
Kutaisi	362	7.1	148	8.6	72	6.9	142	6.2	.	.
Batumi	501	9.9	177	10.3	67	6.4	257	11.1	.	.
Zugdidi	328	6.5	90	5.2	81	7.7	157	6.8	.	.
Gori	42	0.8	6	0.3	5	0.5	31	1.3	.	.
Rustavi	40	0.8	9	0.5	3	0.3	28	1.2	.	.
Lanchkhuti	4	0.1	4	0.2	.	.
Gurjaani	2	0	2	0.1	.	.

SOF Sofosbuvir, RBV Ribavirin, IFN Interferon

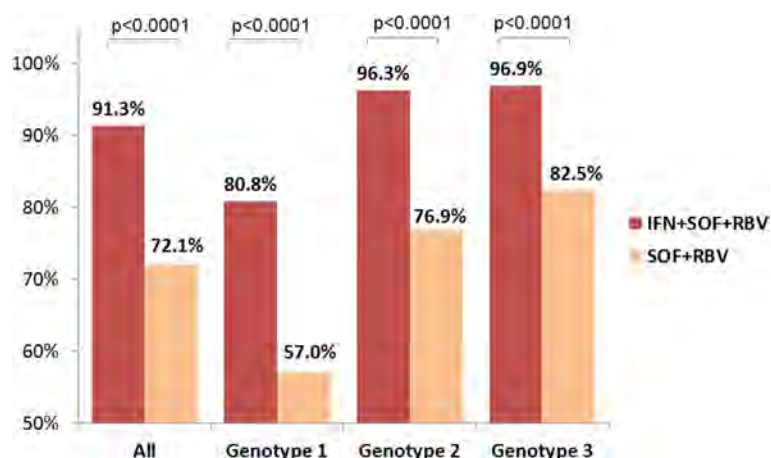


Fig. 1 SVR rates by treatment regimens and genotype ($n = 5076$)

new highly potent and well-tolerated DAAs against genotypes 2 and 3 are not available. Our results suggest the use of SOF/RBV combination for 24 weeks as an option for patients who cannot tolerate IFN.

After examining host and viral factors we found that presence of cirrhosis, and receiving IFN-free regimens were associated with lower SVR in a multivariable model. The low rates of response among cirrhotic patients is consistent with previous studies.

One strength of this study is the large number of patients as well as standardized treatment guidelines and standardized data collection. The diversity of our cohort with respect to sex, age, and genotype distribution makes our findings generalizable, reflecting reported real-world outcomes. Our study has several limitations. First, data from patients in whom prior treatment had failed, was not collected. Second, liver fibrosis was assessed by multiple noninvasive indices, each of which have limitations on accuracy [20–22]. The national treatment database, which captures information on all hepatitis C patients enrolled in the program, provides accurate treatment related information on a national level. However it does not contain detailed information on some variables, including comorbidities (diabetes mellitus, kidney failure, extrahepatic manifestations etc.) as well as nature of deaths, adverse events and reasons of self-discontinuation. Also data available in the national system has limited ability to answer questions as to why people are lost to follow-up along the continuum of care. Significant number of patients who were lost to follow-up after treatment completion is a serious challenge of the treatment program. However, in 2017 the program offered SVR assessment free of charge that would lead to reducing missing SVR data. Despite notable progress of the Georgia HCV elimination program,

challenges to Georgia achieving the national targets for HCV elimination by 2020 remain. Pangenotypic DAAs that are effective across the different genotypes of HCV introduced in late 2018 could have a substantial impact on improving access and simplifying diagnosis and treatment.

Conclusion

In conclusion, in this large cohort study, a combination of SOF and weight-based RBV with or without IFN appeared to be an effective regimen to treat chronic HCV-infected patients, especially for HCV Genotype 2 and 3 patients. SOF formed the foundation of the HCV elimination program in Georgia. Cure rates in patients without cirrhosis were high, which are comparable with those reported in clinical trials. However, consistent with previous studies, the presence of liver cirrhosis were associated with lower SVR12 rates. Our results provide clear evidence that SOF plus IFN and RBV for 12 weeks can be considered a treatment option for eligible patients with all three HCV genotypes. With the introduction of next generation DAAs, replacement of IFN-based regimens by IFN-free regimens and significantly improved response rates are expected, paving the way for Georgia to achieve the goal of HCV elimination. High cure rates obtained with SOF/LDV combinations for all HCV genotypes within Georgia program highlights effectiveness of service delivery model, which is based on simplified modalities that can be successfully replicated in non-specialty settings, which is important in light of ongoing decentralization process. Strong governmental commitment coupled with effective local and international partnerships provide a basis for turning the ambitious goal of elimination into reality.

Table 2 Treatment outcomes and associated factors among adult persons with complete SVR data receiving SOF-based regimens within the national hepatitis C elimination program, April 28, 2015 – October 31, 2018

	Total N	Achieved SVR		Bivariate analysis			Multivariate analysis		
		N	%	RR	95% CI	p value	RR	95% CI	p value
Age category									
18–45	1635	1440	88.07	1					
46–60	2838	2259	79.60	0.90	0.88–0.93	<0.0001			
60+	606	471	77.72	0.88	0.84–0.92	<0.0001			
Gender									
Female	698	560	80.23	1					
Male	4381	3610	82.40	1.03	0.99–1.07	0.18			
HCV Genotype									
1	1724	1198	69.49	1			1		
2	1047	852	81.38	1.17	1.12–1.22	<0.0001	1.10	1.05–1.15	<0.0001
3	2305	2117	91.84	1.32	1.28–1.37	<0.0001	1.14	1.11–1.18	<0.0001
4	3	3	100.00	–	–	–	–	–	–
HCV RNA categories, n (%)									
< 800,000 IU/mL	2922	2408	82.41	1					
≥ 800,000 IU/mL	2145	1754	81.77	0.99	0.97–1.02	0.56			
FIB-4 Tests									
< 1.45	200	177	88.50	1			1		
1.45–3.25	1763	1573	89.22	1.01	0.96–1.06	0.76	1.00	0.93–1.07	0.95
> 3.25	1546	1166	75.42	0.85	0.80–0.90	<0.0001	0.95	0.87–1.02	0.17
Metavir score									
< F4	2021	1761	87.14	1			1		
F4	2783	2161	77.65	0.89	0.87–0.97	<0.0001	0.95	0.93–0.98	0.0001
Co-infections									
HBsAg-	4777	3897	81.58	1					
HBsAg+	108	89	82.41	1.01	0.92–1.10	0.82			
Treatment regimen									
IFN/SOF/RBV (12 wk)	2646	2416	91.31	1			1		
SOF/RBV (12 wk)	364	276	75.82	0.83	0.78–0.88	<0.0001	0.85	0.81–0.91	<0.0001
SOF/RBV (20 wk)	395	302	76.46	0.84	0.79–0.89	<0.0001	0.86	0.82–0.92	<0.0001
SOF/RBV (24 wk)	1418	979	69.04	0.76	0.73–0.78	<0.0001	0.88	0.85–0.91	<0.0001
SOF/RBV (48 wk)	256	197	76.95	0.84	0.79–0.90	<0.0001	0.92	0.87–0.98	0.005
City of treatment site									
Tbilisi	3800	3127	82.29	1			1		
Kutaisi	362	272	75.14	0.91	0.86–0.97	0.004	0.96	0.92–1.01	0.10
Batumi	501	435	86.83	1.06	1.02–1.10	0.005	1.01	0.97–1.05	0.60
Zugdidi	328	258	78.66	0.96	0.90–1.01	0.13	0.96	0.92–1.00	0.07
Gori	42	40	95.24	1.16	1.08–1.24	<0.0001	1.01	0.87–1.17	0.91
Rustavi	40	32	80.00	0.97	0.83–1.14	0.72	0.95	0.80–1.13	0.55
Lanchkhuti	4	4	100.00	–	–	–	–	–	–
Gurjaani	2	2	100.00	–	–	–	–	–	–

SOF Sofosbuvir, RBV Ribavirin, IFN Interferon, CI Confidence interval, RR Risk ratio, SVR Sustained virologic response

Abbreviations

CI: Confidence intervals; DAAs: Direct acting antivirals; HCV: Hepatitis C virus; INF: Pegylated interferon; mITT: modified intent-to-treat; RBV: Ribavirin; RR: Risk ratio; SOF: Sofosbuvir; SVR: Sustained virologic response

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Authors' contributions

Concept and design (TT, AG, FA, NC, AA), statistical analyses (SS, NC, AA), interpretation of the data (TT, AG, MN, LS, JM, SS, LG, MB, DM, VK, ME, NC, AA, VK, FA), drafting the manuscript (TT) and critical revision of the manuscript for intellectual content (TT, AG, MN, LS, JM, SS, LG, MB, DM, VK, ME, NC, AA, VK, FA). All authors read and approve the final manuscript.

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Availability of data and materials

The data that support the findings of this study are property of Georgia's HCV elimination program. In case the data is requested, please contact scientific committee of Georgia's HCV elimination program (Secretary Dr. Tinatin Kuchuloria, email: drkuchuloria@yahoo.com).

Ethics approval and consent to participate

The study was approved by the Institutional review board of the Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Tuberculosis, HIV, and viral hepatitis diagnostics in eastern Europe and central Asia: high time for integrated and people-centred services

Masoud Dara*, Soudeh Ehsani, Antons Mozalevskis, Elena Vovc, Daniel Simões, Ana Avellon Calvo, Jordi Casabona i Barbarà, Otar Chokoshvili, Irina Felker, Sven Hoffner, Gulmira Kalmambetova, Ecatarina Noroc, Natalia Shubladze, Alena Skrahina, Rasim Tahirli, Tengiz Tsertsvadze, Francis Drobniowski*

Globally, high rates (and in the WHO European region an increasing prevalence) of co-infection with tuberculosis and HIV and hepatitis C virus exist. In eastern European and central Asian countries, the tuberculosis, HIV, and viral hepatitis programmes, including diagnostic services, are separate vertical structures. In this Personal View, we consider underlying reasons for the poor integration for these diseases, particularly in the WHO European region, and how to address this with an initial focus on diagnostic services. In part, this low integration has reflected different diagnostic development histories, global funding sources, and sample types used for diagnosis (eg, typically sputum for tuberculosis and blood for HIV and hepatitis C). Cooperation between services improved as patients with tuberculosis needed routine testing for HIV and vice versa, but financial, infection control, and logistical barriers remain. Multidisease diagnostic platforms exist, but to be used optimally, appropriate staff training and sensible understanding of different laboratory and infection control risks needs rapid implementation. Technically these ideas are all feasible. Poor coordination between these vertical systems remains unhelpful. There is a need to increase political and operational integration of diagnostic and treatment services and bring them closer to patients.

Introduction

In the past 20 years rapid molecular tools have revolutionised the work of tuberculosis laboratories. Classic microbiology-based culture examinations of patient specimens and drug-susceptibility testing are increasingly replaced, at least in part, with rapid molecular tests, offering results in hours or days rather than weeks or months.^{1–4} Understanding of how specific mutations in the *Mycobacterium tuberculosis* genome are related to drug resistance is rapidly increasing, and molecular detection of such resistance-predicting mutations is often used to rapidly detect drug-resistant tuberculosis^{5–11} and potentially could be used to initiate personalised treatment regimens.¹² An additional added value of replacing conventional tuberculosis diagnostic methods, based on mycobacterial culture, to modern molecular assays, is that, although they still require training of laboratory staff, they permit tuberculosis diagnosis to take place in less specialised laboratories, closer to patients. A similar trend is seen in using PCR and sequencing-based technologies for detection of drug-resistant HIV.¹³ Although a commercially available and automated diagnostic tool recommended by WHO, such as the GeneXpert system (Cepheid; Sunnyvale, CA, USA), has shown its applicability in a combined diagnostic landscape, the full role of sequencing-based technologies, increasingly used in characterisation of different infectious disease pathogens offers great opportunities in the near future. Next-generation sequencing (NGS), including both targeted sequencing and whole-genome sequencing (WGS), is becoming increasingly affordable and thus more widely used in, for example, the study of resistance mutations in viruses and bacteria such as *M tuberculosis*.^{11,14–16} At present, for tuberculosis, reliable NGS approaches are confined to grown cultures but

successful attempts have been made to do NGS on sputum specimens^{17–19} or by using a targeted gene approach.²⁰

Great progress has been achieved in HIV diagnostics. Nowadays, wider use of rapid HIV tests and confirmation of positive results with additional rapid ELISA confirmatory testing²¹ is simpler, faster, and more accurate and cost-effective than before. Use of modern fourth-generation combined antigen and antibody tests can now increase the accuracy of HIV diagnosis and reduce the number of misdiagnosed patients within the so-called window period in HIV testing.²¹

With increasing access to effective treatment of hepatitis C globally, any simplification of diagnostic algorithms for the disease allows for more rapid implementation of national control programmes.^{22,23}

Background and current situation

Global and European policy

The commitments contained in the UN General Assembly political declarations on the fights against tuberculosis²⁴ and HIV/AIDS,²⁵ and the globally endorsed End TB strategy,²⁶ the *Global Health Sector Strategy on HIV, 2016–2021*,²⁷ and the *Global Health Sector Strategy on Viral Hepatitis 2016–2021*,²⁸ collectively agreed on universal health coverage and collaboration between diverse stakeholders to achieve their objectives. The WHO European region has translated these goals into regional action plans for tuberculosis (for 2016–20),²⁹ for HIV³⁰ and for viral hepatitis,³¹ which were endorsed at the 65th³² and 66th³³ sessions of the Regional Committee for Europe.

Integrating programmes benefits patients by maximising available infrastructure and resources (including staff) and minimising diagnostic and therapeutic delay

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Panel: A good example of diagnostic service integration in Georgia

- Georgia provides an excellent example of what can be achieved when countries with vertical health systems for HIV, tuberculosis, and viral hepatitis management integrate to produce more people-centred health delivery models⁴⁶
- During the past decade, access to full HIV and tuberculosis services (eg, screening, confirmation, treatment, and care) was guaranteed to patients in the capital city Tbilisi and in regional centres; the decentralisation was accelerated by an initiative to eliminate hepatitis C by 2020; this right to access has catalysed HIV and tuberculosis testing interventions with hepatitis C screening services at all different levels of health care⁴⁷
- In 2018, a pilot project was started in the Samegrelo-Zemo Svaneti region to test the potential for integration of HCV, HIV, and tuberculosis screening services at the regional level and to engage primary health-care providers in detection and management of all three diseases (Khonelidze I, National Center for Disease Control and Public Health, Tbilisi, Georgia, personal communication)
- The project enabled both the development of a sustainable public-private partnership for effective integration of HIV, tuberculosis, and hepatitis C screening and early disease detection, and the decentralisation of diagnostic services (HIV and hepatitis C confirmation tests) at district level at non-specialised facilities
- Based on the promising results of the pilot, a national roll-out is planned for 2019–20 (Khonelidze I, National Center for Disease Control and Public Health, Tbilisi, Georgia, personal communication)
- A strong collaboration exists between tuberculosis and HIV services, including HIV screening of all people with active tuberculosis disease, tuberculosis case finding among people with HIV, and provision of treatment for both diseases; estimates of tuberculosis and HIV treatment coverage is over 90% and substantially exceeds global and European coverage.⁴⁷ For 2018, the global coverage was 48% and European 58%. The coverage for Georgia was 68%. Alternatively, the standard indicator is ART coverage among tuberculosis patients with known HIV-status who are HIV-positive. In 2018, the global coverage was 86% and European 73%. The coverage for Georgia in 2018 was 100%.³⁶

for patients with multiple infections. Decreasing financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) necessitates a maximising of efficiency especially for costly diagnostics and therapeutics. Nevertheless, despite the potential to improve diagnosis and treatment, HIV, tuberculosis, and viral hepatitis remain positioned as separate programmes.

Despite a substantial increase in access to antiretroviral therapy (ART), only 1·3 million of the 2·3 million people living with HIV in the WHO European region are on treatment.³⁴ HIV rates continue to increase in this region.³⁵ Tuberculosis remains one of the leading causes of death worldwide, and despite reductions, tuberculosis mortality among people living with HIV remains high;^{35,36} high tuberculosis and HIV co-infection rates are still prevalent globally.^{35–37} Viral hepatitis accounts for 171000 deaths per year in the WHO European region³¹ mainly due to hepatitis-related liver cirrhosis and cancer, attributable to hepatitis B and C virus infections.³¹ Despite the high burden of chronic viral hepatitis, the response in most countries in the region has been inadequate.²⁸ Effectiveness of ART and anti-tuberculosis therapy is dependent on the ability to diagnose, treat, and monitor treatment outcomes. Additionally, WHO recommends the use of viral load testing for monitoring HIV ART.³⁸ Consequently, the need for timely viral load testing is increasing in low-resource, high-burden settings because more people are initiated on ART with the test-and-treat approach.³⁹ Scale-up of hepatitis C treatment has also increased the need for molecular diagnostic methods for hepatitis C virus infection confirmation and assessment of virological cure.²² The need to diagnose HIV and tuberculosis rapidly,⁴⁰ together with high rates of loss to follow up, supports both integration and decentralising testing services in specific situations.^{41–45}

Examples of these vertical structures are found worldwide, but particularly in the Eastern European and Central Asian (EECA) part of the WHO European region, where typically we find two scenarios depending on whether a patient presents initially to a tuberculosis or HIV service.

The diagnostic path of a patient with active tuberculosis

In many EECA countries with a high tuberculosis and HIV burden, all tuberculosis patients will be tested for HIV, hepatitis C, and hepatitis B in tuberculosis facilities. This approach is enshrined in local legislation and for tuberculosis patients, this screening will be free of charge. Blood samples collected in tuberculosis facilities will go to the AIDS centre for testing in their laboratories. Test results will be transferred to the tuberculosis facility and the doctor there will inform the patient about their HIV status. However, once a tuberculosis patient is identified as HIV positive, it is the patient's own responsibility to go to the AIDS centre. Although some countries have developed successful joint tuberculosis and HIV working services (panel), many have major challenges and gaps in HIV service delivery due to long delays before presentation to an AIDS specialist. Patients might avoid the AIDS centre because of stigma and try to hide their HIV status, and counselling, psychological, and community support is often missing within tuberculosis centres for people living with HIV.

Often, national guidance prevents smear-positive tuberculosis patients from attending AIDS centres on the basis of risk to infection control. In this case, the HIV specialist will visit the patient in the tuberculosis facility, but because of the unavailability of HIV specialists, initiation of ART is delayed.

The diagnostic path of a people living with HIV

In many EECA countries, legislation requires that all people living with HIV are tested for tuberculosis, hepatitis C virus, and hepatitis B virus in AIDS centres. The patient cannot be sent to a tuberculosis facility to prevent possible contact between immunocompromised patients and active tuberculosis patients. Screening is free of charge for people living with HIV.

Gaps exist in the tuberculosis service delivery from AIDS centres to people living with HIV. Patients are frequently delayed in seeing tuberculosis specialists because of restricted funding, too few specialists, and rapid increases in the number of people living with HIV. In addition, although some AIDS centres have the facilities to identify *M tuberculosis* (including GeneXpert machines), most AIDS centres collect sputum and send them to tuberculosis laboratories on the basis of local agreements. However, funding limitations often lead to delays in testing potential tuberculosis samples from AIDS centres. Both scenarios show the need and benefits of better integration of tuberculosis and HIV services and prospective integration of viral hepatitis services where relevant.

The current vertical design contributes to increased loss to follow-up of patients due to separate diagnostic and monitoring procedures, and the consequent burden for patients including the doubling of diagnostic visits and medical appointments with different specialists. Integrated models of care are thus highly desirable, as is decentralisation of services, making them available closer to patients.²⁶

We address the inadequate integration of care for people with tuberculosis, HIV, and, hepatitis C particularly in low-income and middle-income, high disease-burden settings. We discuss barriers to better integration and opportunities to overcome the challenges.

Recommendations on rapid testing strategies

The new global 90-90-90 targets⁴⁸ call for 90% of all people with HIV to be diagnosed, 90% of people living with HIV to receive ART, and 90% of individuals on ART to have a suppressed viral load by 2020. WHO guidance⁴⁹ recommends expanding the setting where HIV testing is available and confirmation testing for HIV diagnosis, with swift linkage to care. Integration of HIV testing with testing services for other infections is clearly recommended in new European Centre for Disease Prevention and Control guidance around combined testing interventions for HIV, hepatitis B virus, and hepatitis C virus.⁵⁰ Expansion of this integrated approach to include tuberculosis has

been restricted by the substantial differences in necessary training, equipment, and facilities required, despite recommendations for screening for tuberculosis in people living with HIV and vice versa.

Advances in point-of-care molecular diagnostics for tuberculosis, HIV, and hepatitis C

Since 2010, WHO has endorsed rapid automated molecular diagnostic technology using the GeneXpert platform (and the Xpert MTB/RIF assay [Cepheid]) for the detection of tuberculosis and rifampicin resistance directly from sputum.⁵¹ The GeneXpert system can also be used for HIV-1 treatment monitoring Xpert HIV-1 Viral Load (Cepheid) and early infant diagnosis (eg, the Xpert HIV-1 Qual assay [Cepheid]) for measuring HIV-1 viral load in plasma, dried blood spots, or whole blood samples. Xpert HIV-1 Viral Load was prequalified by WHO in 2017 and Xpert HIV-1 Qual assay in 2016.^{52,53} The Genexpert HIV Viral Load (Cepheid) has an estimated sensitivity of 40 copies per mL from plasma or serum samples and, overall, functions well compared with current reference tests.^{54,55}

The Xpert HCV Viral Load (Cepheid) quantifies hepatitis C virus RNA in human serum or plasma and has an estimated sensitivity of 10 IU/mL with good correlation with reference techniques.⁵⁶ Therefore, the GeneXpert system can be used for confirmation of chronic infection (as for any other PCR-based test) and for the assessment of treatment outcome (ie, sustained virological response).

The GeneXpert system, even when implemented in low-income areas such as at the district health level in Zimbabwe, had the shortest overall median turnaround time for result delivery to the clinician (1 day) when compared with testing in reference laboratories (turnaround time of 17–125 days).⁴⁰ Similar results are found in middle-income and high-income countries.^{57,58}

As other commercial multidisease platforms now exist (table), countries with existing (or planning on purchasing) multidisease platforms should consider collaborating to integrate HIV and hepatitis C viral load, or tuberculosis testing or both. This testing includes both high-throughput laboratory-based instruments for HIV viral load measurement and near point-of-care instruments, such as GeneXpert systems for HIV, hepatitis C virus, and tuberculosis.²³

This array of available assays offers a range of possibilities for high-throughput and near-point-of-care diagnostics for tuberculosis, HIV, and hepatitis C. These new techniques also offer the potential of using more generalist rather than specialist staff.⁶⁰ The portability of point-of-care platforms might make it possible to decentralise first-line diagnosis and monitoring, taking services directly to affected communities, and enabling service delivery in proximity settings (eg, community centres or mobile units in outreach settings), and so maximising access.

	Manufacturer	HIV	Hepatitis C virus	Tuberculosis	Multidrug-resistant tuberculosis	Description
m2000 RealTime System	Abbott Laboratories (Chicago, IL, USA)	Yes	Yes	Yes	Yes	PCR-based platform
qTOWER3 system	Analytik Jena (Jena, Germany)	Yes	Yes	Yes	No	PCR-based platforms
GeneXpert System	Cepheid (Sunnyvale, CA, USA)	Yes	Yes	Yes	Yes	PCR-based platform
Cobas platforms	Roche (Basel, Switzerland)	Yes	Yes	Yes	No	PCR-based platforms
SaCycler-96	Sacace Biotechnologies (Como, Italy)	Yes	Yes	Yes	No	PCR-based platform
GeneXpert I	Cepheid (Sunnyvale, CA, USA)	Yes	Yes	Yes	Yes	Point-of-care or near-point-of-care device
SLAN	LG Life Sciences (Hongshi Tech, Shanghai, China)	No	Yes	Yes	No	PCR-based platforms
QIAasymphony SP/AS	QIAGEN (Venlo, Netherlands)	No	Yes	Yes	No	PCR-based platforms

Table: Molecular multidisease nucleic acid testing platforms for at least two of HIV, hepatitis C, and tuberculosis⁵⁹

Public health and patient benefit of greater collaboration

The End TB strategy recognises the importance of collaboration between tuberculosis and HIV programmes.²⁶ Benefits of integration between programmes include: efficient use of resources currently allocated separately to programmes through sharing of staff expertise, health facilities, equipment and infrastructure; rapid and coordinated identification and management of patients with co-infections; and simplified, people-centred rather than disease-centred service delivery systems.

Integration with additional services, might increase both service uptake and retention for target populations. For example, co-infection with tuberculosis and HIV, or hepatitis C virus and HIV disproportionately affects key populations, such as people who inject drugs or patients residing in prisons. Because these people are less likely to use formal health settings, assuring timely access to other relevant health services, such as ART, opioid substitution treatment, and access to viral hepatitis diagnostic and therapeutic services, is crucial.⁶¹

Additionally, with the global increase in life expectancy^{62,63} the burden of chronic disease, and the prevalence of multiple morbidities,⁶⁴ will increase. Wider integration might permit, in the longer term, the delivery of both infectious and chronic disease diagnostic and therapeutic services in more cost-effective ways.^{65,66}

Challenges to integrating vertical programmes

EECA tuberculosis laboratory networks generally have a tiered structure, with microscopy and rapid molecular diagnostics such as GeneXpert platforms at the district level, culture and GeneXpert at the intermediate level, and culture and drug susceptibility testing with use of conventional and molecular genetic methods at the national or regional reference laboratory. The HIV programme has had a more centralised service by comparison. HIV laboratories at a district level are not integrated into primary health-care services and usually do not have GeneXpert or equivalent platforms. For these

systems, in which samples are transported to regional and national laboratories, results take time to come back to clinicians. The situation is exacerbated by inadequate laboratory information management systems and less than timely communication between treating clinicians in the case of co-infections.

Technology has driven potential decentralisation furthest for HIV diagnosis where people can self-test in their own home using oral buccal swabs.⁶⁷ Confirmatory testing is still required, however.

Opportunities: use of multidisease diagnostic platforms

The GeneXpert tuberculosis assays, while considering appropriate biosafety considerations, can be successfully operated by staff with basic or less-specialist training.⁶⁰

Testing with, for example, GeneXpert platforms, is possible in most health-care settings, although some additional resources and adaptation are required. For facilities with tuberculosis GeneXpert instruments and assays, modest upgrades to enable multiple disease testing might be required (eg, different cartridges or software, refrigerators for plasma sample storage, centrifuges) and protocols are available for this.

Taking advantage of existing GeneXpert equipment, especially at district and regional levels, can enable their wider use, maximise their effectiveness, and enable quicker delivery of not only tuberculosis test results, but also HIV-1 and hepatitis C diagnosis, viral load monitoring in people living with HIV, and early infant diagnosis of HIV-1. As novel hepatitis C virus treatments are highly effective, initial viral load monitoring would be needed but would not be essential longer term (as is the case in HIV).

In the last decade an increase in the provision of community and non-governmental organisation (NGO) services offering HIV, viral hepatitis, and other sexually transmitted infection testing has occurred, and evidence exists showing their ability to reach key populations and detect previously unknown HIV, hepatitis C, and

hepatitis B infections.^{49,50,68–70} Although most of these services use rapid serological tests and often do not have the equipment for more complex procedures, some have incorporated point-of-care platforms, which allow diagnosis of HIV and other infections.

The sharing of technological platforms will also facilitate implementation of modern diagnostic connectivity solutions leading to streamlining of record keeping of test results and better communication and follow-up.

Efficient use of restricted funding

The balance between disease-specific programmes and strategies, and the need for further integration and strengthening of health services, has received attention from the Global Fund not only at a strategic,⁷¹ but also at an implementation level.⁷²

Currently the Global Fund, which supports diagnostic activities in many countries, has requested that ministries of health shift from donor budget funding to state budget funding covering at least 30% of all activities and ideally 100% of costs through domestic funds by the end of 2020.⁷³ This change makes consideration of the value of integration of separate tuberculosis, HIV, and hepatitis C diagnostic services more crucial and multidisease diagnostic platforms make this possible.

Promoting change: the role of governments, donors, and international organisations

Political and donor support, and civil society advocacy for greater integration of diagnostic services for tuberculosis, HIV, and viral hepatitis are necessary. So far, contributions from governments, international NGOs, and public-private partnerships have improved access to the GeneXpert platforms following the WHO recommendation for their use in 2010, which led to a transformation of tuberculosis and rifampicin-resistance testing globally.⁷⁴

Ministries of health are key for moving forward the integration of these services. However, political willingness needs to be supported and complemented by streamlined communication with donors, and funding strategies of national and international agencies need to be in line with this goal. Stimulating the development of solid investment cases and fostering the involvement of ministries of finance in the planning and analysis of integrated service delivery models might help systematic-level change because increasing effectiveness without increasing resource allocation is a rare opportunity.

Additionally, reduced requirement for external resources (by maximising the use of diagnostic equipment) within the national health systems will be an added benefit for countries and the people affected by these diseases.

Programme managers (and laboratory experts) have a key role in maximising patient outcomes and cost-effectiveness by deciding on placement of multidisease diagnostic platforms and determining testing volumes, reliable sample and result transport systems, and human resource capacity. For example, because of their

experience of using GeneXpert platforms in tuberculosis services, HIV or hepatitis C viral load testing could be easily delegated to tuberculosis laboratory technicians with existing practical experience of Xpert MTB/RIF testing. This shared experience includes training on regular maintenance, troubleshooting, annual calibration, and replacement of modules.

Having a single, efficient sample transport system building on any existing well functioning in-country system would also be more beneficial than having completely parallel systems.

Conclusion

Evidence supports the feasibility of integrated diagnostic testing using multidisease diagnostic platforms within district and sub-district health facilities.⁴⁰ Improved access to optimised laboratory-based testing services would be mutually beneficial for tuberculosis, HIV, and hepatitis C programmes.

Contributors

The initial draft was prepared by MD, SE, GK, DS, and FD. The revised version was produced by FD. MD, and FD contributed equally to the Personal View. All remaining authors contributed equally to rewriting and producing the final draft.

Declaration of interests

We declare no competing interests.

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Blood transfusion safety in the country of Georgia: collateral benefit from a national hepatitis C elimination program

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BACKGROUND: In April 2015, the government of Georgia (country) initiated the world's first national hepatitis C elimination program. An analysis of blood donor infectious screening data was conducted to inform a strategic plan to advance blood transfusion safety in Georgia.

STUDY DESIGN AND METHODS: Descriptive analysis of blood donation records (2015-2017) was performed to elucidate differences in demographics, donor type, remuneration status, and seroprevalence for infectious markers (hepatitis C virus antibody [anti-HCV], human immunodeficiency virus [HIV], hepatitis B virus surface antigen [HBsAg], and *Treponema pallidum*). For regression analysis, final models included all variables associated with the outcome in bivariate analysis (chi-square) with a *p* value of less than 0.05.

RESULTS: During 2015 to 2017, there were 251,428 donations in Georgia, representing 112,093 unique donors; 68.5% were from male donors, and 51.2% of donors were paid or replacement (friends or family of intended recipient). The overall seroprevalence significantly declined from 2015 to 2017 for anti-HCV (2.3%-1.4%), HBsAg (1.5%-1.1%), and *T. pallidum* (1.1%-0.7%) [*p* < 0.0001]; the decline was not significant for HIV (0.2%-0.1%). Only 41.0% of anti-HCV seropositive donors underwent additional testing to confirm viremia. Infectious marker seroprevalence varied by age, sex, and geography. In multivariable analysis, first-time and paid donor status were associated with seropositivity for all four infectious markers.

CONCLUSION: A decline during the study period in infectious markers suggests improvement in blood safety in Georgia. Areas that need further improvement are donor recruitment, standardization of screening and diagnostic follow-up, quality assurance, and posttransfusion surveillance.

Hepatitis C virus (HCV) is a virulent, bloodborne pathogen and a major cause of chronic hepatitis worldwide. In 2015, over 71 million people were infected with HCV, and nearly 400,000

ABBREVIATIONS: anti-HCV = hepatitis C virus antibody; EQAS = external quality assurance; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IDU = injection drug use; NAT = nucleic acid amplification test; SVR = sustained virologic response; TTIs = transfusion-transmitted infections; VNRBDs = voluntary nonremunerated donors; WHO = World Health Organization.

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deaths were ascribed to hepatitis C.¹ Although infection may be subclinical, a high proportion (75%-85%) of infected individuals will develop chronic hepatitis, of whom 10%-20% will proceed to cirrhosis and/or hepatocellular carcinoma.² The advent of combination treatment with ledipasvir (an inhibitor of nonstructural protein 5A thus affecting HCV replication) and sofosbuvir (a nucleotide polymerase inhibitor affecting RNA synthesis) has revolutionized treatment of HCV infection, attaining sustained virologic response ([SVR] undetectable HCV RNA \geq 12 weeks following completion of treatment), representing virologic cure for the overwhelming majority (95%-99%) of those who are treated.³⁻⁶

Hepatitis C is a major public health challenge in the country of Georgia. With dissolution of the Soviet Union, economic and social hardship followed,⁷ contributing to a rise in injection drug use (IDU), a major mode of HCV transmission.⁸ In 2015, a national serosurvey found that an estimated 5.4% of the adult population of Georgia (approximately 150,000) had chronic HCV infection, of whom nearly two-thirds were unaware of their infection.⁹ While IDU has been shown to be the major mode of HCV transmission in Georgia,^{10,11} blood transfusion is an independent risk factor for HCV infection.^{9,12}

Given the high prevalence of hepatitis C, the government of Georgia, in partnership with Gilead and with technical assistance provided by the US Centers for Disease Control and Prevention, initiated a national public health program to eliminate hepatitis C in Georgia by 2020.¹³ The program, launched in April 2015, combines hepatitis C screening and provision of antiviral treatment with a goal of identifying 90% of HCV-infected individuals, treating 95% of those with chronic HCV infection, and curing 95% of those who undergo treatment. In addition to IDU, this comprehensive program has sought to address all modes of transmission, including unsafe medical or dental procedures as well as blood transfusion.¹⁴ The latter is a well-established mode of transmission for HCV.⁹ While mandatory blood donor screening for hepatitis C virus antibody (anti-HCV) has been in effect in Georgia since 1997, a 1998 analysis found the anti-HCV seroprevalence in blood donors to be 6.9%, reflecting the high background prevalence of HCV infection coupled with deficient blood donor selection.¹⁵ In the same survey, the respective donor seroprevalences of hepatitis B virus surface antigen (HBsAg), human immunodeficiency virus (HIV), and *Treponema pallidum* were 3.4, 0.06 and 2.3%, suggesting additional transfusion safety risks.¹⁵ We sought to characterize the epidemiology of the major transfusion-transmitted infections (TTIs) in Georgia as a general measure of national blood transfusion safety. The data are able to inform development of a strategic plan to improve blood safety while also benefiting the hepatitis C elimination program.

METHODS

Setting and overview of blood transfusion services

The country of Georgia, a former Soviet Bloc country, is situated in the Caucasus region of Eurasia.⁹ Following

dissolution of the Soviet Union, blood collection facilities in Georgia were privatized. Donations from paid as well as replacement (friends or family of the intended transfusion recipient) donors are permissible in Georgia. Similar to donor screening practices in other countries, prospective blood donors are assessed before donation, using a donor history questionnaire, to determine their eligibility to donate. A major function of the questionnaire is to identify sociodemographic and medical risk factors for TTIs. While the use of a donor history questionnaire is mandated by ministerial decree in Georgia, there is some variation in the questionnaires that are used by the individual blood centers. If no high-risk behaviors are elicited, then samples are collected from the donor for infectious screening and a blood product is collected. The blood product is maintained in quarantine until the results of the infectious screening results are known. Only blood products that are negative for all screened infectious agents are allowed to be transfused.

A State Safe Blood Program has been in operation in Georgia since 1997. The State Safe Blood Program strives to improve national standards of blood collection and transfusion services, so as to ensure a safe and affordable blood supply that is able to meet the country's transfusion needs. The program's functions include reimbursement of blood centers for serology-based blood donor screening (i.e., for anti-HCV, HBsAg, HIV, and *T. pallidum*), external quality assurance (EQAS) of TTI testing, administration of a Unified Electronic Blood Donor Database, and expansion of efforts to increase voluntary nonremunerated donors (VNRBDs). In 2017, 20 blood establishments held state licenses for blood collection, 12 of which participated in the State Safe Blood Program; only two were not for-profit organizations.¹⁴ Concerted efforts to reform the health care system in Georgia over the past decade include expanded support of vertical programs, such as the hepatitis C elimination program and the State Safe Blood Program.

Source of data and analysis

An analysis was conducted using Georgia's Unified Electronic Blood Donor Database. In the database, unique donor identification numbers are assigned to donors and donations, providing access to donor demographics (age, sex, and geographic region of collection); date(s) of donations; mode of remuneration (i.e., VNRBD, replacement and paid); donor status (i.e., first time vs. repeat); and seroreactivity for anti-HCV, HBsAg, HIV, and *T. pallidum* as reported by the collecting blood center. Information on the blood banks that participated in the State Safe Blood Program was also available for evaluation.

The analysis was confined to blood donation data from January 1, 2015, through December 31, 2017. The minimum age of eligibility for blood donation in Georgia is 18 years. Repeat donor data were included for each year; donors who screened positive for any of the four infectious markers

(i.e., HIV, HBsAg, anti-HCV, or *T. pallidum*) in any of their donations within the study period were reported as positive for that marker. When we analyzed overall findings for the combined 3 years, 2015 through 2017, repeat donor data were counted once and seroreactive results for any donation were prioritized for reporting. The overall 3-year (2015-2017) results that are shown represent cumulative infection prevalence rates over the 3-year period. Thus, the “overall” data reported are not a simple summation of the individual years. If donors had multiple donations within the study period with different levels of remuneration, paid donor status was prioritized, followed by VNRBD and finally replacement. Final remuneration status was assigned accordingly. Individuals with more than one blood donation were classified as repeat donors. Age and region of donation were reported based on the donor’s first/earliest donation in the study period.

For this analysis, *paid donors* refers to individuals who received monetary compensation for their donation. *Replacement donors* comprised friends or family of the intended transfusion recipient; replacement donors were either recruited to donate specifically for the index recipient or to donate with a view to restore the blood bank inventory following the transfusion of the intended recipient. By contrast, VNRBDs have no direct knowledge of transfusion recipients and receive no financial compensation for their donation.

Data management and statistical analysis

Descriptive analysis of donation records was performed to elucidate differences in demographics, donor type, remuneration status, and infectious marker prevalence. Variables with missing values for more than 10% of the sample are shown in the tables. Statistically significant associations in bivariate analysis were determined using chi-square tests with a significance level of p less than 0.05. For regression analysis, final models included all variables available for bivariate analysis (age, sex, region of donation, donor type, and remuneration status), which were tested for goodness of fit and collinearity among predictors. For donors screening positive for anti-HCV, analysis of their continuum of care, including treatment for hepatitis C, was obtained from Georgia’s national hepatitis C screening registry as well as treatment records from the country’s national hepatitis C elimination program, with results through December 31, 2018. Computer software (SAS version 9.4, SAS Institute) was used for all statistical analyses.

RESULTS

A total of 252,019 donations were recorded during the study period; 591 were excluded if the associated donor’s age was either missing or listed as less than 18 years. The final result of 251,428 donations represents 112,093 unique adult donors, corresponding to an average of 83,809 collections per year (Table 1). Of those donors, 68.5% were male

($n = 76,389$), 44.7% ($n = 50,098$) were aged 18 to 29 years, and 51.2% were either paid ($n = 30,806$) or replacement ($n = 26,570$). Missing values were noted for sex (0.5%; $n = 567$) and remuneration (13.2%; $n = 14,835$). The majority were donated in Tbilisi (54.8%), followed by the regions of Imereti (15.1%) and Kvemo Kartli (11.5%). The overall donor prevalences for anti-HCV, HBsAg, HIV, and *T. pallidum* were 2.4, 1.7, 0.2 and 1.1%, respectively.

HCV

For anti-HCV, significant differences were seen by sex, age, and region in bivariate analysis (all $p < 0.0001$; Table 2). The highest rates were seen among male donors (2.8%), those aged 40 to 49 years (4.5%), and in the regions of Samegrelo (5.0%) and Shida Kartli (3.3%; Table 2). After adjusting for covariates, first-time donors were more likely to be anti-HCV positive than repeat donors (odds ratio [OR], 7.95; 95% confidence interval [CI], 7.12-8.88), as were paid (OR, 3.59; 95% CI, 3.21-4.02) and replacement donors (OR, 1.17; 95% CI, 1.02-1.34) as compared to VNRBDs (Table 3). Male (as compared to female) donors (OR, 2.37; 95% CI, 2.15-2.61) and age groups 30 years or older (as compared to those aged 18-29 years) were also more likely to be anti-HCV positive in the adjusted model. Anti-HCV positivity prevalence declined in donors from 2.3% in 2015 to 1.4% in 2017, an overall decline of 39.9% ($p < 0.0001$; Table 1).

Overall, 2.4% ($n = 2745$) of adult donors tested anti-HCV positive over the 3-year period. Of those, 41.0% ($n = 1126$) had an HCV nucleic acid amplification test (NAT) or HCV core antigen test to determine viremia (Fig. 1). Of those who underwent viremia testing, 78.6% ($n = 885$) had evidence of active infection, and 83.3% ($n = 737$) of those completed the additional diagnostic workup and evaluation necessary for enrollment in the national hepatitis C elimination program. After enrollment, 98.1% ($n = 723$) initiated treatment and 94.5% ($n = 683$) of those completed their treatment regimen. SVR, indicative of a cure, was ultimately achieved in 98.2% of those who were tested for SVR ($n = 494/503$).

HBV

In bivariate analysis, HBsAg positivity prevalence differed by sex, age, and region of donation (all $p < 0.0001$), and was highest in males (2.0%), donors aged 30 to 39 (2.7%), and in the regions of Adjara (3.4%), Samegrelo (2.7%), and Imereti (2.5%; Table 2). After adjusting for covariates, first-time donors (OR, 7.67; 95% CI, 6.66-8.84) were more likely to be HBsAg positive as compared to repeat donors, as were paid (OR, 2.00; 95% CI, 1.74-2.30) and replacement (OR, 1.25; 95% CI, 1.08-1.44) donors as compared to volunteers, males as compared to females (OR, 1.79; 95% CI, 1.60-2.00) and age groups 30 years or older as compared to those aged 18-29 years (Table 3). Donor hepatitis B prevalence declined by 27.2% from 1.5% in 2015 to 1.1% in 2017 ($p < 0.0001$; Table 1).

TABLE 1. Demographic characteristics of donor population and blood product collections in Georgia, 2015-2017

	Overall n (%) [*]	Blood donation year		
		2015	2016	2017
Donations	251,428	79,191	84,503	87,734
Unique donors	112,093	48,634	50,893	51,689
Sex [†]				
Female	35,137 (31.5)	14,494 (29.9)	15,956 (31.6)	16,330 (31.6)
Male	76,389 (68.5)	33,931 (70.1)	34,592 (68.4)	35,277 (68.4)
Age, y				
18-29	50,098 (44.7)	22,584 (46.4)	22,668 (44.5)	22,959 (44.4)
30-39	30,492 (27.2)	12,659 (26.0)	13,651 (26.8)	13,877 (26.8)
40-49	19,794 (17.7)	8,170 (16.8)	9,015 (17.7)	9,384 (18.2)
50+	11,709 (10.4)	5,221 (10.7)	5,559 (10.9)	5,469 (10.6)
Region of donation				
Tbilisi	61,457 (54.8)	28,289 (58.2)	28,196 (55.4)	27,704 (53.6)
Adjara	11,572 (10.3)	3,075 (6.3)	4,594 (9.0)	5,575 (10.8)
Imereti	16,935 (15.1)	6,902 (14.2)	7,240 (14.2)	6,639 (12.8)
Kvemo Kartli	12,919 (11.5)	5,687 (11.7)	6,581 (12.9)	7,396 (14.3)
Samegrelo	4,273 (3.8)	1,655 (3.4)	1,681 (3.3)	1,585 (3.1)
Shida Kartli	4,937 (4.4)	3,026 (6.2)	2,601 (5.1)	2,790 (5.4)
Donor type				
Repeat	55,116 (49.2)	30,267 (62.2)	31,822 (62.5)	32,071 (62.0)
First time	56,977 (50.8)	18,367 (37.8)	19,071 (37.5)	19,618 (38.0)
Remuneration				
Volunteer	39,882 (35.6)	13,747 (28.3)	17,703 (34.8)	16,573 (32.1)
Paid	30,806 (27.5)	18,705 (38.5)	18,640 (36.6)	16,964 (32.8)
Replacement	26,570 (23.7)	9,088 (18.7)	11,003 (21.6)	9,896 (19.1)
Missing	14,835 (13.2)	7,094 (14.6)	3,547 (7.0)	8,256 (16)
Anti-HCV results				
-	109,348 (97.6)	47,495 (97.7)	50,011 (98.3)	50,962 (98.6)
+	2,745 (2.4)	1,139 (2.3)	882 (1.7)	727 (1.4)
HBsAg results				
-	110,165 (98.3)	47,892 (98.5)	50,280 (98.8)	51,115 (98.9)
+	1,928 (1.7)	742 (1.5)	613 (1.2)	574 (1.1)
HIV				
-	111,862 (99.8)	48,559 (99.8)	50,807 (99.8)	51,619 (99.9)
+	231 (0.2)	75 (0.2)	86 (0.2)	70 (0.1)
<i>T. pallidum</i>				
-	110,831 (98.9)	48,122 (98.9)	50,519 (99.3)	51,313 (99.3)
+	1,262 (1.1)	512 (1.1)	374 (0.7)	376 (0.7)

^{*} The overall 3 years, 2015-2017, results shown represent cumulative infection prevalence rates over the 3 years period.
[†] Missing values not shown.
anti-HCV = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus.

HIV

HIV prevalence differed by sex ($p = 0.002$) and region ($p < 0.0001$), with the highest rates among males (0.2%) and donors in the regions of Adjara (0.5%) and Samegrelo (0.4%; Table 2). Rates were similar among all age groups at 0.2%. In multivariable analysis, first-time versus repeat (OR, 1.66; 95% CI, 1.25-2.21), paid versus volunteer (OR, 1.90; 95% CI, 1.29-2.79) and male as compared to female (OR 2.37; 95% CI, 2.15-2.61) donors were more likely to be HIV positive (Table 3). A significant decline over time was not observed.

T. pallidum

Prevalence of *T. pallidum* increased with age from 0.4% among 18- to 29-year-old donors to 2.8% among those aged 50 years or older ($p < 0.0001$). Region of collection was significant in bivariate analysis ($p < 0.0001$); prevalence was highest in Adjara (2.3%), Imereti (1.7%), and Samegrelo

(1.7%; Table 2). Prevalence did not differ significantly by sex in bivariate analysis. In multivariable analysis, first-time donors were more likely than repeat donors (OR, 2.08; 95% CI, 1.85-2.34) to be positive as were paid (OR, 3.86; 95% CI, 3.20-4.67) and replacement (OR, 2.39; 95% CI, 1.97-2.89) donors as compared to VNRBDs (Table 3). Also, males versus females (OR, 1.34; 95% CI, 1.19-1.52), and age groups 30 years or older versus those aged 18 to 29 years were more likely to be *T. pallidum* positive. *T. pallidum* rates declined in donors by 30.9%, from 1.1% in 2015 to 0.7% in 2017 ($p < 0.0001$; Table 1).

Coinfections

Over the 3 years of analysis, 5933 (5.3%) of 112,093 blood donors tested positive for at least one infectious marker. Of those, 223 (3.8%) were coinfecting with two markers; the most common coinfection was hepatitis B virus/HCV

TABLE 2. Bivariate analysis of infectious marker seropositivity by demographic characteristics of blood donors in Georgia, 2015-2017

	Infectious markers n (%)												p value
	Anti-HCV+	Anti-HCV -	p value	HBsAg +	HBsAg -	p value	HIV +	HIV -	p value	T. Pallidum +	T. Pallidum -	p value	
Overall	2,745 (2.4)	109,348 (97.6)		1,928 (1.7)	110,165 (98.3)		231 (0.2)	111,862 (99.8)		1,262 (1.1)	110,831 (98.9)		
Sex													
Female	596 (1.7)	34,541 (98.3)	<0.0001	423 (1.2)	34,714 (98.8)	<0.0001	50 (0.1)	35,087 (99.9)	0.002	406 (1.2)	34,731 (98.8)	0.56	
Male	2,135 (2.8)	74,254 (97.2)		1,492 (2.0)	74,897 (98.0)		179 (0.2)	76,210 (99.8)		852 (1.1)	75,537 (98.9)		
Age (years)													
18-29	577 (1.2)	49,521 (98.8)	<0.0001	570 (1.1)	49,528 (98.9)	<0.0001	103 (0.2)	49,995 (99.8)	0.70	208 (0.4)	49,890 (99.6)	<.0001	
30-39	824 (2.7)	29,668 (97.3)		828 (2.7)	29,664 (97.3)		69 (0.2)	30,423 (99.8)		273 (0.9)	30,219 (99.1)		
40-49	890 (4.5)	18,904 (95.5)		386 (2.0)	19,408 (98.0)		35 (0.2)	19,759 (99.8)		450 (2.3)	19,344 (97.7)		
50+	454 (3.9)	11,255 (96.1)		144 (1.2)	11,565 (98.8)		24 (0.2)	11,685 (99.8)		331 (2.8)	11,378 (97.2)		
Region													
Tbilisi	1323 (2.2)	60,134 (97.8)	<0.0001	784 (1.3)	60,673 (98.7)	<0.0001	103 (0.2)	61,354 (99.8)	<0.0001	491 (0.8)	60,966 (99.2)	<.0001	
Adjara	245 (2.1)	11,327 (97.9)		395 (3.4)	11,177 (96.6)		53 (0.5)	11,519 (99.5)		267 (2.3)	11,305 (97.7)		
Imereti	521 (3.1)	16,414 (96.9)		416 (2.5)	16,519 (97.5)		29 (0.2)	16,906 (99.8)		286 (1.7)	16,649 (98.3)		
Kvemo Kartli	280 (2.2)	12,639 (97.8)		159 (1.2)	12,760 (98.8)		20 (0.2)	12,899 (99.8)		77 (0.6)	12,842 (99.4)		
Samegrelo	213 (5.0)	4,060 (95.0)		117 (2.7)	4,156 (97.3)		17 (0.4)	4,256 (99.6)		74 (1.7)	4,199 (98.3)		
Shida Kartli	163 (3.3)	4,774 (96.7)		57 (1.2)	4,880 (98.8)		9 (0.2)	4,928 (99.8)		67 (1.4)	4,870 (98.6)		
Donor type													
Repeat	462 (0.8)	54,654 (99.2)	<0.0001	243 (0.4)	54,873 (99.6)	<0.0001	87 (0.2)	55,029 (99.8)	0.0005	403 (0.7)	54,713 (99.3)	<.0001	
First Time	2,283 (4.0)	54,694 (96.0)		1,685 (3.0)	55,292 (97.0)		144 (0.3)	56,833 (99.7)		859 (1.5)	56,118 (98.5)		
Remuneration													
Volunteer	672 (1.7)	39,210 (98.3)	<0.0001	574 (1.4)	39,308 (98.6)	<0.0001	67 (0.2)	39,815 (99.8)	0.12	215 (0.5)	39,667 (99.5)	<.0001	
Paid	879 (2.9)	29,927 (97.1)		400 (1.3)	30,406 (98.7)		63 (0.2)	30,743 (99.8)		354 (1.1)	30,452 (98.9)		
Replacement	836 (3.1)	25,734 (96.9)		727 (2.7)	25,843 (97.3)		66 (0.2)	26,504 (99.8)		496 (1.9)	26,074 (98.1)		
Missing	358 (2.4)	14,477 (97.6)		227 (1.5)	14,608 (98.5)		35 (0.2)	14,800 (99.8)		197 (1.3)	14,638 (98.7)		

anti-HCV = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus.

TABLE 3. Multivariable analysis of risk factors for infectious marker seroreactivity in blood donors in Georgia, 2015-2017

	Infectious markers												
	Anti-HCV positive			HBsAg positive			HIV positive			<i>T. pallidum</i> positive			
	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Ref	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Ref	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Ref	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Ref	
Sex													
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.67 (1.52-1.83)	2.37 (2.15-2.61)	1.64 (1.47-1.82)	1.79 (1.60-2.00)	1.65 (1.20-2.56)	1.65 (1.20-2.56)	1.65 (1.19-2.27)	0.97 (0.86-1.09)	1.34 (1.19-1.52)				
Age, y													
18-29	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
30-39	2.38 (2.14-2.65)	3.13 (2.80-3.51)	2.43 (2.18-2.70)	2.63 (2.35-2.94)	1.10 (0.81-1.49)	1.10 (0.81-1.49)	1.11 (0.81-1.53)	2.17 (1.81-2.60)	2.27 (1.89-2.73)				
40-49	4.04 (3.63-4.49)	5.60 (5.00-6.26)	1.73 (1.52-1.97)	1.85 (1.62-2.12)	0.86 (0.59-1.26)	0.86 (0.59-1.26)	0.86 (0.58-1.28)	5.58 (4.73-6.58)	5.67 (4.78-6.72)				
50+	3.46 (3.06-3.92)	4.97 (4.35-5.67)	1.08 (0.90-1.30)	1.23 (1.02-1.48)	1.00 (0.64-1.56)	1.00 (0.64-1.56)	1.07 (0.67-1.68)	6.98 (5.86-8.31)	7.04 (5.87-8.45)				
Region of donation													
Tbilisi	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Adjara	0.98 (0.86-1.13)	0.90 (0.77-1.04)	2.74 (2.42-3.09)	2.37 (2.07-2.71)	2.74 (1.97-3.82)	2.74 (1.97-3.82)	2.89 (2.00-4.17)	2.93 (2.52-3.41)	2.60 (2.19-3.07)				
Imereti	1.44 (1.30-1.60)	1.13 (0.99-1.29)	1.95 (1.73-2.20)	1.44 (1.23-1.68)	1.02 (0.68-1.54)	1.02 (0.68-1.54)	0.98 (0.60-1.60)	2.13 (1.84-2.47)	1.31 (1.09-1.57)				
Kvemo Kartli	1.01 (0.88-1.15)	1.17 (1.03-1.35)	0.96 (0.81-1.15)	1.14 (0.96-1.36)	0.92 (0.57-1.49)	0.92 (0.57-1.49)	0.85 (0.52-1.39)	0.74 (0.59-0.95)	0.75 (0.58-0.96)				
Samegrelo	2.39 (2.06-2.77)	1.84 (1.53-2.21)	2.18 (1.79-2.65)	1.52 (1.21-1.90)	2.38 (1.42-3.98)	2.38 (1.42-3.98)	2.39 (1.30-4.38)	2.19 (1.71-2.80)	1.27 (0.96-1.68)				
Shida Kartli	1.55 (1.32-1.83)	1.32 (1.10-1.57)	0.90 (0.69-1.19)	1.08 (0.82-1.42)	1.09 (0.55-2.15)	1.09 (0.55-2.15)	0.93 (0.45-1.94)	1.71 (1.32-2.21)	1.09 (0.83-1.42)				
Donor type													
Repeat	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
First time	4.94 (4.47-5.46)	7.95 (7.12-8.88)	6.88 (6.01-7.88)	7.67 (6.66-8.84)	1.60 (1.23-2.09)	1.60 (1.23-2.09)	1.66 (1.25-2.21)	2.08 (1.85-2.34)	2.43 (2.13-2.78)				
Remuneration													
Volunteer	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Paid	1.71 (1.55-1.90)	3.59 (3.21-4.02)	0.90 (0.79-1.02)	2.00 (1.74-2.30)	1.22 (0.86-1.72)	1.22 (0.86-1.72)	1.90 (1.29-2.79)	2.14 (1.81-2.54)	3.86 (3.20-4.67)				
Replacement	1.90 (1.71-2.10)	1.17 (1.02-1.34)	1.93 (1.73-2.15)	1.25 (1.08-1.44)	1.48 (1.05-2.08)	1.48 (1.05-2.08)	1.19 (0.78-1.81)	3.51 (3.00-4.12)	2.39 (1.97-2.89)				

* Final models included age, sex, region of donation, donor type, and remuneration status.
 HBsAg = Hepatitis B surface antigen; Anti-HCV = hepatitis C virus antibody; HIV = human immunodeficiency virus.

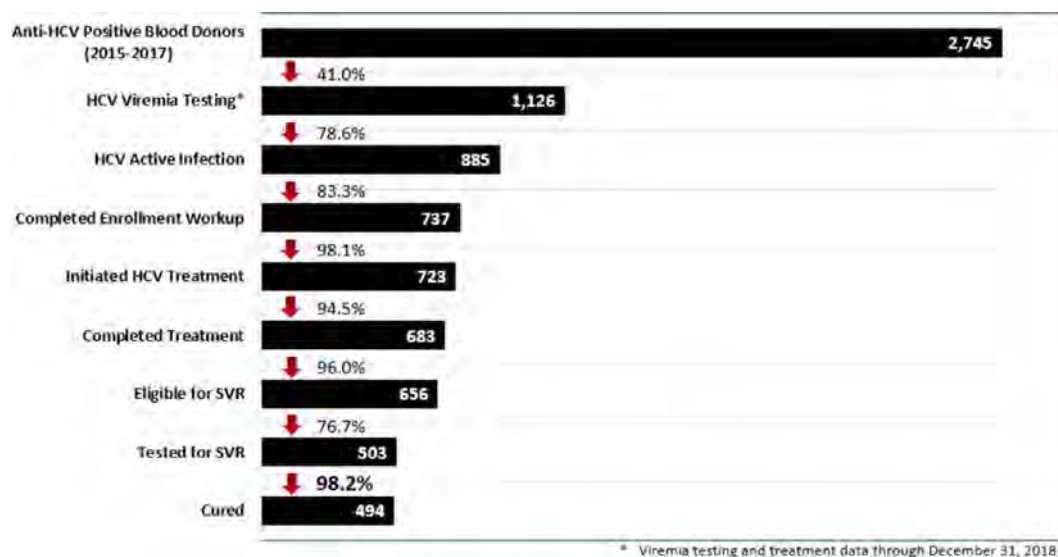


Fig. 1. Hepatitis C care cascade among anti-HCV-positive blood donors in Georgia. [Color figure can be viewed at wileyonlinelibrary.com]

among 90 donors, followed by 79 HCV/*T. Pallidum* coinfecting, and 35 with HBV/*T. pallidum* coinfection. Five donors tested positive for three infectious markers.

DISCUSSION

The findings indicate ongoing challenges surrounding blood transfusion safety in Georgia. Over a 3-year period, there was a high proportion of male, first-time, and paid or replacement blood donors, characteristics that were significantly associated with TTI seropositivity. Nonetheless, a significant decline in anti-HCV, HBsAg, and *T. pallidum*, with rates that were lower than those of the general population, suggest improved donor selection. Blood transfusion was identified as a risk factor for anti-HCV positivity in a 2015 serosurvey,⁹ prompting its inclusion as a key strategy in the national hepatitis C elimination program. Therefore, resources have been directed to improve blood safety, which is an area of need that might not otherwise have received the same attention. Further, blood donors found to be anti-HCV positive were referred to the hepatitis C treatment program for confirmatory testing. Pairing hepatitis C elimination with a blood transfusion safety initiative has been mutually beneficial.

Despite their public health role, blood centers deliberately separate themselves from provision of care given the potential incentive for test-seeking behavior, which confers risk of TTIs. The findings in Georgia challenge this dogma, as evidenced by a significant decline in anti-HCV, HBsAg, and *T. pallidum* positivity in blood donors, while still advancing the national hepatitis C elimination program. Georgia has also had a long-standing state-sponsored HIV program, which predates the national hepatitis C elimination program,

whereby blood donors who screen positive are referred for confirmatory testing and treatment (free of charge) if positive. Donor HIV seroprevalence remains low in Georgia, suggesting that absolute separation of blood collection from public health screening may not be necessary.

Donor recruitment and predonation evaluation (i.e., use of the donor history questionnaire) play an important role in the prevention of TTIs. Specifically, risk-based deferral reduces reliance on laboratory-based screening.¹⁶ Pertinent to our study, both first-time and paid blood donors are considered higher risk for TTIs than VNRBDs.¹⁷⁻²⁰ By contrast, repeat donation selects for individuals of lower infectious risk, given that those who screened positive during an initial donation would have been permanently deferred from blood donation.²¹ In Georgia, the odds of anti-HCV seroreactivity were almost eightfold higher in first-time as compared to repeat donors. Given that over half of donors in Georgia are first-time donors, there is a need to bolster recruitment, with renewed focus on transitioning first-time donors to a stable pool of repeat donors.

Paid donation is actively discouraged in most high-income countries,²²⁻²⁴ given that remuneration serves as a disincentive to admit any high-risk behavior during predonation screening. Consequently, the World Health Organization (WHO) advocates exclusively for VNRBDs.²⁵ Early evidence of risk includes a 1962 study that observed the incidence of posttransfusion viral hepatitis to be fourfold higher in recipients of blood from paid donors (i.e., as compared to those who received blood from VNRBDs).²⁴ Paid donation still remains common in former Soviet Union countries, where its risk has not been well characterized. Available data, including those from our study, corroborate the high risk¹⁹; paid donation in Georgia was associated with increased odds (e.g., over 3.5-fold for anti-HCV) of

infectious marker seropositivity. Ultimately, there is a need to convert the donor pool to a volunteer base. Such a complex undertaking requires an infrastructure to recruit donors, educate the general population and ultimately change human behavior.

Recent examples of countries that have transitioned to voluntary blood donor bases are few. China is one example that transitioned from paid to nonremunerated (albeit compulsory), and subsequently VNRBDs, under a broad blood safety initiative.²⁶ The latter included legislative changes coupled with a massive investment in infrastructure with reorganization and centralization of transfusion services, expanded quality management, and adoption of NAT. The transition in China took almost 15 years (1998-2012), which may be ascribed to the absence of voluntary donors at the start of the blood safety initiative.

There are other factors besides donor selection that are likely contributing to TTI risk in Georgia. Foremost is nearly exclusive reliance on antibody-based methods for donor screening. Incidence data are lacking for the major TTIs, but the high prevalence in the general population, particularly given suboptimal donor selection, raises concern of preseroconversion infections that are being missed.²⁰ HCV, in particular, has a long preseroconversion window period (approx. 70 days), which can otherwise be minimized (approx. 10 days) with donor HCV NAT.^{27,28} Adoption of HCV core antigen testing and ultimately HCV NAT screening of blood donations would reduce the window period, thus minimizing the risk of transfusion-transmitted HCV.²⁰ It would also confer other benefits to transfusion safety through addition of infrastructure and quality oversight. In the case of hepatitis B, NAT has the added benefit of being able to capture occult HBV infections (i.e., DNA+/HBsAg-), which otherwise go undetected in the absence of HBV core antibody testing. A counterpoint is that NAT is high cost and NAT yield (DNA/RNA+/Ab or Ag-) rates are highly variable.^{27,29-32} Assessment of the incremental benefit (i.e., above extant serological testing) is needed. In the case of Georgia, classic incidence modeling^{33,34} is an unlikely substitute for rigorous laboratory surveillance given incomplete data on key input variables for a determination of transmission risk.

The hepatitis C elimination program in Georgia has benefited blood transfusion safety. Similarly, blood donor screening has identified seroreactive individuals, enabling those donors to enter the cascade of care with confirmatory testing and treatment (when indicated), thus benefiting the elimination program directly. Nevertheless, only 41% of anti-HCV seropositive blood donors underwent further testing for viremia, indicating a need to improve linkage to care. While linkage to care is a challenge of the elimination program in general, the rates of donors who underwent follow-up testing after being identified through donor screening was below those in the general population (71.5%).³⁵ Given that in Georgia, SVR has been achieved in 98.2% of those who completed a standard hepatitis C antiviral regimen,³⁵

this merits investigation given the scope for improvement. While beyond the analysis, routine HCV confirmatory testing to ascertain the presence of viremia was initiated in 2018 for blood donors who are found to be HCV seroreactive during screening. This further highlights the reciprocal benefits of the hepatitis C elimination program.

The study had limitations. Foremost was the absence of confirmatory testing coupled with a lack of consistency in testing algorithms used (i.e., whether reactive samples underwent repeat and necessary additional diagnostic testing), heterogeneity in the assays (i.e., manufacturers of the screening kits) and variability in their level of automation (i.e., spanning rapid testing to fully automated platforms). This lack of standardization impeded interpretation of some of the results. For instance, anti-HCV positivity alone is not evidence of active infection; approximately 15% to 25% of infected individuals will clear the virus spontaneously.² For another, *T. pallidum* results were reported qualitatively without knowledge of whether treponemal-specific versus non-treponemal tests were used.³⁶ Nontreponemal tests have a risk of false positivity. While this detracts from the *T. pallidum* findings, we still believe that its presentation is important and supports the hypothesis that HCV elimination had broader benefits beyond HCV testing alone. Although not included in this analysis, there has been significant work in EQAS of donor screening. Such has served to document the variability in performance coupled with the diversity of testing platforms and methods in use for each TTI marker. As one example, of 12 laboratories that were evaluated during a round of EQAS, six assays were in use for anti-HCV alone. Second, nonuniform capture of data pertaining to remuneration (missing in 13% of donors) could impact the findings. Similarly, risk factors for infection, such as IDU or history of blood transfusion, were not available for analysis, which could bias results. Third, there is uncertainty surrounding the extent to which the seroprevalence findings are generalizable to the nondonor population. While blood donors offer a convenient population for infectious disease surveillance, blood donation selects for a healthier subset of the population.³⁷ Indeed, similar prevalence findings in a given donor and general population would suggest deficient selection and predonation screening. Fourth, differences concerning the predonation questionnaire could have introduced variations in seroprevalence by both blood center and the period of blood collection. Further, the absence of a post-donation questionnaire precluded identification of risks factors for TTIs, which could have helped to modify the predonation selection process. Finally, one cannot claim direct causal effect: The decline in donor HCV seroprevalence could reflect a general decline in prevalence stemming from the broader HCV elimination program.

In conclusion, the study highlights collateral benefit of a national hepatitis C elimination program on blood safety in Georgia. Investment in blood safety has afforded dual benefit, serving to contend with risks associated with blood

transfusion, a highly efficient mode of transmission for HCV, while aligning with the national program goals to enroll people with hepatitis C into treatment. Ongoing challenges in Georgia span donor recruitment, testing, quality assurance, and posttransfusion surveillance. Finally, the findings further show replacement and paid donation to be relatively unsafe with respect to infectious risk. Acknowledging the challenges surrounding donor mobilization in low- and low-middle-income countries to meet transfusion demand, the findings support a long-standing position by the WHO that favors blood collection from volunteer donors.²⁵

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CONFLICT OF INTEREST

EK, SS, MA, LG, TK, NC, SMK, AG, AT, VG, MN, FA, MI, and BS have disclosed no conflicts of interest. EMB is an investigator on trials to evaluate pathogen reduction technology funded by the US government. EMB has received education speaker fees for Grifols Diagnostics Solutions.

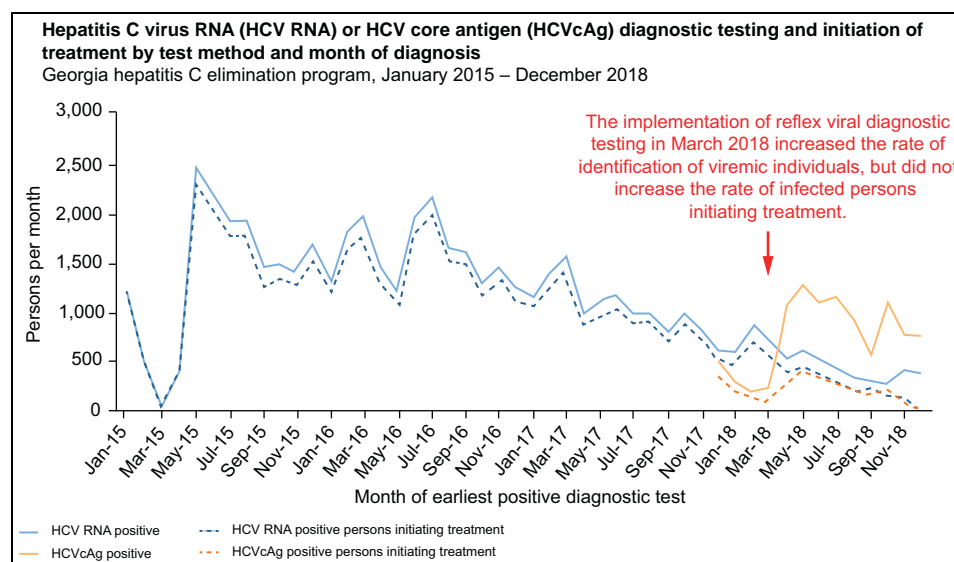
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Progress and challenges of a pioneering hepatitis C elimination program in the country of Georgia

Graphical abstract



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Lay summary

This report describes progress in Georgia's hepatitis C elimination program and highlights efforts to promote hepatitis C virus screening and treatment initiation on a national scale. Georgia has made progress towards eliminating hepatitis C, treating over 50,000 people, approximately one-third of the number infected, and achieving cure for 98.5% of those tested. However, identifying infected individuals and linking them to care remains challenging. Novel approaches to increase diagnostic testing can have unintended consequences further down the care cascade.

Highlights

- One-third of HCV-infected individuals in Georgia have received treatment.
- Use of reflex HCV core antigen greatly increased the number of individuals diagnosed with active infection
- Identification of HCV-infected individuals and treatment initiation continue to be major challenges to HCV elimination in Georgia.



Progress and challenges of a pioneering hepatitis C elimination program in the country of Georgia

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Background & Aims: Georgia, with a high prevalence of HCV infection, launched the world's first national hepatitis C elimination program in April 2015. A key strategy is the identification, treatment, and cure of the estimated 150,000 HCV-infected people living in the country. We report on progress and key challenges from Georgia's experience.

Methods: We constructed a care cascade by analyzing linked data from the national hepatitis C screening registry and treatment databases during 2015–2018. We assessed the impact of reflex hepatitis C core antigen (HCVcAg) testing on rates of viremia testing and treatment initiation (*i.e.* linkage to care).

Results: As of December 31, 2018, 1,101,530 adults (39.6% of the adult population) were screened for HCV antibody, of whom 98,430 (8.9%) tested positive. Of the individuals who tested positive, 78,484 (79.7%) received viremia testing, of whom 66,916 (85.3%) tested positive for active HCV infection. A total of 52,576 people with active HCV infection initiated treatment and 48,879 completed their course of treatment. Of the 35,035 who were tested for cure (*i.e.*, sustained virologic response [SVR]), 34,513 (98.5%) achieved SVR. Reflex HCVcAg testing, implemented in March 2018, increased rates of monthly viremia testing by 97.5% among those who screened positive for anti-HCV, however, rates of treatment initiation decreased by 60.7% among diagnosed viremic patients.

Conclusions: Over one-third of people living with HCV in Georgia have been detected and linked to care and treatment, however, identification and linkage to care of the remaining individuals with HCV infection is challenging. Novel interventions, such as reflex testing with HCVcAg, can improve rates of viremia testing, but may result in unintended consequences, such as decreased rates of treatment initiation. Linked data systems

allow for regular review of the care cascade, allowing for identification of deficiencies and development of corrective actions.

Lay summary: This report describes progress in Georgia's hepatitis C elimination program and highlights efforts to promote hepatitis C virus screening and treatment initiation on a national scale. Georgia has made progress towards eliminating hepatitis C, treating over 50,000 people, approximately one-third of the number infected, and achieving cure for 98.5% of those tested. However, identifying infected individuals and linking them to care remains challenging. Novel approaches to increase diagnostic testing can have unintended consequences further down the care cascade.

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Introduction

Georgia, a small middle-income country with a population of 3.7 million, located at the cross-roads of Europe and Asia, launched the world's first national hepatitis C elimination program in April 2015, with the ambitious goal of a 90% reduction in hepatitis C prevalence by 2020.¹ At the time the program was initiated, a national seroprevalence survey was conducted that estimated 150,000 Georgians (5.4% of the adult population) were living with HCV infection.² To achieve the elimination goal, Georgia implemented several strategies, including the identification and treatment of all HCV-infected people in the country.³ The feasibility of this strategic goal was made possible by an April 2015 memorandum of understanding (MOU) between the government of Georgia and Gilead Sciences, in which Gilead Sciences agreed to provide direct-acting antiviral (DAA) medications free-of-charge for eligible Georgians with HCV infection.^{3,4} The cost of DAAs in 2015 was prohibitive; without the MOU with Gilead Sciences this program could not have transpired. A large number of Georgians enrolled in the program during the first 3 years, and cure rates exceeded 95% among those treated and tested for cure (*i.e.*, sustained virologic response [SVR]).⁵ Yet, despite the availability of treatment and high cure rates, important challenges remain. We report on progress, key challenges, and lessons learned from Georgia's experience in identifying persons with HCV infection and linking them to hepatitis C care and treatment.

Keywords: Georgia; HCV; Hepatitis C diagnostic testing; Screening; Linkage to care; Reflex testing.

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Patients and methods

Georgia's hepatitis C elimination program

Georgia's hepatitis C elimination program provides hepatitis C testing free-of-charge in a variety of settings (Table 1). Initial screening is conducted using a rapid HCV antibody (anti-HCV) assay that tests for past or present HCV infection; people who screen positive on the antibody test are then referred to authorized treatment sites for diagnosis of active HCV infection by testing for HCV RNA using PCR, before being notified of their results and enrolled for treatment if they test positive for HCV RNA. To increase access by identifying and linking HCV-infected persons to care, in December 2017, HCV core antigen (HCVcAg) testing was introduced in a limited number of settings, and expanded in March 2018 when the program implemented reflex HCVcAg for all anti-HCV positive patients screened in hospitals, antenatal clinics, and blood banks. Each patient with a positive anti-HCV test during their visit had a serum sample obtained and shipped to the National Reference Laboratory (Lugar Center) in Tbilisi for centralized HCVcAg testing. HCVcAg has comparable sensitivity and specificity to HCV RNA testing for identifying active HCV infection.⁶ To minimize false-negative results, all specimens that tested negative or inconclusive by HCVcAg were subsequently tested for HCV RNA. National Centers for Disease Control and Public Health (NCDC) staff informed patients by telephone of the results of the diagnostic testing (HCVcAg or HCV RNA) and referred those that tested positive for treatment.

People confirmed to have active HCV infection by HCVcAg or HCV RNA testing are eligible to enroll in the treatment program.^{3,7} During the enrollment process, patients undergo additional diagnostic testing, including determination of HCV genotype, assessment of degree of liver fibrosis, and screening for comorbidities and contraindications to treatment. Patients found eligible for treatment based on results of the initial workup are prescribed a DAA treatment regimen according to national treatment guidelines⁸ and are followed during the course of their treatment. Within 12–24 weeks of completing treatment, patients are to return to the treatment site for HCV RNA testing to determine whether they had reached an SVR. Those with SVR are considered cured of their HCV infection. Initially, DAA treatment was exclusively sofosbuvir (SOF)-based and included ribavirin with or without pegylated interferon, depending on the HCV genotype, per national guidelines.⁴ Beginning in February 2016, the DAA combination sofosbuvir and ledipasvir (SOF/LED) was introduced, and treatment regimens were revised.⁴ For the first year of the program, treatment

was limited to those with severe liver disease, defined as MET-AVIR score correlating to F3 or F4 (based on liver elastography), or FIB-4 score >3.25.¹ In July 2016, the treatment program was expanded to include all people with HCV infection, regardless of level of liver fibrosis.

Although treatment is free for program enrollees, at the start of the program Georgians were required to pay for diagnostic testing, with prices determined by a sliding scale based on the patients' ability to pay. Recognizing testing costs as a barrier to hepatitis C elimination, the government of Georgia reduced the number of tests required for each patient⁹ and beginning in March 2018, provided HCV RNA or HCVcAg testing free-of-charge to all Georgians.

Data management and analysis

Every Georgian citizen is provided a unique national identification number for accessing healthcare services, including those offered through the hepatitis C elimination program. Georgia developed information systems to collect data from the hepatitis C screening registry, laboratories, and the hepatitis C treatment program, all of which can be linked using each person's unique national identification number. Although this number must be provided by all patients prior to enrolling in the treatment program, screening data from harm-reduction sites (including needle and syringe programs and opioid substitution therapy sites) are collected and reported anonymously to protect the privacy of clients. Beginning in 2017, harm-reduction sites began using the national identification number for consenting beneficiaries as well, allowing for analysis of data from these sites within the national hepatitis C elimination program.¹⁰

We analyzed national screening registry data from January 2015 through December 2018, as well as hepatitis C treatment data from April 2015 through December 2018, to assess the effectiveness of screening, linkage to care and treatment services, as well as outcomes (*i.e.* the care cascade). We calculated the percentage of people who screened positive for HCV antibody, and of those who were positive, we calculated the percentage who received diagnostic testing to determine active, viremic infection. Of those who tested positive for active HCV infection, the rates of treatment initiation, treatment completion, and testing for and achieving virologic cure (SVR) were assessed.

In order to better understand the effectiveness of HCVcAg reflex testing as a diagnostic tool for ensuring treatment initiation, we constructed 2 care cascades among hospitalized patients; one cascade included patients who screened positive for HCV antibody and were referred to a treatment center for diagnosis of active HCV infection, while the other included hospitalized patients who screened positive for HCV antibody and received reflex HCVcAg testing for diagnosis of active HCV infection, and if positive, were referred to a treatment center. To ensure comparability, we limited our care cascade analysis to 4 months following a positive HCV antibody test result and calculated each strata of the cascade based on the percent from the previous strata. The first cascade covered a period of time during which antibody screening was offered to all hospitalized patients and those who screened positive were referred to a treatment center to receive diagnostic viremia testing (1 September 2017 to 28 February 2018). The second cascade covered the period of time when antibody screening was offered to all hospitalized patients and those who screened positive had reflex testing for HCVcAg (1 March 2018 to 31 December 2018),

Table 1. Number of adults aged ≥18 years screened for anti-HCV antibody and percentage testing positive, by group screened – Georgia, 2015-2018.

Group/location of screening	No. adults (aged ≥18) screened	% anti-HCV positive
Blood donors	112,926	3.0%
NCDC	131,479	33.4%
Pregnant women/ANCs	108,776	0.6%
Hospitalized patients	468,479	4.7%
Harm-reduction beneficiaries	10,886	30.6%
Outpatients	612,452	5.0%
Prisoners	7,008	24.3%
Military recruits	19,759	1.5%
Persons living with HIV*	3,889	39.5%

ANC, antenatal clinic; NCDC, National Centers for Disease Control and Public Health. *Data through July 1, 2018.

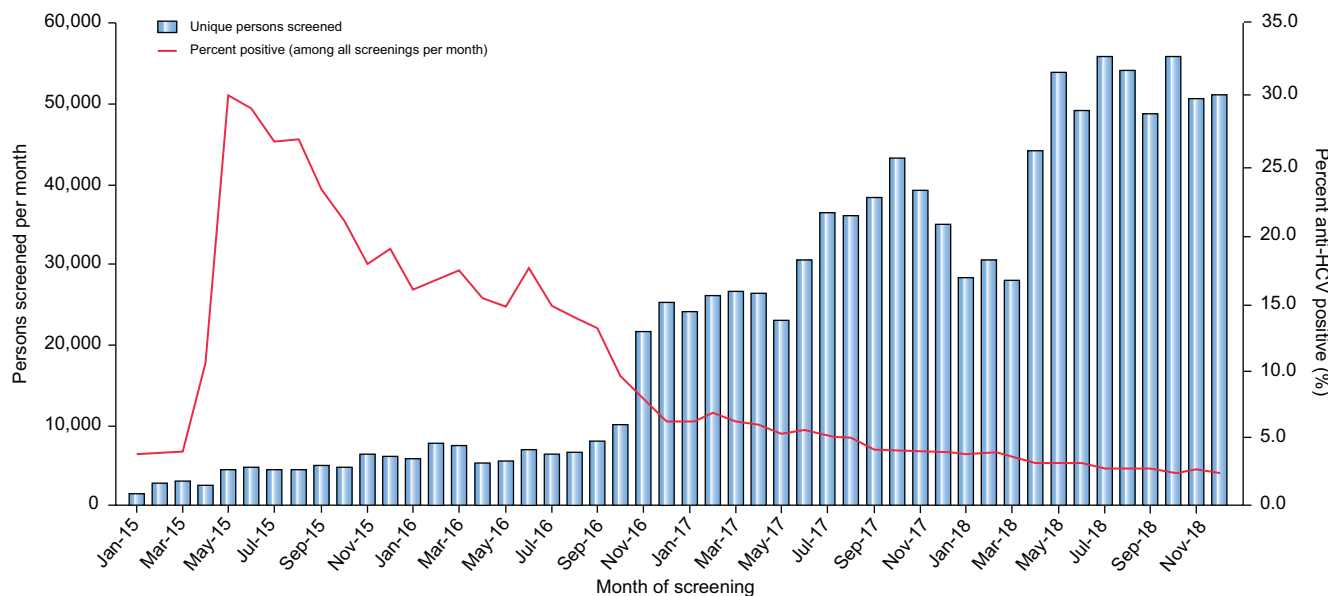


Fig. 1. Adults screened for anti-HCV antibody and percentage testing positive per month, Georgia hepatitis C elimination program, January 2015 – December 2018. (This figure appears in color on the web.)

with results and referral communicated to the patient by telephone as described in the methods.

For our analysis, individuals screened for hepatitis C multiple times were reported only once using data from their most recent screening, and screening rates relative to the adult population were determined using 2014 census data.^{2,11} We limited our analysis to adults aged ≥18 years although treatment is available for children aged 12–17. All data were de-identified prior to analysis. Statistical significance was determined using chi-square test with *p* value <0.05; analysis was performed in SAS version 9.4.

This analysis utilizes data from Georgia's hepatitis C elimination program, which was determined by Georgia's NCDC to be

a program evaluation and deemed by NCDC and CDC to be a non-research public health program activity.

**Results
Screening**

Screening programs for hepatitis C began in early 2015 in anticipation of the program launch in April of that year. As of December 31, 2018, a total of 1,101,530 adults (39.6% of the Georgian adult population) had been screened with a rapid anti-HCV test at various settings throughout the country, with more screened at outpatient settings than any other setting (Table 1). Screening rates greatly increased in November 2016 (Fig. 1) with implementation of the hospital-based screening program, which mandated medical facilities to offer anti-HCV screening to all hospitalized patients; since then, 466,087 hospitalized adults have been screened, an average of 33,292 patients per month through December 2018.

Of those screened, 98,430 (8.9%) had a positive anti-HCV result. The percentage of individuals who tested positive for anti-HCV peaked immediately following launch of the elimination program (29.8%) in May 2015 (Fig. 1). However, over time, the percentage of people who are anti-HCV positive has gradually decreased, dropping to 2.4% by December of 2018 (Fig. 1). Anti-HCV positivity rates varied by site, with the highest rates among harm-reduction centers and correctional facilities; the lowest rates were observed among antenatal clinic attendees (Table 1). Anti-HCV positivity rates also varied by age and sex, with the highest rates occurring among men aged 40–49 years (Fig. 2).

Diagnosis of active HCV infection

Of the 98,430 people with positive anti-HCV test results, 78,484 (79.7%) received HCV RNA or HCVcAg testing to determine whether they had active HCV infection; of those, 66,916 (85.3%) tested positive. Initially, those who screened positive on an antibody test were referred to a specialized treatment site for

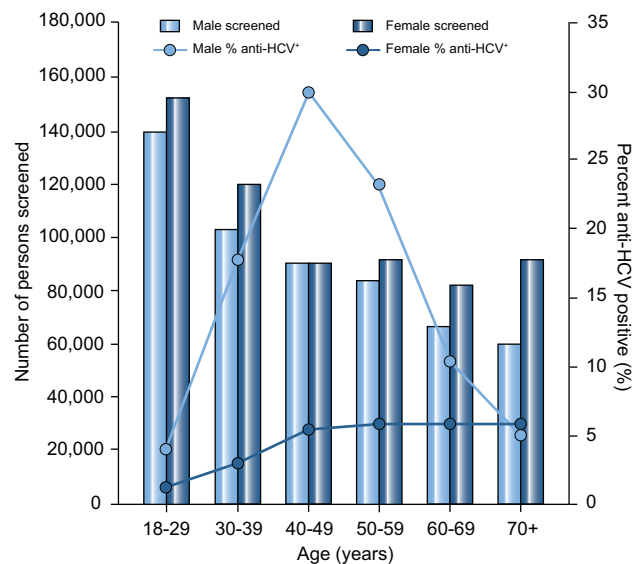


Fig. 2. Anti-HCV antibody screening and percentage testing positive by age and sex, Georgia, January 2015 – December 2018.

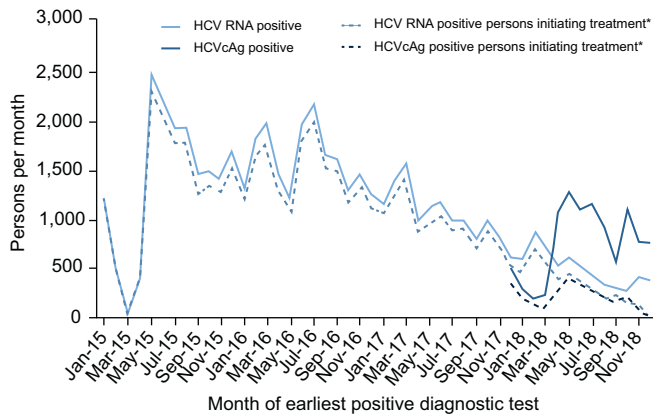


Fig. 3. HCV RNA or HCV core antigen diagnostic testing and initiation of treatment* by test method and month of diagnosis, Georgia hepatitis C elimination program, January 2015 – December 2018. *Beginning in December 2017 HCVcAg testing has been available in a limited number of harm-reduction sites, and these results are included in the analysis of hospitalized patients. HCVcAg, hepatitis C core antigen.

HCV RNA testing. Reflex HCVcAg testing was introduced broadly in March 2018 for those who screened positive for HCV antibody in hospitals, antenatal clinics, and blood banks. In the 6 months prior, from September 2017 – February 2018, 35.7% of individuals who screened positive for HCV antibody received viremia testing for active HCV infection (901/2,401 per month), compared to 74.1% during March – December 2018 (1,517/2,047 per month), a 97.5% increase. This reversed a downward trend since the peak in July 2016, when 2,641 received testing to diagnose active HCV infection (data not shown).

Treatment initiation and outcomes

From April 2015 through December 2018, of 66,916 persons diagnosed with active HCV infection by either HCV RNA or HCVcAg testing (introduced in December 2017), 52,576 (78.6%) initiated treatment. From the launch of the program through December 2017, rates of people testing HCV RNA positive closely paralleled rates of people initiating treatment, 44,617/49,153 (90.8%) (Fig. 3). However, from March 2018 through December 2018 (the period during which hospitalized patients, blood donors and pregnant women received reflex HCVcAg testing), only 2,254 (24.7%) of the 9,118 people who were HCVcAg positive initiated treatment compared with 2,939 (62.9%) of the 4,669 who received HCV RNA testing at a treatment center during the same time period, a decrease of 60.7% ($p < 0.05$).

When the program launched in April 2015, only 4 specialized sites, all located in the capital of Tbilisi were authorized as treatment sites, but by December 2018, treatment capacity had expanded to 41 specialized sites throughout the country. As of December 2018, a total of 52,576 adults had enrolled in the treatment program and initiated treatment. From April 2015 through May 2016, of 9,257 patients who entered treatment, 9,056 (97.8%) had severe liver disease (Fig. 4). When the program was expanded for all HCV-infected individuals, of 43,319 entering the treatment program from July 2016 through December 2018, only 9,691 (22.4%) had severe liver disease (Fig. 4).

The number of patients initiating treatment per month peaked at 4,593 in September 2016, following the treatment

expansion (Fig. 4). During the 2-year period from January 2017 through December 2018, an average of 1,041 patients per month began treatment (Fig. 4). As of December 2018, a total of 48,879 patients had completed at least one course of treatment (1,136 patients initiated a second course of treatment after relapse or discontinuation from their initial regimen). Among 46,574 eligible for SVR, 35,035 (75.2%) received SVR testing, of whom 34,513 (98.5%) ultimately achieved SVR after their latest course of treatment (Fig. 5). When considering the initial treatment regimen only (excluding retreatment data), viral cure rates were lower among 5,077 patients who received SOF-based regimens ($n = 4,170/5,077$; 82.1%) than among 30,236 who received SOF/LED-based regimens ($n = 29,765/30,236$; 98.4%). SVR rates also varied by degree of fibrosis for both SOF-based and SOF/LED-based regimens, and by genotype only among patients receiving SOF-based regimens (data not shown).⁵ Among 52,576 patients initiating treatment, 1,280 (2.4%) discontinued treatment, with the most common causes for not completing treatment being death (49.4%; $n = 632$), self-discontinuation (19.9%; $n = 255$), and loss to follow-up (16.3%; $n = 208$). Of those who died during treatment, the majority 370/632 (58.5%) had severe liver disease (METAVIR scores of F3 or F4).

Effectiveness of HCVcAg reflex testing on treatment initiation

To understand the impact of reflex HCVcAg on treatment initiation, to minimize bias, we did a sub-analysis of care cascades limited to hospitalized patients who received reflex HCVcAg viremia testing to those who were referred for RNA testing. A lower percent, 2,976/6,011 (49.5%) of those who were anti-HCV positive received diagnostic viremia testing when referred to a treatment center for RNA testing, compared to 3,191/4,205 (75.9%) of those diagnosed by reflex HCVcAg testing ($p < 0.05$). However, among those who were diagnosed with active HCV infection by RNA testing, 1,937/2,508 (77.2%) initiated treatment, compared to 600/2,368 (25.3%) of those diagnosed by HCVcAg ($p < 0.05$). When we compare the 2 care cascades, we find that, overall, among those screened and diagnosed by RNA 1,937/6,011 (32.2%) initiated treatment, compared to 600/4,205 (14.3%) of those in the HCVcAg cascade ($p < 0.05$) (Fig. 6).

Discussion

The availability of all-oral DAAs capable of curing HCV infection has transformed the global landscape, providing a novel opportunity to eliminate chronic hepatitis C as a public health threat.^{12,13} Georgia was the first country in the world to formally launch a national hepatitis C elimination program but has recently been joined by other countries, such as Egypt, Iceland, and Australia.^{12,14,15} Georgia's elimination program stands out for its comprehensive approach, with innovative strategies in place to not only identify those infected with HCV and link them to care and treatment services, but also to improve access to quality diagnostics, safeguard the nation's blood supply, and reduce infection with blood borne pathogens among people who inject drugs and in the healthcare setting.^{1,7,16}

Since the launch of the program in 2015, numerous lessons learned have been identified and shared, not only successes, but challenges.^{3,7,8,16} Nevertheless, access to treatment has been, and continues to be, the cornerstone of the program. Georgia has made remarkable progress since launching the elimination program in 2015; of the estimated 150,000 persons living with hepatitis C in the country,² approximately one-third have been

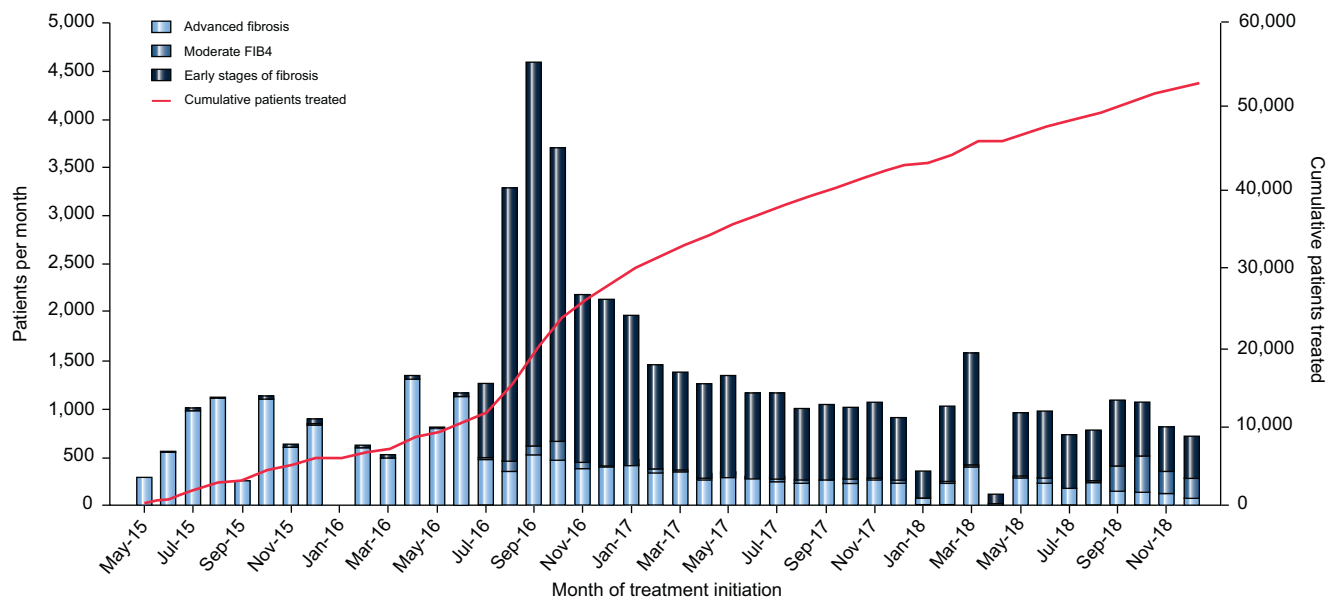


Fig. 4. Fibrosis stage of patients initiating treatment per month, Georgia hepatitis C elimination program, January 2015 – December 2018. Advanced fibrosis defined as fibroscan \geq F3 or FIB-4 $>$ 3.25. Early stages of fibrosis: fibroscan $<$ F3 or FIB-4 $<$ 1.45. Moderate: FIB-4 1.45–3.25 with no fibroscan result. For all classifications, priority given to fibroscan result when available. FIB-4, Fibrosis-4 score. (This figure appears in color on the web.)

identified and received treatment,⁵ averting an estimated 3,000 deaths and preventing over 20,000 new HCV infections.¹⁷ Yet despite this success, Georgia faces challenges in identifying and linking to care the missing thousands still living with hepatitis C in the country that were highlighted in this report.

The program began with 4 treatment centers and limited options for screening. Georgia rapidly expanded access to treatment, and as of December 2018, more than 40 treatment centers were operating throughout the country, some of which were located in high-risk settings like correctional facilities and harm-reduction sites. Enrollment at the start of the program in 2015 and 2016 was high, and can be attributed in part to the large proportion of people who were anti-HCV positive, as high as 30% in May of 2015 (Fig. 1). This is likely reflective of the large

number of people who knew they were infected with HCV prior to program implementation, but had not yet sought or could not afford treatment. The 2015 serosurvey found that 36% of people who tested anti-HCV positive were aware of their infection, but few had sought care, citing the availability and cost of treatment as major barriers.²

During the 18-month period between May 2015 and January 2017, about 20% (30,000 of the 150,000 living with HCV infection in Georgia) of the target population entered treatment, with a spike observed after enrollment restrictions were expanded to include all infected persons regardless of stage of liver disease (Fig. 4). However, the number of patients entering treatment began to decline precipitously in late 2016, likely reflecting an exhaustion of the number of patients who were aware of their infection and motivated to receive treatment- the “low hanging fruit” of the program. In response, the program took steps to decrease barriers, including lowering costs of diagnostic testing, increasing the number of screening and treatment sites, and implementing innovative programs to identify and link to care HCV-infected people. Although treatment was offered to Georgians free-of-charge, diagnostics were not, and testing-related costs were subsequently identified as a barrier to program enrollment, which may partly explain the 25% who were eligible but did not receive SVR testing.^{9,18} In response, the program began aggressively lowering the costs of diagnostics, and simultaneously simplifying testing and care guidelines; for example, the requirement of some diagnostics, such as HCV RNA testing at 4 weeks of treatment and at end-of-treatment, have been eliminated. Studies are underway to identify additional barriers to testing for remaining harder-to-reach HCV-infected populations.

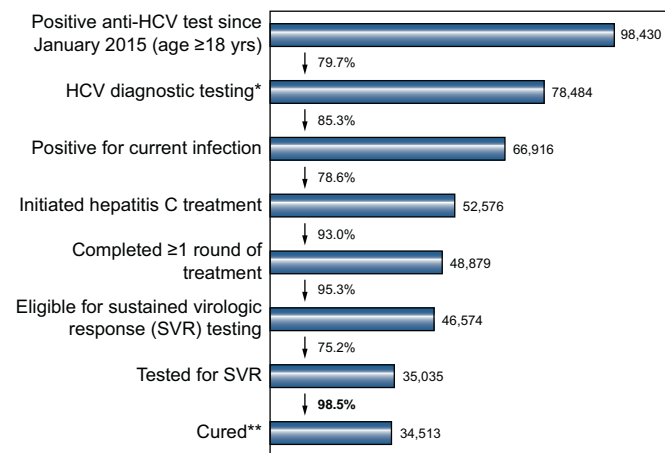


Fig. 5. Georgia hepatitis C elimination program care cascade, April 28, 2015 – December 31, 2018. *Either hepatitis C virus RNA or core antigen testing. **Includes retreatments. Among 35,329 persons tested after their 1st round of treatment, 33,951 (96.1%) achieved SVR. 1,136 persons initiated a 2nd round of treatment, with 93.4% (596/638) of those tested achieved SVR.

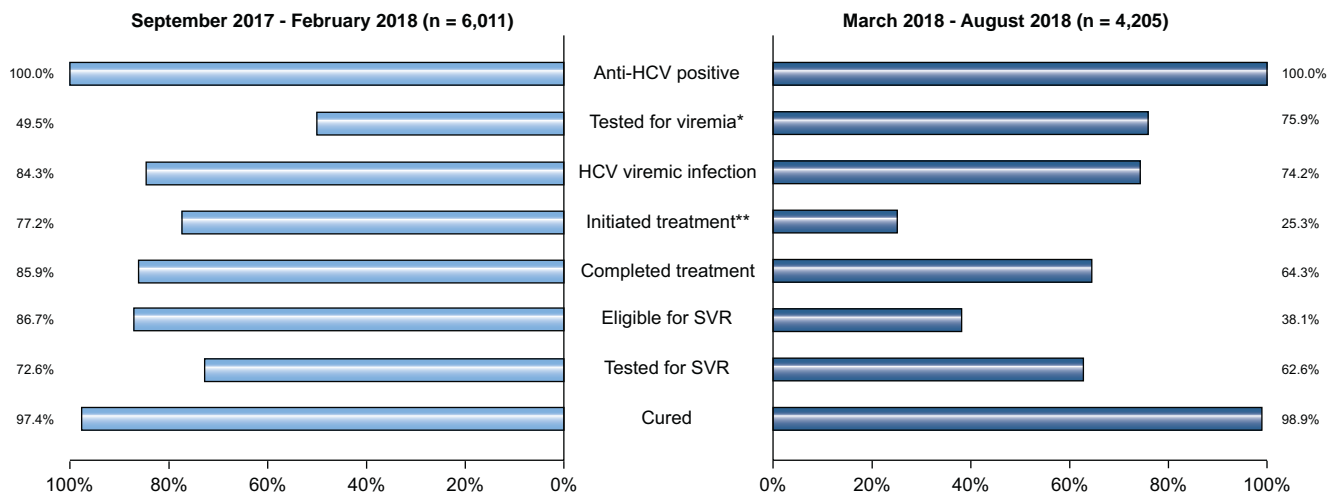


Fig. 6. Care cascade, by percentage, among hospitalized patients before and after the implementation of HCVcAg reflex testing. *September 2017-February 2018 anti-HCV positive patients referred to specialized clinics for viremia testing; March 2018-August 2018 anti-HCV positive patients received reflex CoreAg testing. **Dates for treatment and outcomes extend 4 months beyond end of screening period. HCVcAg, hepatitis C core antigen; SVR, sustained virologic response.

infection. To address this gap, the hospital-based hepatitis C screening program, the blood banks, and antenatal clinics, which screen a large proportion of the monthly total screened, began conducting reflex HCVcAg testing in March 2018. This strategy proved effective in nearly doubling the rate of persons receiving viremia testing following a positive screening test. Paradoxically, while there was a dramatic increase in persons receiving diagnostic testing to determine active infection, rates of treatment initiation among those diagnosed in these settings (hospitals, antenatal clinics, and blood banks), even with reflex testing, were lower than those in other settings (e.g., outpatient care, harm-reduction settings, prisons). This observation may be multifactorial. First, there are inherent differences among the populations seeking healthcare in different settings. Perhaps more significantly, the shift in provider responsibility for linking patients diagnosed with active HCV infection to care from hepatitis C treatment provider clinics (the only sites conducting HCV RNA testing prior to reflex testing) to the National Reference Laboratory, which relies on NCDC for communication of results to patients by telephone, clearly could have contributed to the lower rates observed. Patients who obtained HCV RNA testing at treatment sites had voluntarily taken an important step in seeking care by going to a treatment site, while reflex testing, which automated the process, did not rely on the patient's initiative to seek further care. It is likely that many patients who received reflex testing may not have even been aware of their HCV infection, counseled on the results, or motivated to access treatment. To examine this issue more closely, we analyzed a subset of hospitalized patients and compared the care cascade among those patients receiving diagnostic testing by referral for RNA testing to the patients receiving reflex HCVcAg testing. This analysis revealed that overall treatment initiation rates were significantly lower among the patients tested with the HCVcAg. Of course, this is not a function of the HCVcAg test, but rather the processes of informing and counseling patients of their HCV infection. This is a classic example of the law of unintended consequences.

The reduced treatment initiation rates associated with reflex HCVcAg testing have been recognized and are being addressed

by the program. The ability to recognize and react to challenges can be attributed to Georgia's advanced hepatitis C information system, which links screening, laboratory diagnostics, and treatment data and allows for near real-time analysis and feedback on program performance. This system affords policy makers the ability to quickly identify deficiencies and make evidence-based adjustments. In response to the drop-off in treatment initiation rates, the program is developing and piloting strategies, such as deploying patient navigators in hospitals, and decentralizing diagnostic testing, to overcome this gap in linkage to care. The Georgia experience highlights challenges that may be encountered when screening, testing for viremia, and treatment are conducted at different sites.

A major initiative in 2019 is integration of screening, care and treatment services in primary healthcare settings and harm-reduction centers throughout the country. This allows patients and harm-reduction beneficiaries to receive hepatitis C care and treatment services in familiar and convenient locations, a strategy that has been demonstrated to be effective.^{19,20} Georgia plans to expand treatment services to every district in the country and all harm-reduction sites, expanding not only geographic access, but also providing services to the most marginalized and at-risk populations. The results of these efforts could be the key to accessing the "hardest to reach" populations.

The first of its kind, Georgia's comprehensive HCV elimination program, which was recently recognized as the first European Association for the Study of Liver- international Liver Foundation (EILF) Center of Excellence in Viral hepatitis Elimination,¹⁶ can inform hepatitis C elimination efforts in countries throughout the world. Challenges, as well as best practices, have been identified and are being shared. Georgia's 2015 serosurvey paved the way for the program's success by yielding accurate estimates of the hepatitis C burden and facilitating target setting.² Gilead Science's commitment to providing program participants with medications free-of-charge resulted in an early and robust enrollment of persons already aware of their HCV infection, but unable to afford out-of-pocket treatment costs. Although the cost of medications was a major barrier in 2015 when Georgia launched the program, given the dramatic reductions in cost of

DAA in many countries, this may no longer be an important impediment in much of the world.²¹ However, it is clear from the experience in Georgia that even with no-cost medications, reaching a substantial proportion of those living with hepatitis C can be a major challenge; additional barriers encountered included the cost of diagnostics, which contributed to relatively low treatment initiation and SVR testing rates, geographic access to care, stigmatized and marginalized populations, and lack of awareness or motivation by the public and possibly by health care providers. Another important lesson from Georgia's HCV elimination program is that a comprehensive, evidence-based program with near real-time access to program data and indicators, which allows for nimble programmatic adjustments, may be the key to overcoming barriers and achieving timely and cost-effective hepatitis C elimination.

Other countries embarking on hepatitis C elimination efforts will likely experience barriers similar to those encountered by the country of Georgia.^{12,15,22} Georgia offers best practices and lessons learned that can be adapted when developing national elimination plans, particularly in reducing barriers to identifying HCV-infected individuals and linking them to curative treatment. Georgia will encounter new, unforeseen challenges, and must continue to identify and develop innovative approaches to overcoming barriers as the country strives to meet its elimination goals. This country's robust hepatitis C elimination efforts can serve as a model for countries developing programs not only to eliminate viral hepatitis, but other public health threats as they emerge.

Abbreviations

ANC, antenatal clinic; DAA, direct-acting antiviral; FIB-4, Fibrosis-4 score; HCVcAg, hepatitis C core antigen; MOU, memorandum of understanding; NCDC, National Centers for Disease Control and Public Health; SVR, sustained virologic response

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

FA developed the study concept proposal. FA, SS, MN developed the final analysis plan. SS performed statistical analysis. FA, SS, MN interpreted results and drafted the manuscript. AG, TT, LG, DS, MB, TT, LS, JZ, BS, VG provided critical review. All authors approved the final version of the manuscript.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2019.11.019>.

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Screening and linkage to care for hepatitis C among inpatients in Georgia's national hospital screening program

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ABSTRACT

The country of Georgia initiated an ambitious national hepatitis C elimination program. To facilitate elimination, a national hospital hepatitis C screening program was launched in November 2016, offering all inpatients screening for HCV infection. This analysis assesses the effectiveness of the first year of the screening program to identify HCV-infected persons and link them to care. Data from Georgia's electronic Health Management Information System and ELIMINATION-C treatment database were analyzed for patients aged ≥ 18 years hospitalized from November 1, 2016 to October 31, 2017. We described patient characteristics and screening results and compared linked-to-care patients to those not linked to care, defined as having a test for viremia following an HCV antibody (anti-HCV) positive hospital screening. Of 291,975 adult inpatients, 252,848 (86.6%) were screened. Of them, 4.9% tested positive, with a high of 17.4% among males aged 40–49. Overall, 19.8% of anti-HCV+ patients were linked to care, which differed by sex (20.6% for males vs. 18.4% for females; $p = .019$), age (23.9% for age 50–59 years vs. 10.7% for age ≥ 70 years; $p < .0001$), and length of hospitalization (21.8% among patients hospitalized for 1 day vs. 16.1% for those hospitalized 11+ days; $p = .023$). Redundant screening is a challenge; 15.6% of patients were screened multiple times and 27.6% of anti-HCV+ patients had a prior viremia test. This evaluation demonstrates that hospital-based screening programs can identify large numbers of anti-HCV+ persons, supporting hepatitis C elimination. However, low linkage-to-care rates underscore the need for screening programs to be coupled with effective linkage strategies.

1. Introduction

Globally, in 2015 an estimated 71 million people were infected with hepatitis C virus (HCV), with approximately 400,000 HCV-attributable deaths (World Health Organization, 2017). Georgia, a lower-middle income Eurasian country with a population of 3.7 million people (The World Bank, 2017) has a high prevalence of HCV infection. Results from a nationally representative seroprevalence survey among Georgian adults (≥ 18 years) in 2015 found an HCV antibody (anti-HCV)

prevalence of 7.7% (equating to approximately 215,000 persons) and a chronic hepatitis C prevalence of 5.4% (HCV RNA positive by PCR) (approximately 150,000 persons) (Hagan et al., 2019).

On April 28, 2015, in collaboration with international partners including technical assistance from U.S. Centers for Disease Control and Prevention (CDC) and a commitment from Gilead Sciences to provide direct-acting antiviral hepatitis C medications (DAAs) free of charge for all persons living with HCV infection in the country, Georgia launched an ambitious national hepatitis C elimination program (Gvinjilia et al.,

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2016; Nasrullah et al., 2017a; Nasrullah et al., 2017b). The country set a goal of 90% reduction in hepatitis C prevalence by 2020 with the following targets: (1) testing 90% of HCV-infected persons, (2) treating 95% of people with chronic HCV infection, and (3) curing 95% of persons treated for HCV infection (*Strategic Plan for the Elimination of Hepatitis C Virus in Georgia 2016–2020*, 2016). A national hepatitis C treatment database was established to monitor and evaluate program progress.

Screening for hepatitis C began nationally in January 2015, before the launch of the treatment program (Nasrullah et al., 2017a). Rapid anti-HCV testing is provided to Georgian residents at various settings free of charge (Nasrullah et al., 2017a), and a national screening registry was established. By the end of 2017, the treatment program had increased capacity by expanding to 31 sites throughout the country; however, the number of patients entering treatment, after peaking in late 2016, began to decrease with a smaller pool of untreated persons aware of their infection (Nasrullah et al., 2017a). In response, the Georgian government ramped up screening efforts at various locations including antenatal clinics, blood banks, harm reduction centers and prisons (Georgia Ministry of Health, Labour and Social Affairs, 2019). On September 16, 2016, the Ministry of Health released Resolution (N445), which mandated that medical facilities offer and then provide anti-HCV testing to all willing hospital inpatients regardless of diagnosis, and record both positive and negative results in their electronic Health Management Information System (HMIS) established in 2011. The only exceptions to these provisions were for inpatients with documentation of screening within 6 months or ongoing/past hepatitis C antiviral treatment. On November 1, 2016, the national hospital hepatitis C screening program launched nationwide.

We analyzed retrospective data from the hospital screening program and the national treatment program to assess the effectiveness of the hospital program in screening and linkage to care over its first year of implementation.

2. Methods

2.1. Data source

When the elimination program launched, a treatment database (STOP-C) was developed, and was upgraded in June 2016 (ELIMINATION-C) to meet the growing demands of the program (Mitraka et al., 2015). The database was designed to monitor patients enrolled in the treatment program, from confirmation of active HCV infection (with HCV RNA or core-antigen testing), through treatment outcome, including testing for cure (i.e. sustained virologic response [SVR]).

In 2011, Georgia implemented its HMIS for all hospitals in the country. Pursuant to the government decree on screening, results from inpatients' rapid anti-HCV test and/or enzyme assay are entered into the HMIS (Health Management Information System (HMIS) Georgia, n.d.). Two fields were added to the HMIS to indicate: (1) whether HCV screening was performed (Yes/No) and (2) HCV screening result (Positive/Negative).

Monthly, the Georgia National Centers for Disease Control (NCDC) receives electronically transmitted data for patients of all ages admitted to hospitals the previous month, including: national identification number; basic demographic information (age, sex); discharge diagnoses, comorbidities, and complications (ICD10 codes); discharge/death date; length of hospitalization; HCV screening performed; and HCV screening result.

Data for this analysis was compiled from 4 different sources. Hospital HMIS data from November 1, 2016 to October 31, 2017 was used to determine the number of unique inpatients and those who were screened for hepatitis C. For linkage to care analysis and care continuum results among those linked to care, hospital data were cross-referenced with the ELIMINATION-C treatment database as well as vital statistics from November 1, 2016 to January 31, 2018, to allow a

minimum 90 days follow-up for each patient after hospital discharge. Finally, to quantify the national impact of the hospital program, consolidated records were reviewed for all screening venues throughout the country from May 1, 2016 to April 31, 2017. Patients' encrypted unique identification numbers, which are common to all data sources, allow for cross-referencing and deduplication in screening and treatment records.

2.2. Definitions

Definitions for unique hospital inpatients, patients ever/not HCV screened, anti-HCV positive, not anti-HCV positive, linked to care, and not linked to care are outlined in Table 1. Briefly, linkage to care was defined as receiving HCV viremia testing after hospital discharge. During the evaluation period, all anti-HCV positive patients had to visit a specialized HCV treatment provider site for viremia testing at the patients' expense, the results of which are all entered into ELIMINATION-C. Patient inclusion/exclusion criteria are depicted in Fig. 1. For hospital diagnosis comparisons, "Liver-related: Any Hepatitis" ICD10 codes included: B15-B17, B18.0-B18.2, B18.8-B18.9, B19.0, B19.9, and K73, while "Liver-related: Non-Hepatitis" ICD10 codes included: B67.0, B67.5, B67.8, C22, I82.0, K70-K72, K74-K77, R17, R18, R16.0, R16.2, T51, T64, and Z20.5 (Supplementary Table S1). All other ICD10 codes in HMIS were included in the "Non-Liver related" category.

2.3. Data analysis

Descriptive analysis of hospital screening records was performed to elucidate characteristics of patients screened for anti-HCV, patients screening positive, and those linked to care. Patients ever screened were compared to those not screened to assess factors associated with being screened while hospitalized. Likewise, we compared linked-to-care patients to those not linked to care to determine characteristics of anti-HCV positive patients who sought viremia testing following their visit. Statistically significant associations in bivariate analysis were determined using Chi-square test with a significance level of $p < .05$. All statistical analysis was conducted in SAS version 9.4.

This analysis utilizes data from Georgia's hepatitis C elimination program, which was determined by Georgia's NCDC to be a program evaluation and deemed to be a non-research public health program activity.

3. Results

3.1. Screening

Records from 270 out of a total 280 hospitals throughout Georgia were reviewed. Records for 134,641 patients who were < 18 at the time of their hospital visit were excluded. Between November 1, 2016 and October 31, 2017 there were 378,552 documented hospital admissions for 300,615 unique adult patients admitted to and discharged from hospitals in Georgia. We excluded from this analysis 8640 patients with missing, incomplete or indeterminate screening results, leaving 291,975 patients from 253 hospitals that were included in this evaluation. Overall, 252,848 (86.6%) inpatients were screened for anti-HCV (Fig. 1) with 12,385 testing positive, for an overall anti-HCV positivity prevalence of 4.9%. The proportion of inpatients screened was lowest in the first month of the program (65.3%) and increased gradually, reaching 91.6% in October 2017 (data not shown). Of those screened, 40,071 (15.6%) were screened more than once; 29,890 (11.8%) were screened twice and 10,181 (4.0%) screened ≥ 3 times within the evaluation period. Those screened more than once had a median of 2 (IQR: 2, 3) hospital visits during the evaluation period, and the majority (58.7%; $n = 23,514$) were screened ≥ 2 times at the same hospital.

The median age of screened patients was 52 years (interquartile

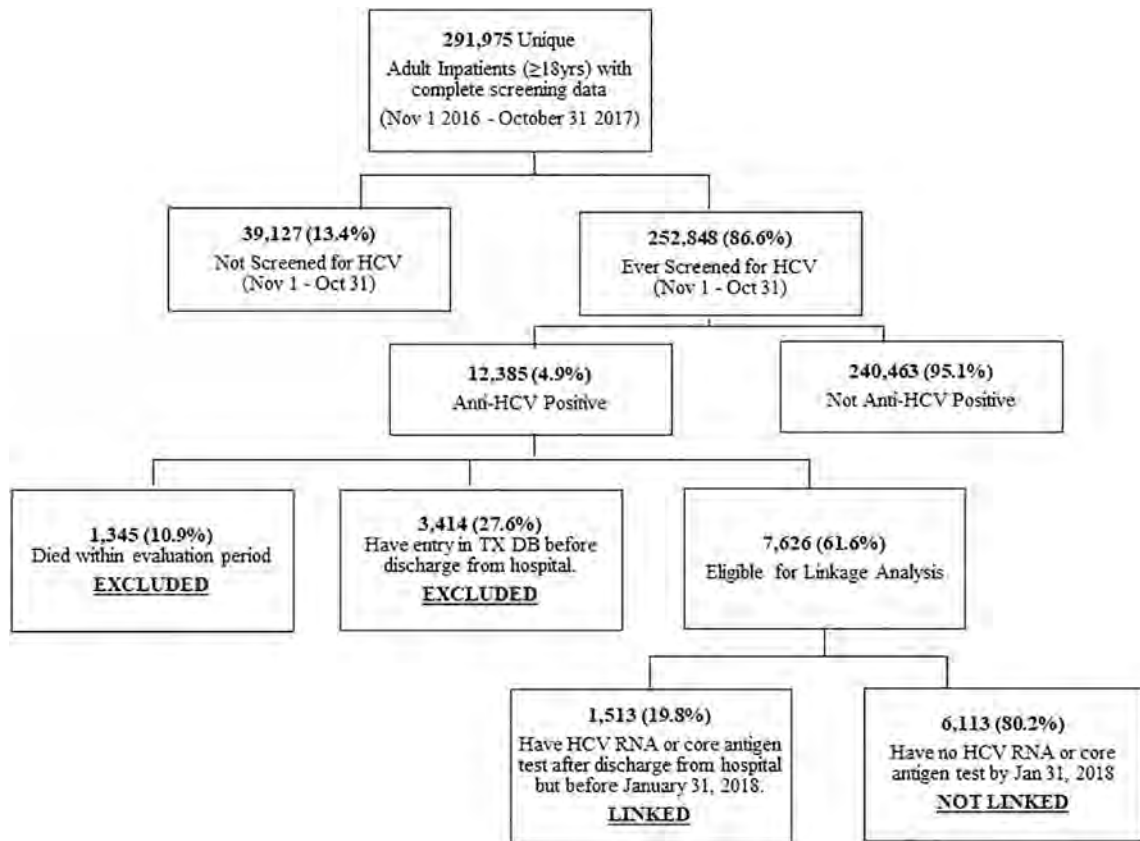


Fig. 1. Inclusion and exclusion methodology for data analysis.

range [IQR]: 31, 68), and women (58.8%) were screened more than men (41.2%); more women ($n = 170,942$) than men ($n = 121,033$) were hospitalized during the evaluation period (Table 2). Although there were statistical differences ($p < .05$), screening rates were similar among men (86.0%) and women (87.0%), and among different age groups (range: 85.2% to 87.2%) (Table 2). More than 40,000 women aged 18–29 years were screened, the largest number of any age/sex group (Fig. 2). Screening varied by length of hospital stay, with patients hospitalized 2–10 days being more likely to be screened than those hospitalized for one day, or > 10 days ($p < .0001$) (Table 2).

Anti-HCV positivity was highest in December 2016 at 5.8% and decreased from February through October 2017 to a low of 3.7% (data not shown). Anti-HCV positivity was higher among men, with 8496/104,100 (8.2%) compared to 3889/148,748 (2.6%) of women testing positive ($p < .0001$). Patients aged 18–29 years had the lowest anti-HCV positivity (1.1%), while patients aged 40–49 had the highest anti-HCV positivity (10.2%) ($p < .0001$). Anti-HCV positivity was higher among males aged 40–49 years (17.4%) than any other age/sex group (Fig. 2). Positivity among females increased with age, from 0.7% among women aged 18–29 years to 4.4% among women aged ≥ 70 years

Table 1
Definitions of patient categories for screening and linkage to care.

Patient category	Definition	Exclusion criteria
Unique hospital inpatient	Any adult (≥ 18 years old at time of death or discharge from the hospital) inpatient with at least one discharge or death date documented between November 1, 2016 and October 31, 2017.	Patients < 18 years old at the time of their first discharge or death date within the evaluation period (treatment was not available for this population in Georgia at the time of assessment).
Ever HCV screened	Any unique inpatient with HCV screened field answer “yes” and a result (positive or negative) entered in the HCV result field. For patients with hospital admissions in the evaluation period, if they had a valid screening result during at least one admission they were counted in the ever HCV screened group.	Any entry with no response in the HCV screening field. Entries with an HCV screened answer “yes” but without a result entered in the HCV result field.
Not HCV screened	Any unique inpatient with HCV screening field answer “no” during hospitalization and no result in the HCV result field.	Entries with “no” in the HCV screening field but with a result (positive/negative) in the HCV result field.
Anti-HCV positive	Affirmative HCV screening field and a positive anti-HCV result. A patient with at least one valid anti-HCV positive result during the evaluation period was defined as anti-HCV positive	
Not anti-HCV positive	Affirmative HCV screening field and negative anti-HCV results on each screening (if screened multiple times, all results negative).	
Linked to care	Any anti-HCV positive patient who had a documented HCV RNA or HCV core antigen test to confirm active infection after the date of hospital discharge, but on or before January 31, 2018.	Patients with documented HCV RNA or core antigen test results in the HCV treatment database dated before the discharge date for the hospital admission in which they screened positive.
Not linked to care	Any anti-HCV positive patient who did not have a test for active HCV infection at one of the HCV testing provider sites within the period between hospital discharge and January 31, 2018.	Patients with documented death date within the evaluation period.

Table 2
 Characteristics of adult patients with complete hepatitis C screening data admitted to the hospital at least once between November 1, 2016 and October 31, 2017, Georgia.

Characteristics	All patients		Patients ever screened ^a		Patients not screened		Chi-square p-value
	n	n	%	n	%		
Overall	291,975	252,848	86.6	39,127	13.4		
Gender							
Female	170,942	148,748	87.0	22,194	13.0	< .0001	
Male	121,033	104,100	86.0	16,933	14.0		
Age category (years)							
18–29	64,288	56,033	87.2	8,255	12.8	< .0001	
30–39	44,224	38,126	86.2	6,098	13.8		
40–49	31,017	26,438	85.2	4,579	14.8		
50–59	39,062	33,566	85.9	5,496	14.1		
60–69	47,397	41,246	87.0	6,151	13.0		
70+	65,987	57,439	87.0	8,548	13.0		
ICD10 code (diagnosis, comorbidity, complication) ^b							
Liver-related: any viral hepatitis	1293	1141	88.2	152	11.8	< .0001	
Liver-related: non-hepatitis	2025	1487	73.4	538	26.6		
Non-liver related	288,657	250,220	86.7	38,437	13.3		
Length of hospital stay (days) ^c							
1	73,337	59,968	81.8	13,369	18.2	< .0001	
2–5	172,442	152,880	88.7	19,562	11.3		
6–10	31,698	27,991	88.3	3,707	11.7		
> 10	14,497	12,008	82.8	2,489	17.2		

^a Patients ever screened (in evaluation period) defined as those patients with HCV screened (yes) and a result in the HCV result field (positive/negative). Patients with multiple admissions who met these criteria at least once included in this group.

^b Liver-related: any hepatitis ICD10 codes included: B15-B17, B18.0-B18.2, B18.8-B18.9, B19.0, B19.9 and K73. Liver-related: non-hepatitis ICD10 codes included: B67.0, B67.5, B67.8, C22, I82.0, K70-K72, K74-K77, R17, R18, R16.0, R16.2, T51, T64, and Z20.5. All other ICD10 codes found in the 066 system were included in the non-liver related category.

^c One patient had missing data on length of hospital stay.

(Fig. 2).

Nationally, among all hepatitis C screening venues, there was a 3.2-fold increase in screening after the hospital program began; an average of 46,648 unique adults were screened per month during November 2016 – April 2017, compared to an average 14,623 per month between May 2016 – October 2016 (data not shown).

3.2. Linkage to HCV care

Of the 12,385 patients who tested anti-HCV positive, 3414 (27.6%) had linked to HCV care (i.e. went to a specialized HCV treatment provider site to receive viremia testing) prior to their hospitalization, and an additional 1345 (10.9%) had a recorded death date within the evaluation period – 94.0% of whom were hospitalized for non-hepatitis-related conditions – totaling 4759 patients excluded from the linkage to care analysis. The remaining 7626 (61.6%) were eligible for the analysis as they had not been linked to hepatitis C care at the time of their hospitalization. Of those eligible, 1513 (19.8%) were successfully linked, while 6113 (80.2%) were not linked to care within 90 days following their discharge.

When we compared patients linked to care to those not linked to care, men (20.6%) were more likely than women (18.4%) to be linked ($p = .019$) (Table 3). Linkage rates varied by age ($p < .0001$) with persons aged ≥ 70 years having the lowest linkage rate (10.7%), although the total number of patients testing positive was highest in this age group. The linkage rate was highest among inpatients hospitalized for one day (21.8%) and decreased to 16.1% among those hospitalized > 10 days ($p = .023$). Length of hospital stay was associated with patient age ($p < .0001$), with those aged 40–59 years more likely to be hospitalized > 10 days (data not shown). Patients with a diagnosis of any viral hepatitis infection were more likely to be linked than patients with non-viral hepatitis, liver-related diagnoses or those with no diagnosis of liver disease ($p < .0001$) (Table 3).

Patients linked to care with a median of 41 (IQR: 12, 116) days between their discharge date and the date of their viremia test. Out of the 1513 patients linked to care, 21.6% ($n = 327$) had their viremia test within 10 days of hospital discharge, while 31.9% ($n = 482$) took > 90 days to be linked to care. Time to linkage did not differ significantly by age or sex.

Among the 1513 patients linked to care, 858 (56.7%) initiated HCV treatment by the end of the evaluation period. Of them, 615 (71.7%) had already completed treatment and of 330 eligible (≥ 12 weeks post-

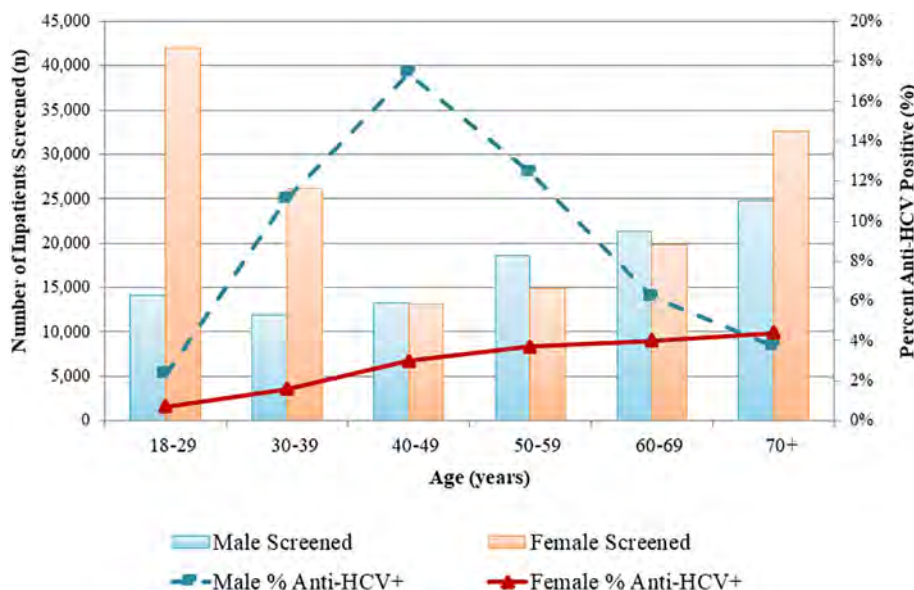


Fig. 2. Number of patients screened and percent tested positive for anti-HCV, by age and sex, November 2016 – October 2017 ($n = 252,848$), Georgia.

Table 3

Characteristics of adult patients who screened anti-HCV positive while admitted to the hospital between November 1, 2016 and October 31, 2017 and linked to care, Georgia.

Characteristic	Anti-HCV positive ^a	Linked to care ^b		Not linked to care		Chi-square p-value
	n	n	%	n	%	
Overall	7626	1513	19.8	6113	80.2	
Gender						
Female	2754	507	18.4	2247	81.6	.019
Male	4872	1006	20.6	3866	79.4	
Age category (years)						
18–29	495	80	16.2	415	83.8	< .0001
30–39	1134	237	20.9	897	79.1	
40–49	1526	354	23.2	1172	76.8	
50–59	1605	383	23.9	1222	76.1	
60–69	1327	295	22.2	1032	77.8	
70+	1539	164	10.7	1375	89.3	
Length of hospital stay (days)						
1	1369	298	21.8	1071	78.2	.023
2–5	4316	859	19.9	3457	80.1	
6–10	1215	239	19.7	976	80.3	
> 10	726	117	16.1	609	83.9	
ICD 10 code (diagnosis, comorbidity, complication) ^c						
Liver-related: any viral hepatitis	343	123	35.9	220	64.1	< .0001
Liver-related: non-hepatitis	146	41	28.1	105	71.9	
Non-liver related	7137	1349	18.9	5788	81.1	

^a Anti-HCV positive patients defined as a patient with screening field “yes” and HCV result field “positive.” Patients with multiple admissions who met these criteria are included in this group. Here $n = 8971$, which is the sum of patients linked to care and not linked to care. From the original 12,385 anti-HCV positive patients, 3412 were excluded from the linkage to care data/analysis due to entry in ELIM-C treatment database prior to hospitalization and screening date and an additional 1345 were excluded for having died in the analysis period (see inclusion/exclusion flow diagram).

^b Linked to care patients defined as any anti-HCV positive patient (previously defined) who subsequently received documented HCV RNA or core-antigen testing at one of the diagnostic testing provider sites after date of hospital discharge but before January 31, 2018.

^c Liver-related: any viral hepatitis ICD10 codes included: B15-B17, B18.0-B18.2, B18.8-B18.9, B19.0, B19.9, and K73. Liver-related: non-hepatitis ICD10 codes included: B67.0, B67.5, B67.8, C22, I82.0, K70-K72, K74-K77, R17, R18, R16.0, R16.2, T51, T64, and Z20.5. All other ICD10 codes in the 066 system were included in the non-liver related category.

treatment completion) and tested for SVR, 326 (98.8%) achieved cure.

4. Discussion

To accelerate identification of HCV infected persons in the country, on November 1, 2016, Georgia launched a program to screen for hepatitis C every patient admitted to any hospital in the country. By analyzing records of nearly 300,000 inpatients, our evaluation reflects great progress made over the first year of the program, and highlights areas in need of improvement. Over a quarter million adult patients were screened for hepatitis C throughout the year, representing nearly 90% of adult inpatients, and monthly national screening rates tripled in the first 6 months of the hospital screening program. Overall, 4.9% of patients screened positive, and 19.8% of eligible anti-HCV positive patients were linked to care. We identified factors associated with linkage to care, which could guide efforts to improve this objective and help Georgia reach its hepatitis C elimination goals.

The proportion of inpatients screened increased as the program progressed, which could be explained by increased access to necessary testing materials at hospitals, and/or increased awareness of the governmental mandate among hospital personnel over time – hospitals could be fined for non-compliance, and automated reminders were built into HMIS to remind personnel to screen patients and document results. Previous studies have identified management guidelines and financial resources (Estevez et al., 2016) as well as physician noncompliance and data errors (Patil et al., 2016) to be barriers to hepatitis C screening among healthcare professionals. Therefore, training and acclimation to new procedures among hospital personnel may have increased over the first year of the screening initiative. We found significant differences in screening rates by age and sex; males were less likely to have been screened than females, and the age group least likely to be screened was patients aged 40–49. This is counterproductive to elimination goals, as these two groups had the highest prevalence of anti-HCV positivity

among those screened. Targeted screening could be considered to ensure those most at risk of hepatitis C are screened routinely. Screening men aged 30–59 instead of general screening may increase efficiency, as 13.6% of men aged 30–59 were anti-HCV positive, compared to only 2.5% of females in the same age group.

The proportion of patients screening anti-HCV positive decreased over time. The cause of this is unknown but could be a reflection of the successes of the national HCV treatment program (Gvinjilia et al., 2016; Nasrullah et al., 2017a), which had identified > 45,000 and treated > 40,000 chronically infected Georgians by the end of our evaluation period (Georgia Ministry of Health, Labour and Social Affairs, 2019). Those aware of their status, if hospitalized, may have declined re-testing thereby reducing anti-HCV positivity among those screened. It's also possible that some providers were still practicing more thorough screening among high-risk patients early in the program, despite the mandate to offer screening to all. Of those who screened positive, 27.6% had received a viremia test prior to their hospital visit, indicating that added scrutiny to prevent redundant screenings could save valuable resources. Many states in the United States require all hospitalized baby boomers (born between 1945 and 1965) to be screened for hepatitis C, and one study in New York state found 63.7% of detected anti-HCV patients had already been diagnosed or treated prior to their admission, more than double our findings (Hung et al., 2016). Furthermore, > 23,000 inpatients were screened multiple times within the same hospital during our evaluation period, indicating that mandatory screening could lead to over-testing. Linkage of the HMIS to the national screening registry and ELIMINATION-C treatment database would allow for real-time determination of a patient's screening and hepatitis C treatment history. This could facilitate a “flagging” system to help eliminate unnecessary screening of patients already aware of their status.

While identification of anti-HCV positive patients is essential for the success of the hepatitis C elimination program, referral of anti-HCV

positive patients for further evaluation and provision of comprehensive treatment services is equally important. At the time of this evaluation, after a patient screened anti-HCV positive, he/she needed to independently seek HCV viremia testing, and subsequent evaluation and treatment at a specialized hepatitis C treatment site. Whereas screening is conducted at a wide range of facilities throughout Georgia, access to hepatitis C evaluation services and treatment was more limited. As of October 2017, treatment was provided at 31 health facilities throughout the country by 139 physician providers (Mitraka et al., 2015). Since the elimination program's inception in 2015, a substantial proportion of anti-HCV positive patients have failed to seek viremia testing or further evaluation/treatment (Mitraka et al., 2015). Evaluation of the hospital screening program suggests a similar challenge: only 19.8% of patients eligible for linkage to care analysis sought follow-up testing after their hospital discharge. Thus, over four-fifths of the anti-HCV positive patients identified by the hospital program were not linked to care. At the time of this evaluation, there was no systematic method for counseling patients or informing them where to go for further care, but was instead at the hospitals' discretion, and based on their varying resources and capabilities. Standardized methods for screening and linking patients to care could be considered. Interventions in which hospital personnel assist in coordinating HCV-infected patients' next steps can significantly improve linkage to care (Deming et al., 2018). Another potential barrier is financial; although screening and treatment are free of charge, the cost of diagnostics, including viremia testing, determination of genotype and degree of liver fibrosis, as well as other testing during treatment, were the responsibility of the patient (Gvinjilia et al., 2016; Nasrullah et al., 2017a). These costs could be significant for persons of low income. In 2017, Georgians' average monthly nominal earnings were 999 Georgian lari (GEL) (National Statistics Office of Georgia (GEOSTAT), n.d.), and the cost of pre-treatment diagnostic testing ranged from 279 to 335 GEL (Adamia, 2018), or 28–34% of their monthly income. We were unable to assess financial barriers, though other studies in Georgia have shown costs to be a barrier (Averhoff et al., 2019). At the time of this analysis only 57% of linked-to-care patients had initiated treatment, far lower than the 92% reported nationally (Nasrullah et al., 2017a). This proportion is likely to increase as patients have more time to enroll in the program, but could also reflect challenges among persons with possible comorbid conditions that required their hospitalization, in addition to financial barriers.

Linkage-to-care varied by age, with patients aged ≥ 70 years obtaining viremia testing at substantially lower rates than other age groups. Although our analysis could not assess the reasons for this, it could be related to costs, mobility and access to treatment sites, comorbid conditions, or other social and behavioral factors. A study of inpatient screening among baby boomers at a medical center in the United States (Mehta et al., 2017), in which linkage to care was defined as scheduling a follow-up appointment after RNA confirmation, found linkage rates for that age group slightly less than our analysis (18% for baby boomers vs. 22.2% in our 60–69 year age group). Length of hospital admission also influenced linkage to care and screening; patients with longer hospital stays sought HCV viremia testing and were screened at lower rates. This could suggest that more critical conditions requiring longer hospital admissions may have taken priority over diagnosing past or current HCV infection (Junius-Walker et al., 2010). This finding appears independent of age; the age group least likely to be linked to care (≥ 70) were less likely than those aged 40–59 year to have an extended hospital stay.

Providing increased access to diagnostic testing and treatment is a priority in the elimination program, and a rollout of decentralization of care began in 2018, whereby HCV-infected individuals can seek treatment at selected primary care and harm reduction sites (Adamia, 2018). Several other interventions, such as lowering costs of diagnostics are being implemented (Adamia, 2018). This hospital screening program was expanded by a follow-up governmental decree in May of 2018 to

ensure all emergency room patients are offered HCV screening in addition to inpatients. Additionally, in March 2018, Georgia instituted a policy in which hospitals are mandated to obtain and send serum specimen of all patients who screen anti-HCV positive to the national reference laboratory for reflex HCV core antigen testing, free of charge to patients (Averhoff et al., 2019). This change in policy resulted in increased viremia testing, though rates of subsequent hepatitis C treatment initiation decreased among patients diagnosed viremic - the next step in the care continuum that the elimination program must seek to facilitate (Averhoff et al., 2019).

Interventions to improve screening and linkage to care should decrease barriers to the program. However, it is essential to continually monitor and evaluate the care continuum to identify deficiencies and bolster screening and treatment rates. Since the time of this evaluation, hospital screening data was incorporated into a national screening registry, creating a unified database that allows monitoring of the hepatitis C continuum of care at the individual-patient level (Georgia Ministry of Health, Labour and Social Affairs, 2019). This more efficient information system can help prevent unnecessary and repeat screenings, thereby reducing costs.

4.1. Study limitations

There were several limitations to this evaluation. First, erroneous data entries and entries with missing HCV fields (2.9% of patients) in the HMIS could have affected our findings. Second, the HMIS did not collect information to assess reasons for the screening and linkage-to-care rates observed. The database did not report eligibility criteria (e.g. previous screening results, prior initiation of hepatitis C treatment, patient refusal), nor demographic information such as income or education level; thus, it was impossible to determine reasons for variations in screening rates across different populations. Also, no data was available regarding post-screening counseling to confirm when, how, or if the patient was informed of his/her results, if the patient was counseled about how to seek follow-up diagnostic testing, the importance thereof, or if any potential barriers to linkage were identified. Third, some patients may have had contraindications to hepatitis C treatment, or terminal diseases that would hinder follow-up diagnostics, leading to underestimation of linkage-to-care rates. Finally, anti-HCV positive patients discharged at the end of the evaluation period had only 90 days to seek diagnostic testing, though our analysis found that nearly a third of patients linked to care took > 90 days to do so.

5. Conclusion

Identification of HCV-infected persons, and subsequent care and treatment is essential for the success of Georgia's hepatitis C elimination program. Our evaluation reports on the first year of the country's initiative to screen all hospital inpatients for hepatitis C. We highlighted great progress that was made to identify anti-HCV positive patients, as well as some shortfalls that can be addressed to promote screening and linkage to care in the country and can help meet their hepatitis C elimination targets.

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Disclaimer

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CRedit authorship contribution statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Original Research

The burden and epidemiology of hepatitis B and hepatitis D in Georgia: findings from the national seroprevalence survey

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ABSTRACT

Objectives: The burden of hepatitis B virus (HBV) and hepatitis D virus (HDV) infections is unknown in Georgia. This analysis describes the prevalence of hepatitis B and coinfection with HDV and the demographic characteristics and risk factors for persons with HBV infection in Georgia.

Study design: This is a cross-sectional seroprevalence study.

Methods: A cross-sectional, nationwide survey to assess hepatitis B prevalence among the general adult Georgian population (age ≥ 18 years) was conducted in 2015. Demographic and risk behavior data were collected. Blood specimens were screened for anti-hepatitis B core total antibody (anti-HBc). Anti-HBc-positive specimens were tested for hepatitis B surface antigen (HBsAg). HBsAg-positive specimens were tested for HBV and HDV nucleic acid. Nationally weighted prevalence estimates and adjusted odds ratios (aORs) for potential risk factors were determined for anti-HBc and HBsAg positivity.

Results: The national prevalence of anti-HBc and HBsAg positivity among adults were 25.9% and 2.9%, respectively. Persons aged ≥ 70 years had the highest anti-HBc positivity (32.7%), but the lowest HBsAg positivity prevalence (1.3%). Anti-HBc positivity was associated with injection drug use (aOR = 2.34; 95% confidence interval [CI] = 1.46–3.74), receipt of a blood transfusion (aOR = 1.68; 95% CI = 1.32–2.15), and sex with a commercial sex worker (aOR = 1.46; 95% CI = 1.06–2.01). HBsAg positivity was associated with receipt of a blood transfusion (aOR = 2.72; 95% CI = 1.54–4.80) and past incarceration (aOR = 2.72; 95% CI = 1.25–5.93). Among HBsAg-positive persons, 0.9% (95% CI = 0.0–2.0) were HDV coinfecting.

Conclusions: Georgia has an intermediate to high burden of hepatitis B, and the prevalence of HDV coinfection among HBV-infected persons is low. Existing infrastructure for hepatitis C elimination could be leveraged to promote hepatitis B elimination.

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Introduction

Globally, an estimated 257 million persons (3.5% of the world's population) were living with chronic hepatitis B virus (HBV) infection in 2015,¹ and an estimated 900,000 persons died from HBV infection, primarily from the sequelae of chronic infection,

liver failure, and hepatocellular carcinoma.¹ Superinfection with hepatitis D virus (HDV) worsens the outcome of HBV infection, and an estimated 5% of HBV-infected persons are also coinfecting with HDV.¹

Introduction of hepatitis B vaccine into the childhood vaccination schedule has dramatically reduced the prevalence of chronic HBV infection from 4.7% to 1.3% in children <5 years of age globally.¹ HBV infection occurring during birth and early childhood accounts for most of the burden of chronic hepatitis B; the majority of people currently living with HBV infection were born before the hepatitis B vaccine was widely available.¹ In 2018, global coverage of three doses of hepatitis B vaccine was 84%, however, birth dose coverage was only 42%; many developing countries are not using

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the birth dose of hepatitis B vaccine as part of their national strategy.² In 2016, the World Health Assembly endorsed viral hepatitis elimination goals, defined as a reduction of 90% in incidence and 65% in mortality worldwide of both hepatitis B and hepatitis C by 2030.^{1,3}

Georgia, a lower-middle-income country with a population of 3.7 million situated at the crossroads of Europe and Asia, implemented a national program in 2015 to eliminate hepatitis C by 2020.^{4–6} To inform this effort, the country conducted a national seroprevalence survey in 2015 to estimate the burden of hepatitis C virus (HCV) infection, but also included testing for HBV infection.^{7–9} The hepatitis B vaccine has been included in Georgia's national immunization schedule since 2002, and the birth dose has been included since 2003. Coverage for routine vaccination has been >90% for most years during 2005–2018.¹⁰ This article describes the national prevalence of HBV infection and associated risk factors, as well as coinfection with HDV, in Georgia's adult population born before 1998.

Methods

Study population

A cross-sectional, nationwide survey for hepatitis B and hepatitis C prevalence among the general population aged ≥ 18 years was conducted in Georgia in 2015 using a stratified, multistage cluster design with random sampling.⁹ A sample size of 7000 was based on an estimated hepatitis C prevalence of 6.7%, a design effect of 2, and a 70% anticipated response rate.⁹ After obtaining informed consent from the study participants, interviewers collected demographic information, medical and behavioral history, information about potential risk factors and exposures, knowledge about HBV infection, and vaccination information. A blood sample was collected from the study participants. Trained interviewers verbally administered the survey in the language of the participant (either Georgian, Armenian, Russian, or Azerbaijani). Data were entered into handheld electronic devices in real time and uploaded to a secure database. The details of sampling methods, specimen and data collection details, and hepatitis C testing and statistical methods are described in the study by Hagan et al.⁹

Laboratory methods

Blood specimens were centrifuged, and serum was separated, aliquoted, and stored at -20°C . Weekly, the specimens were shipped on dry ice to the Lugar Center, Georgia's national reference laboratory, where they were stored at -70°C until tested. The specimens were screened for anti-hepatitis B core total antibody (anti-HBc) by enzyme immunoassay (anti-HBc Ab, EIA IVD; Dia.Pro. Diagnostic Bioprobes Srl., Italy).¹¹ Anti-HBc-positive specimens were tested for hepatitis B surface antigen (HBsAg) (EIA IVD; Dia.Pro. Diagnostic Bioprobes Srl., Italy).¹² To confirm the presence of HBsAg, all HBsAg-positive samples were tested with the HBsAg confirmation neutralization assay (EIA IVD; Dia.Pro. Diagnostic Bioprobes Srl., Italy).¹³ The Diagnostic Reference Team of the Division of Viral Hepatitis Laboratory Branch at the US Centers for Disease Control and Prevention (CDC) retested all anti-HBc-positive specimens and a comparable-size subset of negative specimens using the highly sensitive, Food and Drug Administration-licensed VITROS Immunodiagnostic System (aHBc and HBsAg, IVD; Ortho Clinical Diagnostics, Raritan, NJ, USA).^{14,15} Specimens that tested positive for HBsAg were tested at the CDC using nucleic acid tests (NATs) for HBV DNA and for HDV RNA. NAT-positive samples were sequenced and genotyped using previously established procedures.¹⁶ HBsAg-positive samples with

undetectable HBV DNA using a laboratory developed test (LDT) with a lower limit of detection (LOD) of 500 IU/mL were further tested by ion vapor deposition (IVD) assay with a LOD <20 IU/mL.

Definitions

Persons testing negative for anti-HBc were classified as 'never infected with HBV,' those testing positive for anti-HBc were considered 'ever infected with HBV.' Persons positive for both anti-HBc and HBsAg were classified as 'currently infected.' Patients with incomplete or missing anti-HBc results were excluded from the analysis.

Statistical analyses

All data were weighted at cluster, household, and individual levels using 2014 Georgia census data to account for selection probability, non-response, and sampling differences between regions to produce nationally representative estimates. We estimated the national prevalence of anti-HBc and HBsAg positivity as well as coinfections with HCV (both antibody to HCV [anti-HCV] and HCV RNA) and HDV. The results are presented as weighted percentages with 95% confidence intervals (CIs). Statistically significant bivariate associations between anti-HBc/HBsAg positivity and demographic and other risk factors were determined using chi-squared tests. All factors found to be statistically significant ($P < 0.05$) were included in a multivariable logistic regression model. Statistical analysis was conducted using SAS version 9.4 (Cary, North Carolina, USA).

Results

Of the 7000 persons selected to participate in the study, 6296 (89.9%) gave consent and completed the questionnaire, and 6014 (85.9%) completed both the questionnaire and provided a blood specimen. Seven of these respondents were excluded for having missing or inconclusive hepatitis B test results; the final sample comprised valid anti-HBc and HBsAg results from 6007 adults. Demographic and exposure history for the overall sample of study participants is described in the study by Hagan et al.⁹ In the sample, total anti-HBc positivity was detected in 1634 specimens, of which 188 tested positive for HBsAg. Overall, the weighted prevalence of anti-HBc positivity among adults was 25.9% (95% CI = 24.2–27.6), and the prevalence of HBsAg positivity was 2.9% (95% CI = 2.4–3.5), corresponding to an estimated 80,000 adults living with chronic HBV infection in Georgia. Of 174 HBsAg-positive specimens tested for HBV DNA using the LDT, 97 (55.7%) were positive and 77 had undetectable HBV DNA levels. Of those 77 samples, 40 samples had sufficient volume for an IVD assay test, with 28 (70.0%) testing positive. Thus, of 137 HBsAg-positive specimens that were tested by both HBV DNA assays, 125 (91.2%) tested positive for HBV DNA. Of those, 77 were successfully genotyped; HBV genotype A was identified in 28 (36.4%) specimens, and genotype D was identified in 49 (63.6%) specimens.

Anti-HBc positivity prevalence and risk factors

Anti-HBc positivity prevalence differed significantly by age, with the lowest prevalence among persons aged 18–29 years (11.9%; 95% CI = 9.2–14.5) and highest among those aged ≥ 70 years (32.7%; 95% CI = 28.4–36.9) ($P < 0.0001$), but did not differ by sex (Table 1). Anti-HBc positivity prevalence differed by geographic region, ranging from a low of 18.8% (95% CI = 12.4–25.2) to a high of 33.0% (95% CI = 29.2–36.9; $P < 0.001$) (Fig. 1).

Table 1
Characteristics associated with anti-HBc and HBsAg positivity, Georgia seroprevalence survey, 2015.

Demographic characteristics	Total sample		Anti-HBc positivity			HBsAg positivity		
	No.	Weighted %	No.	Weighted % (95% CI)	P-value	No.	Weighted % (95% CI)	P-value
Overall	6007	100.0	1634	25.9 (24.2, 27.6)		188	2.9 (2.4, 3.5)	
Sex								
Male	2338	46.9	676	27.0 (24.5, 29.6)	0.15	85	3.4 (2.5, 4.3)	0.10
Female	3669	53.1	958	24.9 (22.9, 26.9)		103	2.5 (1.9, 3.2)	
Age (years)								
18–29	1063	19.2	138	11.9 (9.2, 14.5)	<0.0001	45	4.2 (2.7, 5.7)	0.001
30–39	1140	19.9	329	27.5 (23.9, 31.2)		64	4.5 (3.2, 5.8)	
40–49	1026	18.5	320	31.1 (26.9, 35.4)		27	2.7 (1.2, 4.1)	
50–59	1096	16.9	327	28.3 (25.0, 31.7)		30	2.4 (1.3, 3.5)	
60–69	884	13.6	262	27.2 (23.5, 30.9)		12	1.4 (0.4, 2.4)	
70+	798	12.0	258	32.7 (28.4, 36.9)		10	1.3 (0.4, 2.2)	
Urban vs rural								
Urban	3154	55.8	848	24.8 (22.3, 27.3)	0.16	108	3.1 (2.2, 3.9)	0.67
Rural	2853	44.2	786	27.3 (24.9, 29.7)		80	2.8 (2.1, 3.5)	
Employment status								
Employed, student, homemaker, retired	4940	80.2	1335	25.8 (23.8, 27.7)	0.73	135	2.5 (2.0, 3.1)	0.001
Unemployed	1065	19.8	298	26.4 (23.0, 29.8)		53	4.6 (3.1, 6.1)	
Highest level of education completed								
Elementary/primary school or less	621	9.2	162	26.0 (21.4, 30.5)	0.047	15	2.9 (1.3, 4.6)	0.13
Secondary school	2464	40.5	697	27.3 (24.5, 30.0)		92	3.7 (2.7, 4.7)	
Professional/technical school	1110	16.7	322	28.2 (24.8, 31.6)		27	2.4 (1.3, 3.4)	
University/college or higher	1811	33.6	453	23.1 (20.4, 25.8)		54	2.4 (1.6, 3.2)	
Healthcare worker, ever								
Yes	315	5.1	91	26.5 (19.5, 33.4)	0.87	— ^a	1.7 (0.0, 3.7)	0.35
No	5687	94.9	1542	25.9 (24.1, 27.6)		183	3.0 (2.4, 3.6)	
Provider who administered the last injection								
Healthcare worker	2381	49.7	627	24.4 (22.0, 26.8)	0.01	63	2.3 (1.6, 3.0)	0.43
Dentist	929	19.2	213	24.1 (20.2, 28.0)		33	3.2 (1.9, 4.6)	
Pharmacist	8	0.1	— ^a	33.2 (0.0, 70.9)		— ^a	9.9 (0.0, 27.4)	
Non-healthcare worker (family/neighbor)	1358	25.9	421	30.7 (27.4, 33.9)		43	3.1 (1.9, 4.3)	
Myself	281	5.1	98	29.4 (22.1, 36.6)		13	2.8 (0.8, 4.7)	
Ever received kidney dialysis								
Yes	17	0.3	— ^a	57.8 (26.3, 89.4)	0.02	— ^a	15.1 (0, 38.4)	0.06
No	5973	99.5	1618	25.7 (24.0, 27.4)		187	2.9 (2.4, 3.5)	
Ever received blood transfusion								
Yes	447	7.1	158	38.3 (32.8, 43.9)	<0.0001	22	6.0 (3.0, 8.9)	0.003
No	5555	92.9	1475	24.9 (23.2, 26.7)		166	2.7 (2.2, 3.3)	
Frequency of dental cleanings								
Once/year or more	671	15.1	155	23.5 (19.1, 27.9)	0.23	19	2.6 (1.0, 4.3)	0.44
Less than once/year	593	11.2	167	25.4 (21.0, 29.9)		14	2.1 (0.7, 3.5)	
Never	4174	73.8	1185	27.2 (25.3, 29.2)		140	3.3 (2.5, 4.0)	
Ever injected drugs								
Yes	205	4.5	107	48.1 (38.6, 57.6)	<0.0001	15	5.6 (0.7, 10.5)	0.12
No	5763	95.5	1518	24.9 (23.2, 26.6)		172	2.8 (2.3, 3.3)	
Number of lifetime sexual partners								
0	411	7.2	67	16.0 (11.4, 20.6)	<0.0001	— ^a	3.0 (0.3, 5.7)	0.21
1–5	3958	60.8	1057	25.4 (23.3, 27.4)		113	2.5 (1.9, 3.1)	
> 5	1630	32.1	507	29.0 (26.1, 31.9)		65	3.8 (2.5, 5.0)	
Ever had sex with a commercial sex worker (among men)								
Yes	357	15.3	120	34.0 (27.8, 40.1)	0.003	16	5.2 (2.3, 8.1)	0.08
No	1979	84.7	556	25.8 (23.1, 28.4)		69	3.1 (2.2, 4.0)	
Use condoms with sexual partners								
Always	382	8.9	78	18.5 (13.6, 23.5)	0.003	17	3.2 (1.1, 5.2)	0.99
Sometimes/often	1617	33.3	436	25.2 (21.9, 28.4)		56	3.0 (2.0, 4.0)	
Never	2993	49.4	864	28.3 (26.1, 30.5)		89	3.0 (2.2, 3.9)	
Ever incarcerated								
Yes	236	4.8	100	39.5 (30.3, 48.7)	<0.001	15	8.0 (2.2, 13.7)	0.003
No	5758	95.2	1530	25.2 (23.4, 26.9)		172	2.7 (2.2, 3.2)	
Any body piercings								
Yes	2714	38.9	691	23.2 (21.3, 25.2)	0.002	81	2.6 (1.9, 3.3)	0.29
No	3284	61.1	939	27.5 (25.2, 29.9)		106	3.1 (2.4, 3.9)	
History of any chronic disease								
Yes	2791	44.0	828	27.6 (25.5, 29.7)	0.04	81	2.7 (1.9, 3.4)	0.33
No	3211	56.0	805	24.5 (22.2, 26.9)		107	3.2 (2.4, 4.0)	

anti-HBc = anti-hepatitis B core total antibody; HBsAg = hepatitis B surface antigen; CI = confidence interval.

^a Suppressed because of the small sample size (<10).

Bivariate analysis revealed that testing positive for anti-HBc was associated with the type of provider (i.e., a healthcare worker, dentist, or family member) who administered the last therapeutic (medical or dental) injection that a participant reported receiving,

history of renal dialysis, ever having received a blood transfusion, history of any other chronic disease, past or present injection drug use, the number of lifetime sexual partners, having engaged in sex

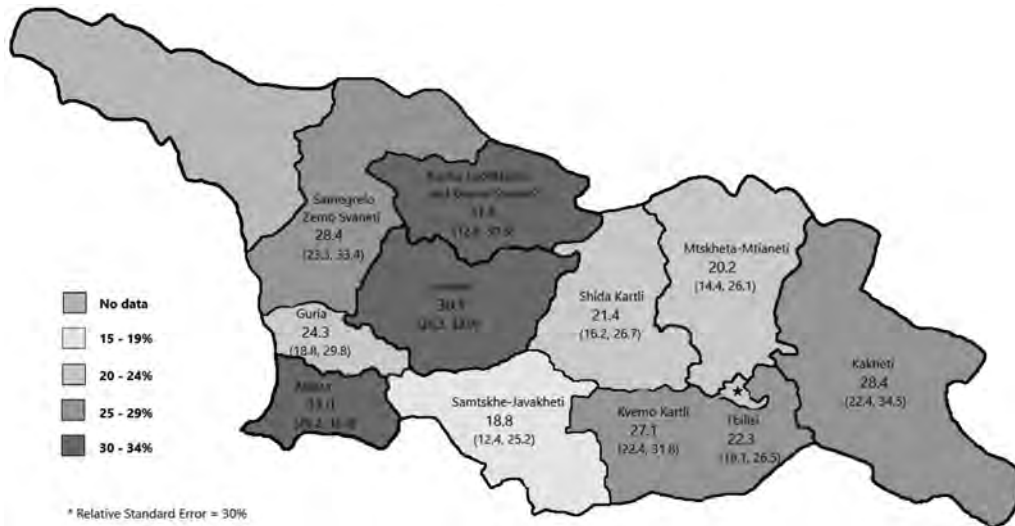


Fig. 1. Estimated anti-hepatitis B core total antibody positivity prevalence (95% confidence intervals) by region, Georgia serosurvey, 2015.

with a commercial sex worker, condom use, history of incarceration, and having a body piercing ($P < 0.05$ for all) (Table 1).

After adjusting for covariates in a model, significant risk factors for anti-HBc positivity included ever injecting drugs (adjusted odds ratio [aOR] = 2.34; 95% CI = 1.46–3.74); ever having received a blood transfusion (aOR = 1.68; 95% CI = 1.32–2.15); ever having sex with a commercial sex worker (aOR = 1.46; 95% CI = 1.06–2.01); and receipt of last medical injection by a neighbor or family member vs a healthcare worker (aOR = 1.31; 95% CI = 1.07–1.62) (Table 2).

HBsAg positivity prevalence and risk factors

HBsAg positivity prevalence varied by age, with the highest prevalence of infection among the youngest age-groups including those aged 18–29 years (4.2%; 95% CI = 2.7–5.7) and 30–39 years (4.5%; 95% CI = 3.2–5.8), whereas the lowest prevalence was among those aged ≥ 70 years (1.3%; 95% CI = 0.4–2.2) (Table 1). HBsAg positivity prevalence was significantly higher (4.6%; 95% CI = 3.1–6.4) among those who self-reported being unemployed at the time of the survey than among others (2.5%; 95% CI = 2.0–3.1) ($P < 0.001$). In bivariate analysis, testing positive for HBsAg was associated with ever having received a blood transfusion ($P < 0.01$) and a history of incarceration ($P < 0.01$). These associations remained significant after adjusting for all covariates significant in bivariate analysis, with aORs of 2.72 (95% CI = 1.54–4.80) and 2.72 (95% CI = 1.25–5.93), respectively.

Coinfection with hepatitis C or hepatitis D

Anti-HBc positivity was associated with both past and current HCV infection. Among anti-HBc-positive persons, 12.9% (95% CI = 10.2–15.5) were anti-HCV positive, compared with 5.9% (95% CI = 4.8–7.0) of anti-HBc-negative persons ($P < 0.0001$; data not shown). Likewise, 9.2% (95% CI = 6.9–11.6) of anti-HBc-positive persons were HCV RNA positive, compared with 4.1% (95% CI = 3.2–4.9) among those never infected with HBV ($P < 0.0001$).

Among HBsAg-positive persons, 13.3% (95% CI = 5.8–20.8) were anti-HCV positive and 9.8% (95% CI = 2.6–17.0) were HCV RNA positive, although these were not significantly higher than those in HBsAg-negative persons (7.5%; 95% CI = 6.4–8.6 and 5.3%; 95% CI = 4.4–6.2, respectively [$P > 0.05$]).

Among HBsAg-positive persons, 0.9% (95% CI = 0.0–2.0) were positive for HDV RNA ($n = 4/175$ [2.3%] of samples tested). All HDV specimens were genotype 1.

Hepatitis B vaccination

Overall, 1.1% (95% CI = 0.8–1.4) of the surveyed population reported ever having been vaccinated against hepatitis B (data not shown), although the number of doses received could not be verified. Vaccination coverage was highest (2.1%) among those aged 18–29 years and lowest (0.2%) among those aged ≥ 60 years ($P < 0.001$). Of the 798 participants aged ≥ 70 years, none could recall having been vaccinated against hepatitis B.

Hepatitis B-related knowledge

Slightly more than one-third of the participants (36.7%; $n = 2004$) had ever heard of hepatitis B or HBV. About one in five participants (20.6%; $n = 1093$) was aware that HBV could be transmitted by sharing needles or syringes, and 18.7% ($n = 1010$) were aware HBV could be transmitted by sharing household objects such as razors. Only 8.7% ($n = 461$) knew it was vaccine preventable, and 15.4% ($n = 819$) knew that condom use could prevent HBV infection. Of those who had heard of HBV, 42.8% ($n = 884$) were aware that this infection could be treated, and 42.5% ($n = 849$) knew that it could be asymptomatic.

Discussion

This is the first serosurvey to report hepatitis B prevalence on a national scale in Georgia. Overall, the rate of current or past HBV infection (anti-HBc) was 25.9%, and the prevalence of chronic HBV infection, defined by prevalence of HBsAg positivity, was 2.9%. A study conducted in 2006–2007 among healthcare workers in Georgia found similar prevalence of anti-HBc (29%) and HBsAg (2%) positivity.¹⁷

Georgia's anti-HBc positivity prevalence is high, but the country has low to intermediate HBsAg positivity prevalence (defined as 2.00–4.99%) compared with other countries in the World Health Organization European region.¹⁸ Risk factors associated with HBV infection included injection drug use, receipt of a blood transfusion, history of incarceration, sex with a commercial sex worker, and

Table 2

Results of multivariate regression models of the association of anti-HBc and HBsAg positivity with selected variables, Georgia seroprevalence survey, 2015.

Characteristics	Anti-HBc		HBsAg	
	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)
Age (years)				
18–29	Ref	Ref	Ref	Ref
30–39	2.83 (2.08, 3.84)	2.71 (2.00, 3.68)	1.07 (0.66, 1.72)	1.03 (0.65, 1.63)
40–49	3.36 (2.51, 4.50)	2.90 (2.15, 3.90)	0.63 (0.31, 1.25)	0.57 (0.30, 1.10)
50–59	2.94 (2.17, 4.00)	2.55 (1.88, 3.46)	0.56 (0.30, 1.03)	0.50 (0.28, 0.89)
60–69	2.78 (2.04, 3.79)	2.49 (1.78, 3.48)	0.33 (0.15, 0.74)	0.33 (0.14, 0.75)
70+	3.61 (2.66, 4.88)	3.10 (2.19, 4.41)	0.31 (0.14, 0.67)	0.32 (0.14, 0.74)
Employment status				
Employed, student, homemaker, retired	— ^b	—	Ref	Ref
Unemployed (able or unable to work)	—	—	1.88 (1.28, 2.74)	1.41 (0.96, 2.09)
Highest level of education completed				
Elementary/primary school or less	1.17 (0.88, 1.55)	1.10 (0.81, 1.49)	—	—
Secondary school	1.25 (1.03, 1.51)	1.24 (1.03, 1.50)	—	—
Professional/technical school	1.25 (1.03, 1.51)	1.24 (0.99, 1.57)	—	—
University/college or higher	Ref	Ref	—	—
Provider who administered the last injection				
Healthcare worker	Ref	Ref	—	—
Dentist	0.99 (0.78, 1.24)	1.10 (0.86, 1.40)	—	—
Pharmacist	1.54 (0.28, 8.33)	1.55 (0.24, 10.05)	—	—
Non-HCW (family/neighbor)	1.37 (1.12, 1.68)	1.31 (1.07, 1.62)	—	—
Myself	1.29 (0.89, 1.87)	1.04 (0.71, 1.51)	—	—
Ever received kidney dialysis				
Yes	3.97 (1.08, 14.53)	2.53 (0.76, 8.47)	—	—
No	Ref	Ref	—	—
Ever received blood transfusion				
Yes	1.87 (1.48, 2.37)	1.68 (1.32, 2.15)	2.28 (1.31, 4.00)	2.72 (1.54, 4.80)
No	Ref	Ref	Ref	Ref
Injection drug use (ever)				
Yes	2.80 (1.91, 4.09)	2.34 (1.46, 3.74)	—	—
No	Ref	Ref	—	—
Number of lifetime sexual partners				
0	Ref	Ref	—	—
1–5	1.78 (1.25, 2.54)	0.84 (0.51, 1.37)	—	—
> 5	2.14 (1.47, 3.12)	0.86 (0.49, 1.50)	—	—
Sex with a commercial sex worker (among men)				
Yes	1.48 (1.10, 1.99)	1.46 (1.06, 2.01)	—	—
No	Ref	Ref	—	—
Use condoms with sexual partners				
Always	Ref	Ref	—	—
Sometimes/often	1.48 (1.02, 2.15)	1.24 (0.83, 1.86)	—	—
Never	1.74 (1.25, 2.42)	1.48 (1.00, 2.17)	—	—
Ever incarcerated				
Yes	1.94 (1.32, 2.86)	1.33 (0.88, 2.02)	3.14 (1.41, 6.99)	2.72 (1.25, 5.93)
No	Ref	Ref	Ref	Ref
Any body piercings				
Yes	0.80 (0.69, 0.92)	0.90 (0.74, 1.10)	—	—
No	Ref	Ref	—	—
History of any chronic disease				
Yes	1.17 (1.01, 1.36)	0.95 (0.81, 1.12)	—	—
No	Ref	Ref	—	—

anti-HBc = anti-hepatitis B core total antibody; HBsAg = hepatitis B surface antigen; OR = odds ratio; CI = confidence interval; HCW = healthcare worker; Ref = reference category.

^a Adjusted models included all variables associated with the outcome ($P < 0.05$) in bivariate analysis.

^b Omitted owing to lack of association in bivariate analysis.

receipt of therapeutic injections from family members. Overall, these findings highlight the need to address blood safety, harm reduction for people who inject drugs, and unsafe infection control practices—issues currently being addressed by the hepatitis C elimination program.⁴

A quarter of respondents reported that their last therapeutic injection was from a neighbor or family member, suggesting the need to better understand the degree to which ‘informal’ health-care practices are used in the country and to better communicate the risk of unsafe injections in transmitting HBV and HCV.

This analysis is the first to our knowledge to report nationally representative data on HBV/HDV coinfection. HDV infection burden is reported to be substantial in several countries of Eastern Europe

and Central Asia.^{19,20} Globally, approximately 5% of HBsAg carriers are estimated to be coinfecting with HDV.²¹ Although nationally representative data are lacking from most countries, several studies indicate that HDV coinfection burden covers a large spectrum, from 1.6% in Central Asia (South Kazakhstan),²² 18.3% in Eastern Europe (Moldova),²³ to 57% in Mongolia.²⁴ In comparison, hepatitis D prevalence in Georgia among those currently infected with HBV is low (0.9%).

It is noteworthy that HBsAg positivity prevalence was highest and anti-HBc positivity prevalence was lowest among the youngest age cohorts (age of 18–39 years). This finding suggests that most HBV infections in Georgia likely occurred either perinatally from mother to child or horizontally during childhood when the risk of

chronic infection is highest.² Routine hepatitis B vaccination was included in the national immunization schedule in 2002, and the hepatitis B birth dose was introduced in 2003, so persons in this survey would not have benefitted from childhood and birth dose vaccination programs. Cohorts of Georgian children born after 2002 and 2003 will benefit from the protection of hepatitis B vaccination.²⁵ In addition, a dose of hepatitis B immunoglobulin (HBIG) is administered to infants born to pregnant women who have been screened and tested positive for HBsAg since August 2006.²⁶ In 2017–2018, of 103,828 registered live births, HBIG was administered to 1532 (1.5%) newborns.²⁵ Given these developments, Georgia could consider implementation of a hepatitis B serosurvey among cohorts born after vaccine introduction to assess the impact of vaccination on disease burden and report on progress toward the achievement of the European region hepatitis B control goal of HBsAg <0.5% among vaccinated cohorts by 2020²⁷ and global goal of elimination which is defined as HBsAg <0.1% among children aged 5 years by 2030.¹ In addition, in 2019, the government of Georgia approved a decree mandating hepatitis B vaccination be made available to all healthcare workers.²⁸ Fewer than 9% of persons were aware that hepatitis B can be prevented with a vaccine, suggesting public awareness campaigns could boost vaccination uptake among older populations.

Several key risk factors for HBV infection identified in this analysis were also found to be associated with HCV infection in Georgia, including history of incarceration (in bivariate analyses), receipt of a blood transfusion, and past or current injection drug use.⁹ HBV and HCV, both blood-borne pathogens, are known to have similar modes of transmission,²⁹ and nearly 10% of HBsAg-positive persons in this analysis were coinfecting with HCV. Coinfection can increase the likelihood of developing cirrhosis, decompensated liver disease, and hepatocellular carcinoma.³⁰ Georgia's hepatitis C elimination program was launched in 2015 and offers hepatitis C treatment free of charge; however, there is currently no such program for hepatitis B treatment. Nonetheless, the public health infrastructure established for hepatitis C screening and treatment as part of the hepatitis C elimination program could be leveraged to support hepatitis B elimination as well.^{4–6} Furthermore, Georgia can take advantage of reductions in the price of hepatitis B antivirals observed globally to improve treatment access.³¹ Cost-effectiveness studies and modeling for hepatitis B elimination are needed to further inform the Georgian government's consideration of undertaking hepatitis B elimination.

This analysis was subject to several limitations. Owing to its cross-sectional design, causal associations are difficult to be made; hepatitis B could have been acquired at any time and in any setting before survey participation. Risk factor data were self-reported and could not be independently verified and could be subject to recall and social desirability bias. Our survey only included persons ≥ 18 years of age who were not eligible for hepatitis B vaccination at the time of birth, so hepatitis B prevalence could not be estimated for persons in younger age-groups and children who were born after vaccine introduction. However, lower HBV infection rates are anticipated among children born after hepatitis B vaccine introduction. In addition, currently incarcerated persons were not surveyed in this analysis, which could lead to underestimation of national prevalence of hepatitis B. Demographic and behavioral differences between survey participants who did or did not provide a blood specimen could have skewed results. The relatively low number of HBsAg-positive persons sampled prevented reliable analysis of regional HBsAg prevalence and likely affected risk factor analysis, which could explain differences observed between anti-HBc and HBsAg positivity, especially with respect to injection drug use (IDU) and sex with a commercial sex worker. The sampling method of this study was not designed to produce precise

prevalence estimates for HDV infection; owing to low prevalence among the sampled population, national estimates should be interpreted with caution.

To conclude, the overall rate of exposure to HBV in Georgia is high, suggesting significant transmission, although the prevalence of chronic HBV infection is low to intermediate. Considering the overlap in the population and risk factors for HCV and HBV infection, existing programs and efforts within the ongoing national hepatitis C elimination program may be mitigating the risk of continued HBV transmission in the country; preventive measures aimed at reducing the risk of HCV transmission will also reduce the risk of HBV infection. The future burden of hepatitis B in Georgia will also decrease as a result of childhood vaccinations begun in the early 2000s. Nevertheless, more than 80,000 adults are estimated to be living with chronic HBV infection and are at risk of sequelae including cirrhosis and hepatocellular carcinoma, as well as continued transmission to additional susceptible individuals. Incorporating hepatitis B into Georgia's successful ongoing hepatitis C elimination efforts offers an opportunity for Georgia to be among the first countries in the region to undertake hepatitis B elimination. Studies to assess the feasibility and cost-effectiveness of undertaking hepatitis B elimination in Georgia could help inform policy decisions.

Author statements

Ethical approval

Ethical approval was not required. This survey was deemed by the Centers for Disease Control and Prevention to be a routine public health activity for public health surveillance and therefore judged to not involve human subject research.

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Competing interests

None declared.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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RESEARCH NOTE

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High sustained viral response among HCV genotype 3 patients with advanced liver fibrosis: real-world data of HCV elimination program in Georgia

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Abstract

Objective: In 2015, Georgia launched HCV elimination program. Initially, patients with advanced liver disease were treated with sofosbuvir-based regimen—the only DAA available for all genotypes. Purpose of the study was assessing real-world data of treatment outcome among patients with HCV GEN3 and advanced liver fibrosis with sofosbuvir-based regimens.

Results: Totally 1525 genotype 3 patients were eligible for analysis; most (72.6%) were aged > 45 years, majority were males (95.1%), and all (100%) had advanced liver disease (F3 or F4 by METAVIR score based on elastography). Of those who received sofosbuvir/ribavirin (SOF/RBV) for 24 weeks, 79.3% achieved SVR, while 96.5% who received sofosbuvir/pegylated interferon/ribavirin (SOF/PEG/RBV) for 12 weeks achieved SVR ($p < 0.01$). Among patients with liver cirrhosis (defined as F4) overall cure rate was 85.7% as opposed to 96.4% for those with F3. Females were more likely to be cured (98.7% vs 89.7%; OR = 8.54). Patients aged 31–45 years had higher likelihood of achieving SVR compared to patients aged 46–60 years (95.7% vs 87.4%; OR = 0.32). Independent predictors of SVR were treatment with SOF/PEG/RBV (aOR = 6.72) and lower fibrosis stage (F3) (aOR = 4.18). Real-world experience among HCV GEN3 patients with advanced liver fibrosis and treated by sofosbuvir regimen w/o PEGIFN, demonstrated overall high SVR rate.

Keywords: HCV, SVR, Genotype 3, Fibrosis, Liver, Elimination

Introduction

The World Health Organization (WHO) estimates, globally 71 million people are living with chronic hepatitis C virus (HCV) infection, and 400,000 die annually, mostly from complications of cirrhosis and hepatocellular carcinoma [1]. Recently introduced direct-acting antivirals (DAAs) offer an opportunity for curing the vast majority of infected persons, which will reduce the transmission risk and prevalence of HCV in the population.

Georgia has a high burden of HCV infection; a 2015 national serosurvey found that an estimated 5.4% of adults are currently infected with HCV [2]. On April 28, 2015, Georgia launched the world's first National HCV Elimination Program that included free of charge treatment with DAAs for all HCV infected persons [3]. The DAAs for the elimination program are donated by Gilead Sciences, and sofosbuvir was the first DAA available for the program. In the initial phase of the program, patients with moderate or severe liver disease were prioritized to receive treatment [3]. Cure rates for HCV infection (i.e., FSustained Virologic Response or SVR) varies depending on the genotype, degree of liver fibrosis, and the specific

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DAA's used [4–11]. HCV infected patients with genotype 3 are considered difficult to treat with SOF/RBV and SOF/PEG/RBV regimens, compared to other genotypes [5, 12, 13].

The HCV elimination treatment program in Georgia, with a large number of patients with genotype 3 patients offers a unique opportunity to study the outcomes among these hard to treat patients in a real-world setting. We aimed to study the real-world treatment outcomes among genotype 3 HCV infected patients with advanced disease treated with SOF/RBV and SOF/PEG/RBV regimens. Despite the fact that IFN-containing regimens are no longer standard of care in developed world, developing countries still use some of these regimens.

Main text

Methods

The Georgia National HCV Elimination Program collects data on enrolled patients' pre-treatment, during treatment, and post treatment. Data collected includes socio-demographic information, clinical and laboratory data, and prescribed medications based on national guidelines upon enrolment. These data are collected using standardized protocols, and entered into a national treatment database, STOP-C, developed for the HCV elimination program. Data collected and stored in STOP-C includes HCV genotype and viral load, level of liver fibrosis, risk factors for HCV infection and treatment-related laboratory data, including SVR at week 12–24 after completion of treatment.

Data from April 28, 2015 through September 30, 2016 from STOP-C were analysed. Characteristics and

outcomes of patients with genotype 3 were extracted. Only patients with advanced fibrosis (F3 or F4 by METAVIR score based on elastography) who had SOF-based regimens and valid SVR 12–24 results were included in the analysis. The treatment for patients with genotype 3 per national guidelines, was either sofosbuvir and ribavirin (SOF/RBV) for 24 weeks, or sofosbuvir, ribavirin and pegylated interferon (PEG IFN) 2a or 2b (SOF/PEG/RBV) for 12 weeks, depending on patient eligibility to receive IFN. SVRs were calculated using per-protocol as well as intent-to-treat (ITT) analysis. Per-protocol analysis included patients with complete SVR data and ITT analysis also included those who discontinued treatment. Treatment outcomes were analysed by degree of liver fibrosis (F4-cirrhosis vs F3-non-cirrhosis) and treatment regimen. Statistical software, SAS version 9.4, was used for data analysis. Bivariate associations between treatment outcome with different factors, such as treatment regimen, fibrosis stage, age, and gender were analysed using Chi square. Multivariate analysis with logistic regression was used to estimate odds ratios adjusted for age and gender (aORs) and define independent predictors of SVR.

Results

A total of 1525 genotype 3 patients completed their SOF-based treatment and had an SVR result available for analysis (Table 1). The overall cure rate i.e., SVR for the genotype 3 patients was 90.1% (1374/1525). Among patients with liver cirrhosis (F4 by elastography) the overall cure rate was 85.7% (764/892) as compared to non-cirrhotic patients (F3 or F3/F4) where 610/633

Table 1 Sustained virologic response (SVR) by age, gender and fibrosis stage (N = 1525), nationwide HCV elimination program, Georgia, April 28, 2015–September 30, 2016

	Total n (%) N = 1525	SVR achieved n (%) N = 1374	Unadjusted OR and 95% CI	Adjusted OR and 95% CI
Age group				
18–30	7	7 (100.00)	–	
31–45	411	393 (95.62)	1	
46–60	986	862 (87.42)	0.32 (0.19, 0.53)	
> 60	121	112 (92.56)	0.57 (0.25, 1.30)	
Gender				
Male	1450	1300 (89.66)	1	
Female	75	74 (98.67)	8.54 (1.18, 61.87)	
Fibrosis stage				
F4	892	764 (85.65)	1	1
F3 or F3/F4	633	610 (96.37)	4.44 (2.82, 7.01)	4.18 (2.64, 6.61)
Treatment regimen				
SOF/RBV	566	449 (79.33)	1	1
SOF/INF/RBV	959	925 (96.45)	7.09 (4.76, 10.56)	6.72 (4.49, 10.06)

(96.4%) achieved SVR. The SVR rate was significantly higher among those treated with SOF/INF/RBV containing regimen compared to those ineligible for prescribing interferon-based treatment. Out of 959 patients receiving PEG IFN 2a or 2b with SOF and RBV for 12 weeks, 925 (96.5%) achieved SVR compared to 79.3% cure rate among those treated with SOF and RBV for 24 weeks (449 out of 566). The SVR rate in intent-to-treat analysis for IFN/SOF/RBV regimens was 76.9% and for SOF/RBV regimen—61.2%.

By bivariate analysis, gender was significantly associated with SVR rate. Females (74/75 [98.7%] were more likely to be cured compared to males 1300/1450 [89.7%]; OR = 8.54, 95% CI 1.18–61.87). Patients aged 31–45 years had higher chance of achieving SVR (95.7% vs 87.4%) compared to patients aged 46–60 years (OR = 0.32, 95% CI 0.19–0.53).

Multivariate analysis showed that the independent predictors of achieving SVR were treatment regimen (patients treated with SOF/INF/RBV combination were more likely to be cured—aOR = 6.72, 95% CI 4.49–10.06) and fibrosis stage (non-cirrhotic patients having higher chance of SVR—aOR = 4.18, 95% CI 2.64–6.61) (Table 1).

Discussion

In this analysis of the real-world experience among HCV genotype 3 infected patients with advanced liver fibrosis treated with SOF containing regimen with or without pegylated interferon, we found patients achieved overall high SVR rates of > 90%. Higher SVR rate was observed among women. This finding is comparable to other studies [6, 14, 15] where SVR rate varied by gender with males having lower HCV cure rate. The factors account for this difference are not well understood. Patients with liver cirrhosis in our cohort achieved higher SVR rates with this “first generation” DAA compared to previous published reports that enrolled cirrhotic patients with HCV genotype 3 [13, 16]. Several studies demonstrated SVR rates of 60% to 70% among those receiving the SOF and RBV 24-week regimen [6, 16–19]. The VALENCE trial reported an overall SVR rate of 85% among genotype 3 infected patients receiving the 24-week SOF/RBV regimen [6]. In the VALENCE trial, SVR rates at 12-weeks post-treatment (SVR 12) were 91% for the non-cirrhotic group and 68% for the group of study participants with liver cirrhosis, and multivariate analysis identified the presence of liver cirrhosis as a predictor of non-response to treatment [6]. Our cohort, which included only those with advanced liver disease, had a similar overall SVR rate as the one reported among patients without cirrhosis in the VALENCE study (90.12% vs 91% SVR rate).

In June of 2016, sofosbuvir/ledipasvir (SOF/LED) was introduced in Georgia [2] and the treatment guidelines

were modified to include this combination DAA, resulting in little to no PEG IFN use for treatment. The Georgia treatment guidelines differ from those of the American Association for the Study of Liver Diseases (AASLD) or The European Association for the Study of the Liver (EASL), providing a unique opportunity to observe population-based outcomes with alternative HCV treatment regimens. These results can inform clinicians and policy makers in countries with a large proportion or burden of HCV genotype 3 infection that may not have access to DAAs or combinations of DAAs that are available in high-income countries of North America and Western Europe.

Limitations

This is a short report of a study limited to HCV infected genotype 3 patients with advanced liver disease treated during the first year of National HCV Elimination Program which was launched in 2015. Until 2016 HCV infected individuals with low fibrosis level were not eligible to be enrolled. The treatment outcomes were limited to two antiviral regimens: SOF/PEG/RBV and SOF/RBV. Interferon-free regimen (SOF/RIBA for 24 weeks) was used for patients with contraindication of IFN therapy, including mental illness. National HCV elimination program was not collecting data about IFN ineligibility; accordingly, we couldn't analyze impact of comorbidities on treatment outcome. Another limitation is that we have not adjusted for the previous treatment history because at the beginning of the program this information was not entered into the elimination program database. This information is available for the patients enrolled after 2016, when program database was updated and several variables added.

It is hoped that pan-genotypic regimens will soon be introduced in Georgia, presenting the opportunity to greatly simplify testing and treatment regimens, supporting the realization of HCV Elimination in Georgia by 2020 [20].

In conclusion, high SVR rates can be achieved among patients with HCV genotype 3 and advanced liver fibrosis, particularly among those treated with a 12-week SOF/PEG/RBV regimen. This may inform treatment for HCV infected patients in countries with limited access to newer DAAs.

Abbreviations

HCV: Hepatitis C virus; WHO: World Health Organization; DAAs: Directly acting antivirals; SVR: Sustained viral response; SOF: Sofosbuvir; RBV: Ribavirin; PEG: Pegylated; INF: Interferon; aOR: Adjusted odds ratio; LED: Ledipasvir; AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver.

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Disclaimer

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Authors' contributions

MB was a major contributor in conception, design and writing of the manuscript. LG participated in interpretation of data and revision of the manuscript. GK contributed in analysis and interpretation of data. DM participated in data collection and revision of the manuscript. SD participated in data collection. TR participated in data collection. AG contributed in revision of the manuscript. MN contributed in conception, design and revision of the manuscript. SS participated in analysis and interpretation of data. JM contributed in revision of the manuscript. FA contributed in conception, design and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Health Research Union (IRB00009520; IORG005619). Study participants were enrolled in the study after signing informed consent form specially developed for this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Sensitivity and Specificity of Rapid Diagnostic Tests for Hepatitis C Virus With or Without HIV Coinfection: A Multicentre Laboratory Evaluation Study

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Background. Hepatitis C virus (HCV) screening is critical to HCV elimination efforts. Simplified diagnostics are required for low-resource settings and difficult-to-reach populations. This retrospective study assessed performance of rapid diagnostic tests (RDTs) for detection of HCV antibodies.

Methods. Two lots of 13 RDTs were evaluated at 3 laboratories using archived plasma samples from 4 countries (Nigeria, Georgia, Cambodia, and Belgium). HCV status was determined using 3 reference tests according to a composite algorithm. Sensitivity and specificity were evaluated in HIV-infected and HIV-uninfected populations. Operational characteristics were also assessed.

Results. In total, 1710 samples met inclusion criteria. In HIV-uninfected samples (n = 384), the majority of RDTs had sensitivity $\geq 98\%$ in 1 or both lots and most RDTs had specificity $\geq 99\%$. In HIV-infected samples (n = 264), specificity remained high but sensitivity was markedly lower than in HIV-uninfected samples; only 1 RDT reached $>95\%$. The majority of HIV-infected samples for which sensitivity was low did not have detectable HCV viral load/core antigen. Interreader variability, lot-to-lot variability, and rate of invalid runs were low for all RDTs ($<2\%$).

Conclusions. HCV RDTs should be evaluated in the intended target population, as sensitivity can be impacted by population factors such as HIV status.

Clinical Trials Registration. NCT04033887

Keywords. hepatitis C virus; in vitro diagnostics; rapid diagnostic test; low- and middle-income country; HCV screening; specificity; sensitivity.

In 2015, the number of people with chronic hepatitis C (HCV) infection worldwide was estimated at 71 million [1]. However, only around 20% of people with HCV are aware of their HCV status [1]. HCV screening is critical to the success of HCV elimination targets, but in low- and middle-income countries (LMICs), where standardized laboratory tests are expensive and often not covered by public health systems, screening of at-risk populations for HCV infection remains very limited [2]. The burden of HCV in LMICs is particularly high, representing over 70% of the global total [3]. As such, the World Health Organization (WHO) strategy to eliminate HCV has

highlighted an urgent need for simplified diagnostic tests for use in low-resource settings, as well as for difficult-to-reach populations in high-income countries, such as people who inject drugs [4].

Screening for HCV is performed through the detection of HCV-specific antibodies. WHO guidelines recommend the use of a single quality-assured serological in vitro diagnostic test, either a laboratory-based immunoassay or a rapid diagnostic test (RDT) [5]. For many LMICs, where equipped laboratories and trained staff are limited, RDTs may be most appropriate, as they are quick and easy to perform without the need for laboratory equipment. RDTs have proved effective in other disease areas; for example, the wide availability of low-cost RDTs for the diagnosis of human immunodeficiency virus (HIV) has substantially increased access to testing, resulting in more than 600 million people being tested for HIV in LMICs from 2010 to 2014 [6].

The lack of quality-assured RDTs for HCV serology testing has been identified as an important barrier to large-scale access to HCV diagnosis [2]. While a number of HCV RDTs are commercially available, many do not have quality assurance status (eg, stringent regulatory authority approval or WHO

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prequalification [7]). Additionally, data on the quality and performance of many tests are limited, especially in LMICs. WHO recommendations on performance criteria for procurement of in vitro diagnostics for HCV, which also serve as guidance for WHO prequalification, recommend a sensitivity of $\geq 98\%$ and a specificity of $\geq 97\%$ for HCV serology RDTs in plasma or serum specimens [8]. Data on sensitivity and specificity of existing RDTs and RDTs in development can help to determine whether additional tests may be suitable for WHO prequalification, and results of independent performance evaluations can support countries in their choice to procure tests that meet international performance criteria.

Furthermore, some studies have noted a potential negative impact of HIV coinfection on the sensitivity of some HCV RDTs [9–11]. This may be due to the compromised immune system of people living with HIV limiting the production of anti-HCV antibodies; data on RDT performance by CD4 count (an indicator of immune status in HIV-positive people) have been identified as a research gap for HCV serology testing [5]. Given the high burden of HIV in LMICs, and the substantial proportion of people with HCV and HIV coinfection worldwide (approximately 2.3 million) [1], understanding the effect of HIV status on HCV RDT performance will be crucial to HCV elimination efforts.

The objective of this study was to evaluate the performance of a range of HCV RDTs using clinical samples collected from different geographic regions, as well as from HIV-infected individuals, in order to identify tests that could be used for HCV screening in LMICs or difficult-to-reach populations.

METHODS

Study Design

This was an observational, retrospective, multicenter laboratory evaluation of 13 HCV RDTs (NCT04033887; Table 1). Nine RDTs were on-market products, 1 RDT (HCV-only Ab Test;

Biosynex SA) had its configuration adapted to only evaluate the HCV line (the on-market product configuration is a triplex test with additional lines for the detection of HIV antibodies and hepatitis B virus surface antigen; the evaluated version lacked the test lines for HIV and hepatitis B), and 3 RDTs were still in late-stage development at the time of the study (defined here as prototype).

Tests were evaluated at 3 laboratories: the Nigerian Institute of Medical Research (Lagos, Nigeria), the Lugar Center at the National Center for Disease Control and Public Health (Tbilisi, Georgia), and the Institute of Tropical Medicine HIV/Sexually Transmitted Diseases (STD) Reference Laboratory (Antwerp, Belgium). Testing was performed on randomly selected locally archived frozen plasma samples from these 3 laboratories. Additionally, samples obtained from the Sihanouk Hospital Center of Hope (Phnom Penh, Cambodia) were tested at the Institute of Tropical Medicine HIV/STD Reference Laboratory; samples were frozen in Cambodia and remained frozen throughout transportation to Belgium. All sites received approval for the study from the respective institutional review boards. Testing was performed between September 2018 and March 2019.

All samples were ethylenediaminetetraacetic acid (EDTA)-treated plasma samples taken from people aged ≥ 18 years, with a minimum volume of 1.5 mL and known HIV status. Information on HCV and HIV treatment status of the sample donors was available. No further information on the characteristics of the sample donors were collected as part of this study. Samples were nonhemolytic, had < 3 freeze-thaw cycles, and had been stored at or below -70°C . Samples were collected between 2008 and 2018 (92% collected between 2014 and 2018). Samples were excluded if generic consent for further use was missing. Prior to commencement of testing, each site prepared small aliquots from the master samples to eliminate the need for multiple freeze-thaw cycles.

Table 1. HCV RDTs Included in the Study

Manufacturer	Test Name	Country	Test Format
SD Biosensor	Standard Q HCV Ab	Korea	Lateral flow
Antron Laboratories	HCV Hepatitis Virus Antibody Test	Canada	Lateral flow
Beijing Wantal Biological Pharmacy Enterprise	HCV-Ab Rapid Test	China	Lateral flow
InTec	Rapid Anti-HCV Test	China	Lateral flow
Premier Medical Corporation	First Response HCV Card Test	India	Lateral flow
Arkray Healthcare	Signal HCV Version 3.0	India	Flow through
J. Mitra & Co.	TRI DOT HCV	India	Flow through
Biosynex SA	Modified HCV-only Ab Test	France	Lateral flow
Abbott Diagnostics	SD Bioline HCV	United States	Lateral flow
OraSure	OraQuick HCV	United States	Lateral flow
BioLytical Laboratories	Prototype HCV Ab Test	Canada	Flow through
Chembio Diagnostic Systems	Prototype DPP HCV	United States	Lateral flow
Access Bio	Prototype Care Start HCV	United States	Lateral flow

Abbreviations: AB, antibody; HCV, hepatitis C virus; RDT, rapid diagnostic test.

HCV antibody status was determined using 3 reference tests, of which 2 were WHO prequalification approved enzyme immunoassays (EIA; Murex Anti-HCV version 4.0, DiaSorin S.A., and INNOTEST HCV Ab IV, Fujirebio Europe) and 1 was a line immunoassay (LIA; MP Diagnostics HCV blot 3.0, MP Biomedicals). A signal to cutoff ratio of ≥ 1 (based on the measured optical density) was used for the EIAs; interpretation of LIA results was performed according to manufacturer instructions. HCV antibody status of each sample was determined according to a composite algorithm incorporating the results of all 3 reference tests (Supplementary Table 1). A similar algorithm has previously been used in WHO prequalification evaluation protocols, although the WHO algorithm does not require LIA confirmation for samples testing negative on both EIAs [12].

Outcomes

The primary outcomes were point estimates of sensitivity and specificity with 95% confidence intervals of the 13 HCV RDTs in HIV-infected and -uninfected samples. Secondary outcomes included sensitivity and specificity of the 13 RDTs in the overall population (regardless of HIV status), interreader variability, lot-to-lot variability, and the rate of invalid runs. Exploratory outcomes included point estimates of sensitivity and specificity with 95% confidence intervals of the 13 RDTs in HIV-infected and -uninfected samples with active HCV infection measured by the presence of detectable HCV viral load (VL) or core antigen (cAg) in the sample. Analysis of test performance by CD4 count range (<200 cells/mm³ [severely immunocompromised], 200–500 cells/mm³ [immunocompromised], or >500 cells/mm³ [not immunocompromised]) in HIV-infected samples and by HCV genotype in HIV-uninfected and -infected samples was also performed.

RDT Performance Assessments

Each sample was tested on 2 independently produced lots of each RDT and each result was read and recorded by 3 independent readers. RDT results were interpreted according to the manufacturer's instructions. Samples were scored as either positive (reactive), negative (nonreactive), or invalid on each RDT based on the concordance of at least 2 out of 3 reader results. For all samples that were scored invalid, a repeat test was performed once on the same lot.

Operators/readers of the RDTs were blinded to the results of the reference standard tests. The sequence in which samples were tested was varied for each RDT to avoid bias related to recognition patterns. Operators and reader sequences were also varied.

Statistical Analyses

For an average sensitivity of 85% and specificity of 80%, a minimum sample size of 400 for sensitivity analyses and 502 for specificity analyses was required to obtain point estimates with

a precision of $\pm 5\%$ and power of 80% to obtain a confidence interval with total width of 10% or less [13].

Point estimates were obtained, with 95% confidence intervals based on Wilson score method, for sensitivity and specificity. Interreader variability was assessed by Fleiss kappa coefficient (κ) (agreement was defined as concordance between 2/3 or 3/3 results for each RDT). Lot-to-lot variability was evaluated by assessing performance in each lot using final valid RDT outcomes (excluding repeatedly invalid results), and the rate of invalid runs was calculated as the ratio between runs marked as invalid and the total number.

RESULTS

Sample Characteristics

Of 1864 samples selected, 1710 met inclusion criteria. In total, 648 samples were HCV antibody positive, of which 264 were also HIV positive. Of the 852 HCV antibody-negative samples, 626 were HIV positive and 226 were HIV negative. Two hundred and ten samples had indeterminate HCV status due to discrepancies between EIA and LIA results or indeterminate LIA results and were excluded from further analyses as per the composite reference standard algorithm (Figure 1). Although the sample size was not as large as was estimated to be required based on the previously stated test performance assumptions, based on the average test performance observed in this study, the sample size allowed for $\geq 80\%$ power with a precision of ± 5 in all subgroups (Supplementary Table 2).

The numbers of samples with genotype, CD4, count and HCV VL/cAg availability, and the country of sample origin for each sample type, are shown in Table 2. The majority of genotyped samples were of HCV genotype 1, 1a, or 1b (63.2% of HIV-uninfected and 54.2% of HIV-infected samples), followed by genotype 3 in HIV-uninfected samples (31.6%) and genotype 6 in HIV-infected samples (22.9%). The majority of HIV-positive samples had CD4 counts greater than 200 cells/mm³ ($>93\%$). The majority (89%) of HCV-infected and HIV-infected samples were from patients receiving treatment for HIV at the time of sample collection (HIV treatment status was known for 256 of 264 HCV-positive and HIV-positive samples). None of the samples from Nigeria, Cambodia, or Georgia were from people receiving treatment for HCV; of the Belgian samples, 107 were from people who had never received treatment for HCV, 10 were from people who were on active interferon treatment, 7 were from people who had previously received interferon treatment, and 2 had no treatment information available.

Sensitivity and Specificity

In the samples from HIV-uninfected patients, most RDTs showed high sensitivity, with the majority reaching $\geq 98\%$ in 1 or both lots (Figure 2A and Table 3). The large majority of tests showed a specificity of $\geq 99\%$ and several reached 100% (Figure 2B and Table 3). In HIV-infected samples, sensitivity

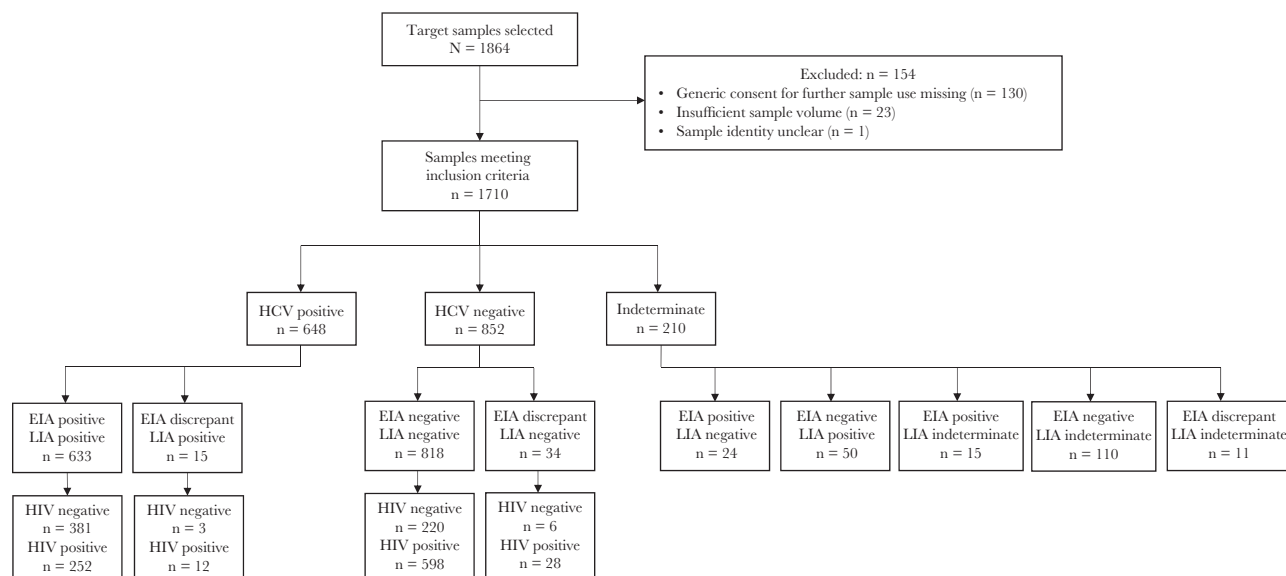


Figure 1. Number of samples by HCV and HIV status. Abbreviations: EIA, enzyme immunoassay; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LIA, line immunoassay.

was markedly lower than in HIV-uninfected samples, with only 1 RDT reaching >95% (Prototype DPP HCV; Chembio Diagnostic Systems) (Figure 2C and Table 3). For the large majority of RDTs, confidence intervals between HIV-uninfected and -infected samples did not overlap. Specificity was comparatively high in HIV-infected samples, with only 4 RDTs showing a specificity of <97% in at least 1 lot (Figure 2D and Table 3). In the combined sample set of HIV-uninfected and HIV-infected samples, results reflected the lower sensitivity for most RDTs, and lower specificity for some RDTs, observed in the HIV-infected samples (Table 3).

False negatives were distributed across 86 different samples. Of these, only 26 (30.2%) had genotype information available, with the most common genotype being genotype 6 ($n = 9$, 34.6%). The distribution of false negatives per CD4 count range (<200, 200–500, and >500 cells/mm³) in HIV-infected samples showed that false negatives occurred at a similar frequency in all CD4 count ranges (Supplementary Table 3).

To evaluate whether RDT sensitivity was associated with detectable HCV VL/cAg, point estimates of sensitivity were calculated for HIV-uninfected and HIV-infected samples only for samples with detectable HCV VL/cAg. In HIV-uninfected samples with detectable HCV VL/cAg, sensitivity increased moderately compared with the overall sample set, while in HIV-infected samples with detectable HCV VL/cAg, sensitivity increased markedly compared with the overall sample set (Figure 3 and Supplementary Table 4). The majority of confidence intervals did not overlap between HIV-infected samples with detectable HCV VL/cAg and all HIV-infected samples (Figure 2A and 2C and Figure 3A and 3B).

Operational Characteristics

There was a very high concordance among readers in terms of interreader variability, with a coefficient of agreement $\geq 95\%$ for all RDTs and lots. Furthermore, there was a high percentage of agreement between lots per RDT, with 10/13 RDTs achieving an agreement of >98% between both tested lots. Invalid runs were uncommon; 11/13 RDTs generated no or only very few invalid results during the first run and none during the repeat (Table 4).

DISCUSSION

To our knowledge, this is the first study to evaluate the performance of HCV RDTs using a large number of samples representing different geographical regions and with a substantial proportion of HIV coinfecting samples. As such, our findings provide valuable insights into HCV RDT performance on archived plasma samples and highlight a number of areas for future study.

WHO guidance on performance criteria for in vitro diagnostics for HCV recommends a sensitivity of $\geq 98\%$ and a specificity of $\geq 97\%$ for HCV serology RDTs [8]. In HIV-uninfected plasma samples in this study, the performance of the 13 RDTs was high; all tests met the WHO specificity criteria and 11 of 13 met the sensitivity criteria for 1 or both lots. This is consistent with previous studies demonstrating high sensitivity and specificity of the SD Bioline [10], First Response HCV Card Test [14], and OraQuick HCV [9, 10, 15] in plasma samples, and high performance of a number of the RDTs in other sample types including serum and oral fluid [9, 10, 16–19]. In 2 systematic reviews of HCV RDTs that included studies with varying designs, references and sample types, overall pooled

Table 2. Number of Samples With Genotype, CD4 Count, and HCV VL/cAg Information, and Country of Sample Origin

	HCV Positive/ HIV Negative (n = 384)	HCV Positive/ HIV Positive (n = 264)	HCV Negative/HIV Positive (n = 626)	HCV Negative/HIV Negative (n = 226)
Country of sample origin, n (%)				
Nigeria	70 (18.2)	20 (7.6)	292 (46.6)	186 (82.3)
Georgia	314 (81.8)	0	0	40 (17.7)
Cambodia	0	126 (47.7)	332 (53.0)	0
Belgium	0	118 (44.7)	2 (0.3)	0
Genotype available, n (%)				
Genotype 1, 1a or 1b ^a	72 (63.2)	97 (54.2)
Genotype 2 ^a	5 (4.4)	5 (2.8)
Genotype 3 ^a	36 (31.6)	10 (5.6)
Genotype 4 ^a	1 (0.9)	26 (14.5)
Genotype 6 ^a	0	41 (22.9)
CD4 count available, n (%)				
<200 cells/mm ^{3a}	...	18 (6.9)	41 (6.6)	...
200–<500 cells/mm ^{3a}	...	117 (44.8)	266 (42.8)	...
≥500 cells/mm ^{3a}	...	126 (48.3)	315 (50.6)	...
HCV VL/cAg available, n (%)				
HCV VL/cAg detectable ^a	262 (74.9)	181 (77.4)
Mean HCV VL, cp/mL (SD)	1.9E + 06 (2.55E + 06) n = 144	4.27E + 06 (6.97E + 06) n = 181
Mean HCV cAg, fmol/L (SD)	3.93E + 03 (4.74E + 03) n = 118
HbsAg status positive, n/N (%)	11/266 (4.1)	11/223 (5.0)	44/626 (7.0)	3/226 (1.3)

Abbreviations: cp, copies; fmol, femto molecules; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation; VL/cAg, viral load/core antigen

^aExpressed as percentage of samples with available information.

sensitivity was 98%–99% [17, 19]. These findings suggest that a number of the RDTs tested may be suitable for in-country use in the HIV-uninfected population.

In HIV-infected samples, however, while specificity remained high (12 of 13 RDTs met the WHO specificity criteria for 1 or both lots), none of the tests evaluated met the WHO sensitivity criteria. The fact that sensitivity improved in the subset of HIV-infected samples with detectable HCV VL/cAg suggests that the reduced sensitivity in HIV-infected samples overall may have been due to low HCV antibody titers. However, the reasons for low HCV antibody titers in HIV-infected samples are unclear, as CD4 counts were generally high, suggesting that the sample donors were not severely immunosuppressed. Other studies have noted declines in HCV antibody levels following treatment-induced or spontaneous HCV clearance in HIV-infected men [20, 21]. In general, our observation of lower HCV RDT performance in HIV-infected individuals is consistent with observations made in other studies, in which 1 or more of the evaluated RDTs showed poor sensitivity in samples from HIV-positive individuals [9–11]. The reasons for lower sensitivity in HIV-positive samples in these studies also remains unclear. More detailed information on HCV VL/cAg, time of coinfection, and initiation of and adherence to HIV treatment should be collected in future studies, in order to further assess the impact of HIV status on RDT performance.

Of the 71 million people worldwide with chronic HCV infection, 2.3 million are also infected with HIV [1]. As such, good RDT

performance in HCV and HIV coinfecting people is essential, particularly in LMICs where the burden of both diseases is high [3, 22]. However, while the false negatives observed in HIV samples in this study are technically concerning, from a clinical perspective, it is reassuring that the diagnostic performance of the evaluated RDTs improved in HIV-infected samples with detectable HCV VL/cAg. HCV VL or cAg testing is used to confirm viremic infection in people who test positive for HCV antibodies [5], thus these samples represent patients who had active HCV infection and are ultimately in need of treatment. As RDT performance was high regardless of HIV status in these samples, the impact of HIV infection on test performance may not be that dramatic.

The majority (69.7%) of samples that were false negative in at least 1 lot of any RDT in this study did not have genotype information available, making it difficult to associate the occurrence of false negatives with any particular HCV genotype. Notably, 34.6% of all samples giving at least 1 false negative were of HCV genotype 6. Given the relatively low total number of genotype 6 samples (41 out of a total of 293 samples with genotype information available), this could potentially have been a contributing factor to the high number of false-negative samples. However, verification of this by statistical analysis was not possible due to the aforementioned low number of samples with genotype information available.

The WHO guidance on performance criteria for HCV serology RDTs recommends an interreader variability and device failure rate of ≤5% [8]. All of the RDTs evaluated in this

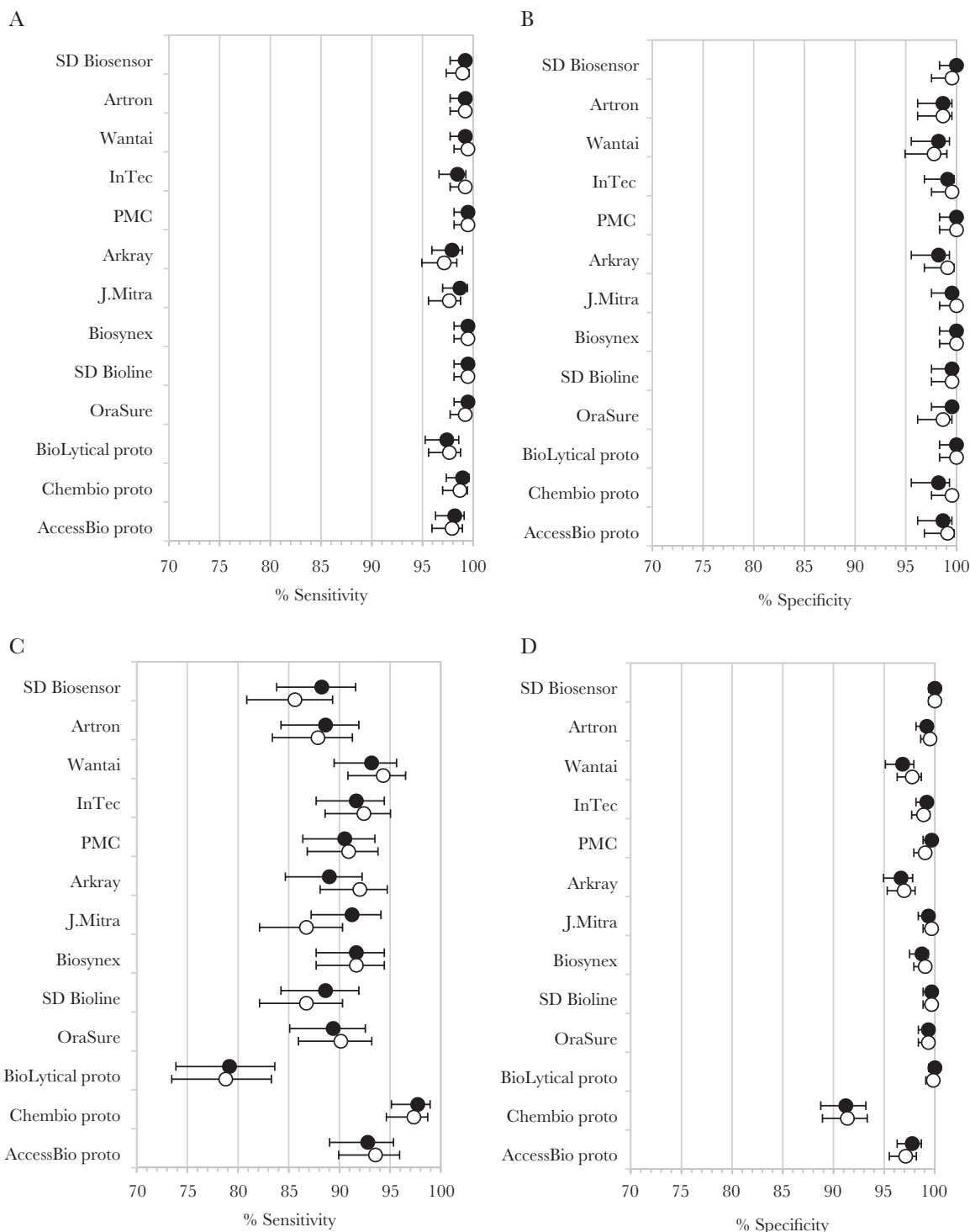


Figure 2. Sensitivity and specificity of 13 HCV rapid diagnostic tests in human immunodeficiency virus (HIV)-uninfected and -infected samples (circles, % sensitivity or specificity; closed circles, lot 1; open circles, lot 2; error bars, upper and lower 95% confidence intervals): (A) sensitivity in HIV-uninfected samples; (B) specificity in HIV-uninfected samples; (C) sensitivity in HIV-infected samples; and (D) specificity in HIV-infected samples.

study met both criteria. Additionally, the performance of all of the RDTs was in high agreement between the 2 lots evaluated, demonstrating a low technical lot-to-lot variability. These data show that the consistency of HCV serology RDTs is high,

providing confidence in the operational quality of the tests across different lots and devices.

The data from this study contribute to the growing evidence on the use of HCV RDTs for HCV screening in LMICs,

Table 3. Summary of Sensitivity and Specificity of RDTs in All Study Populations Based on the Main Composite Reference Standard

RDT	Lot	Overall Population						HIV Uninfected						HIV Infected					
		Sensitivity			Specificity			Sensitivity			Specificity			Sensitivity			Specificity		
		TP	FN	% (LCI, UCI)	TN	FP	% (LCI, UCI)	TP	FN	% (LCI, UCI)	TN	FP	% (LCI, UCI)	TP	FN	% (LCI, UCI)	TN	FP	% (LCI, UCI)
SD Biosensor Standard O HCV Ab	Lot 1	614	34	94.8 (92.8, 96.2)	852	0	100 (99.6, 100)	381	3	99.2 (97.7, 99.7)	226	0	100 (98.3, 100)	233	31	88.3 (83.8, 91.6)	626	0	100 (99.4, 100)
	Lot 2	606	42	93.5 (91.4, 95.2)	851	1	99.9 (99.3, 100)	380	4	99.0 (97.4, 99.6)	225	1	99.6 (97.5, 99.9)	226	38	85.6 (80.9, 89.3)	626	0	100 (99.4, 100)
Arttron HCV Antibody Test	Lot 1	615	33	94.9 (92.9, 96.4)	844	8	99.1 (98.2, 99.5)	381	3	99.2 (97.7, 99.7)	223	3	98.7 (96.2, 99.6)	234	30	88.6 (84.2, 91.9)	621	5	99.2 (98.1, 99.7)
	Lot 2	613	35	94.6 (92.6, 96.1)	846	6	99.3 (98.5, 99.7)	381	3	99.2 (97.7, 99.7)	223	3	98.7 (96.2, 99.6)	232	32	87.9 (83.4, 91.3)	623	3	99.5 (98.6, 99.8)
Wantai HCV Rapid Test	Lot 1	627	32	96.8 (95.1, 97.9)	828	24	97.2 (95.8, 98.1)	381	3	99.2 (97.7, 99.7)	222	4	98.2 (95.5, 99.3)	246	18	93.2 (89.5, 95.6)	606	20	96.8 (95.1, 97.9)
	Lot 2	631	17	97.4 (95.8, 98.4)	833	19	97.8 (96.5, 98.6)	382	2	99.5 (98.1, 99.9)	221	5	97.8 (94.9, 99.1)	249	15	94.3 (90.8, 96.5)	612	14	97.8 (96.3, 98.7)
InTec Rapid Anti-HCV Test	Lot 1	620	28	95.7 (93.8, 97.0)	845	7	99.2 (98.3, 99.6)	378	6	98.4 (96.6, 99.3)	224	2	99.1 (96.8, 99.8)	242	22	91.7 (87.7, 94.4)	621	5	99.2 (98.1, 99.7)
	Lot 2	625	23	96.5 (94.7, 97.6)	844	8	99.1 (98.2, 99.5)	381	3	99.2 (97.7, 99.7)	225	1	99.6 (97.5, 99.9)	244	20	92.4 (88.6, 95.0)	619	7	98.9 (97.7, 99.5)
PMC First Response HCV Card Test	Lot 1	621	27	95.8 (94.0, 97.1)	850	2	99.8 (99.2, 99.9)	382	2	99.5 (98.1, 99.9)	226	0	100 (98.3, 100)	239	25	90.5 (86.4, 93.5)	624	2	99.7 (98.8, 99.9)
	Lot 2	622	26	96.0 (94.2, 97.3)	846	6	99.3 (98.5, 99.7)	382	2	99.5 (98.1, 99.9)	226	0	100 (98.3, 100)	240	24	90.9 (86.8, 93.8)	620	6	99.0 (97.9, 99.6)
Arkray Signal HCV Version 3.0	Lot 1	610	37	94.3 (92.2, 95.8)	827	25	97.1 (95.7, 98.0)	375	8	97.9 (95.9, 98.9)	222	4	98.2 (95.5, 99.3)	235	29	89.0 (84.7, 92.2)	605	21	96.7 (94.9, 97.8)
	Lot 2	615	32	95.1 (93.1, 96.5)	830	21	97.5 (96.3, 98.4)	373	11	97.1 (94.9, 98.4)	224	2	99.1 (96.8, 99.8)	242	21	92.0 (88.1, 94.7)	606	19	97.0 (95.3, 98.1)
J. Mitra TRI/DOT HCV	Lot 1	619	28	95.7 (93.8, 97.0)	842	5	99.4 (98.6, 99.8)	379	5	98.7 (97.0, 99.4)	225	1	99.6 (97.5, 99.9)	240	23	91.3 (87.2, 94.1)	617	4	99.4 (98.4, 99.8)
	Lot 2	603	44	93.2 (91.0, 94.9)	847	2	99.8 (99.2, 99.9)	374	9	97.7 (95.6, 98.8)	226	0	100 (98.3, 100)	229	35	86.7 (82.1, 90.3)	621	2	99.7 (98.8, 99.9)
Biosynex HCV-only	Lot 1	624	24	96.3 (94.6, 97.5)	844	8	99.1 (98.2, 99.5)	382	2	99.5 (98.1, 99.9)	226	0	100 (98.3, 100)	242	22	91.7 (87.7, 94.4)	618	8	98.7 (97.5, 99.4)
	Lot 2	624	24	96.3 (94.6, 97.5)	846	6	99.3 (98.5, 99.7)	382	2	99.5 (98.1, 99.9)	226	0	100 (98.3, 100)	242	22	91.7 (87.7, 94.4)	620	6	99.0 (97.9, 99.6)
Abbott SD Bioline HCV	Lot 1	616	32	95.1 (93.1, 96.5)	849	3	99.7 (99.0, 99.9)	382	2	99.5 (98.1, 99.9)	225	1	99.6 (97.5, 99.9)	234	30	88.6 (84.2, 91.9)	624	2	99.7 (98.8, 99.9)
	Lot 2	611	37	94.3 (92.2, 95.8)	849	3	99.7 (99.0, 99.9)	382	2	99.5 (98.1, 99.9)	225	1	99.6 (97.5, 99.9)	229	35	86.7 (82.1, 90.3)	624	2	99.7 (98.8, 99.9)
OraSure OraQuick HCV	Lot 1	618	30	95.4 (93.5, 96.7)	847	5	99.4 (98.6, 99.8)	382	2	99.5 (98.1, 99.9)	225	1	99.6 (97.5, 99.9)	236	28	89.4 (85.1, 92.6)	622	4	99.4 (98.4, 99.8)
	Lot 2	619	29	95.5 (93.7, 96.9)	845	7	99.2 (98.3, 99.6)	381	3	99.2 (97.7, 99.7)	223	3	98.7 (96.2, 99.6)	238	26	90.2 (86.0, 93.2)	622	4	99.4 (98.4, 99.8)
Biological prototype HCV Ab Test	Lot 1	583	65	90.0 (87.4, 92.1)	852	0	100 (99.6, 100)	374	10	97.4 (95.3, 98.6)	226	0	100 (98.3, 100)	209	55	79.2 (73.9, 83.6)	626	0	100 (99.4, 100)
	Lot 2	583	65	90.0 (87.4, 92.1)	851	1	99.9 (99.3, 100)	375	9	97.7 (95.6, 98.8)	226	0	100 (98.3, 100)	208	56	78.8 (73.5, 83.3)	625	1	99.8 (99.1, 100)
Chembio prototype DPP HCV	Lot 1	638	10	98.5 (97.2, 99.2)	793	59	93.1 (91.2, 94.6)	380	4	99.0 (97.4, 99.6)	222	4	98.2 (95.5, 99.3)	258	6	97.7 (95.1, 99.0)	571	55	91.2 (88.7, 93.2)
	Lot 2	636	12	98.2 (96.8, 98.9)	797	55	93.5 (91.7, 95.0)	379	5	98.7 (97.0, 99.4)	225	1	99.6 (97.5, 99.9)	257	7	97.4 (94.6, 98.7)	572	54	91.4 (88.9, 93.3)
AccessBio prototype CareStart HCV	Lot 1	622	26	96.0 (94.2, 97.3)	835	17	98.0 (96.8, 98.8)	377	7	98.2 (96.3, 99.1)	223	3	98.7 (96.2, 99.6)	245	19	92.8 (89.0, 95.3)	612	14	97.8 (96.3, 98.7)
	Lot 2	623	25	96.1 (94.4, 97.4)	832	20	97.7 (96.4, 98.5)	376	8	97.9 (95.9, 98.9)	224	2	99.1 (96.8, 99.8)	247	17	93.6 (89.9, 95.9)	608	18	97.1 (95.5, 98.2)

Abbreviations: Ab, antibody; FN, false negative; FP, false positive; LCI, lower 95% confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RDT, rapid diagnostic test; TN, true negative; TP, true positive; UCI, upper 95% confidence interval.

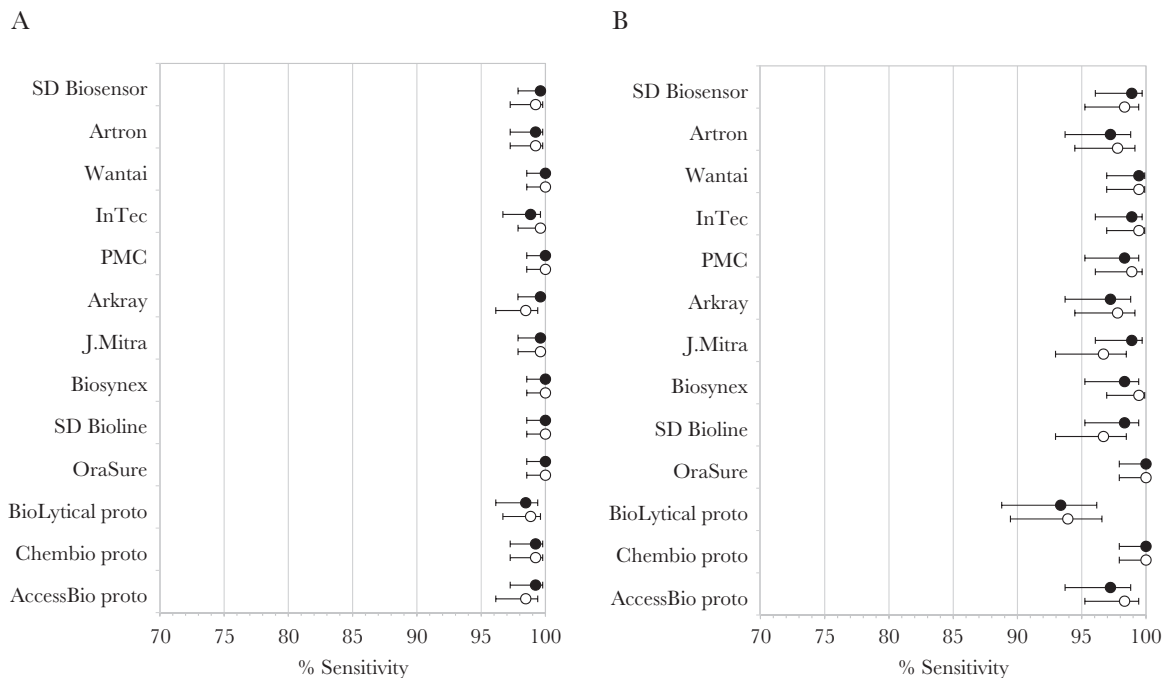


Figure 3. Sensitivity of 13 HCV rapid diagnostic tests in samples with detectable HCV VL/cAg (circles, % sensitivity or specificity; closed circles, lot 1; open circles, lot 2; error bars, upper and lower 95% confidence intervals): (A) HIV-uninfected samples; and (B) HIV-infected samples. Abbreviations: cAg, core antigen; HCV, hepatitis C; HIV, human immunodeficiency virus; VL, viral load.

providing that they are first evaluated in the intended target population to determine whether sensitivity is impacted by population factors. A number of populations are commonly targeted for HCV screening, including sex workers, men who have sex with men, people who inject drugs, and people living with HIV [1, 23]. Procurement of high-performance RDTs will be key to the improvement of HCV testing services for these key populations. Although we did not collect data on sample donor characteristics, it is likely that samples from these target groups were tested in our study, given the countries included. For example, Georgia has one of the highest prevalences of injection drug use globally, with up to 40% of HCV infections attributable to injection drug use [24]. Additionally, in some countries HCV screening is indicated for the general population, as a result of historical unsafe medical practices [25], as is the case in Nigeria [26] and Cambodia [27].

Limitations of this study include the uneven geographical distribution of sample types. Sensitivity in the HIV-uninfected population was primarily assessed in samples originating from Georgia and Nigeria, while sensitivity in the HIV-infected population was assessed almost exclusively in samples from Cambodia and Belgium. This makes comparisons between sensitivity in the HIV-uninfected and -infected populations challenging. We cannot exclude the possibility that differences in population characteristics, such as different types of HIV/HCV risk groups, impacted the results. Notably, Belgium (from which 120 [14.7%] samples were obtained) is a high-income country,

thus population characteristics such as HIV prevalence or HCV cohort may not be comparable to those of LMICs.

While we cannot exclude the possibility that differences in storage conditions between countries had an effect on sample quality, evidence suggests that antibodies remain stable in frozen samples for several years and after multiple freeze-thaw cycles [28–31]; furthermore, we minimized any potential impact by only including samples that appeared nonhemolytic upon visual inspection. A further limitation is the low number of HCV-negative and HIV-negative samples compared with HCV-negative HIV-positive samples, which may have influenced specificity in the overall population. The impact of this was likely minor, however, as most of the RDTs performed well in both study populations.

The design of the composite reference standard led to 210 samples being excluded from the study. It is possible that inclusion of these samples would have affected the sensitivity and specificity estimates. This study did not take into account the impact of treatment for HCV, although only a small number of samples ($n = 17$) were from people who were receiving or who had previously received interferon treatment. Additionally, the HCV-negative samples used may not have precisely represented the target populations for HCV serology testing, leading to patient bias. Finally, tests were performed by well-trained laboratory personnel using archived samples, thus this study does not represent a real-world setting. The performance of the RDTs in primary or community care settings using prospectively collected fresh samples is yet to be established.

Table 4. Operational Characteristics of HCV RDTs

RDT	Lot	Interreader Variability, κ	Lot-to-Lot Variability, % Agreement	Invalid Test Runs, %	
				First Run	Repeat Run
SD Biosensor Standard Q HCV Ab	Lot 1	0.99	99.42	0	0
	Lot 2	0.98		0	0
Artron HCV Antibody Test	Lot 1	0.98	98.65	0	0
	Lot 2	0.98		0	0
Wantai HCV Rapid Test	Lot 1	0.97	99.01	0	0
	Lot 2	0.97		0	0
InTec Rapid Anti-HCV Test	Lot 1	0.98	99.18	0	0
	Lot 2	0.99		0	0
PMC First Response HCV Card Test	Lot 1	0.98	99.12	0	0
	Lot 2	0.98		0.06	0
Arkray Signal HCV Version 3.0	Lot 1	0.95	96.19	1.05	0.12
	Lot 2	0.96		1.35	0.18
J. Mitra TRI DOT HCV	Lot 1	0.95	97.88	1.93	0.41
	Lot 2	0.97		1.70	0.35
Biosynex HCV-only	Lot 1	0.98	99.12	0	0
	Lot 2	0.98		0	0
Abbott SD Bioline HCV	Lot 1	0.98	99.42	0	0
	Lot 2	0.98		0	0
OraSure OraQuick HCV	Lot 1	0.98	99.36	0.12	0
	Lot 2	0.98		0.06	0
BioLytical prototype HCV Ab Test	Lot 1	0.97	98.83	0.06	0
	Lot 2	0.97		0.12	0
Chembio prototype DPP HCV	Lot 1	0.95	98.13	0.35	0
	Lot 2	0.96		0.06	0
AccessBio prototype CareStart HCV	Lot 1	0.97	97.84	0.06	0
	Lot 2	0.95		0	0

Abbreviations: Ab, antibody; HCV, hepatitis C virus; RDT, rapid diagnostic test.

In conclusion, the findings from this study show that a number of available HCV RDTs may be suitable for WHO prequalification and use in HCV screening programs in LMICs. However, HCV RDTs should always be evaluated in the intended target population, as sensitivity can be impacted by population factors such as HIV status. Any evaluation panels used for assessment of HCV RDTs should contain HIV-positive samples. These findings serve as a valuable baseline to investigate RDT performance in prospectively collected whole blood samples in the intended use settings. This will yield further insights into the robustness of the RDTs when used in primary health care settings by local health workers and tested on the most common sample type used for RDTs.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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With the exception of the Abbott SD Bioline HCV RDT, all HCV RDTs under evaluation have been provided free of charge or at reduced cost by the respective manufacturers.

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Original Article

Assessment of treatment options for patients with hepatitis C virus recombinant form 2k/1b

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Aim: Hepatitis C virus (HCV) intergenotype recombinant form (RF) 2k/1b has been actively circulating in HCV-infected patients, and the prevalence of this RF virus in the Republic of Georgia is one of the highest reported worldwide. The aim of this study was to define the optimal treatment regimen for patients with RF_2k/1b.

Methods: We analyzed the data of 2735 patients who started treatment at the Medical Center Mrcheveli within Georgia's hepatitis C elimination program from May 2015 through December 2019. The patients were treated with sofosbuvir (SOF)-based regimens. For identification of RF_2k/1b variants, refinement of standard (INNO-LiPA) genotyping results for all patient samples assigned the unspecific HCV genotypes (GT) 2a/2c was carried out by sequencing of core and non-structural protein 5B genes.

Results: Overall, 444 patients, representing 66% of GT2 and 16% of the total samples, were RF_2k/1b. Treatment of patients with

RF_2k/1b with SOF/ledipasvir and SOF/velpatasvir was highly effective and viral cure rates did not differ among genotypes treated with the same regimen: RF_2k/1b, 99% (343/346); GT1, 99% (876/885); GT2, 96% (156/162); and GT3, 99% (545/552). A separate comparison analysis of sustained virologic response rate, treated with SOF plus ribavirin, showed significantly higher sustained virologic response (96%) in patients with confirmed GT2 (by sequencing) compared to unspecified GT2 (by INNO-LiPA) (79%) ($P < 0.05$).

Conclusion: Sofosbuvir-based regimens are highly effective for treatment of RF 2k/1b patients, and with availability of new pan-genotypic direct-acting antivirals, genotyping to identify RF 2k/1b patients might not be necessary.

Key words: genotype, HCV, RF_2k/1b, sofosbuvir, sustained virologic response

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection is a one of the major causes of liver-related morbidity and mortality,¹ with an estimated 71 million persons with chronic HCV infection worldwide who are at risk of developing cirrhosis and hepatocellular carcinoma.² Treatment for patients with chronic HCV-related liver disease has evolved during the last two decades due to improved

understanding of the disease pathophysiology, developments in diagnostic procedures, and improvements in therapy and prevention. The development of direct-acting antivirals (DAAs) has revolutionized the treatment of HCV infection and has a potential for disease elimination.³

The estimated prevalence of HCV infection in the Republic of Georgia is one of the highest in the world.⁴ Before 2015, patients with chronic HCV infection were often treated with pegylated interferon (PegIFN) and ribavirin

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(RBV), and new-generation DAAs were not affordable for most patients. In April 2015, Georgia launched the National Hepatitis C Elimination Program in partnership with the US Centers for Disease Control and Prevention and Gilead Sciences. The goal of the program is 90% reduction in hepatitis C prevalence by 2020.⁵ Georgia has achieved substantial treatment scale-up with the implementation of the hepatitis C elimination program, which has reduced the prevalence of chronic hepatitis C infection among adults by 37%, the incidence by 37%, and mortality by 14%.⁶

Since 2015, different sofosbuvir (SOF)-based regimens have been used for patients within the National Hepatitis C Elimination Program. The SOF-based regimens were dependent on HCV genotype (GT), presence of liver cirrhosis, drug eligibility, and previous treatment history.⁷ In addition, specific HCV management guidelines have been created and further updated for treatment of patients within the program.

The available data show that unique HCV chimeras, otherwise known as HCV intergenotype recombinant form (RF) _{2k/1b}, have been actively circulating in HCV-infected patients. Earlier data suggested that RF_{2k/1b} prevalence was extremely low and played a minor role in HCV evolution, but it might have been underestimated. Our previous data confirmed that up to 20% of all HCV genotypes are HCV RF_{2k/1b}. The RF_{2k/1b} genotype was identified in only GT2 samples and comprised 72% of samples. Full genome sequencing confirmed the results. The phylogenetic analysis showed that the RF_{2k/1b} viruses from Georgia formed a monophyletic cluster with the previously described RF1_{2k/1b} sequences.^{8,9}

In the current era of more effective pan-genotypic DAA medication, differentiating patients with RF_{2k/1b} from those with GT2 might not be prudent. However, in areas where availability of pan-genotypic DAAs is limited, identification of recombinants could be important for making the most cost-effective treatment choices for low-income countries.

There are case reports that detail the cure rate of patients with RF_{2k/1b} and their treatment with the limited spectrum of DAAs. According to the available data of sustained virologic response (SVR) rates, patients with RF_{2k/1b} could be more similar to patients with GT1 than to patients with GT2.^{10,11}

The aim of this study was to define the optimal SOF-based treatment regimens for patients with RF_{2k/1b}, estimating SVR rates, and comparing these data to the results of other HCV genotypes treated with the same regimen within the National Hepatitis C Elimination Program in the country of Georgia.

METHODS

Study design and population

WE EVALUATED HCV genotype distribution among 2735 patients who initiated treatment within the National Hepatitis C Elimination Program in the Medical Center Mrcheveli (Tbilisi, Georgia) from May 2015 to December 2019. A sample of 2280 patients were included in the intention-to-treat analysis. Seventeen percent of patients ($n = 455$) were excluded for the following reasons: unable to undertake HCV genotyping, lost to follow-up, treatment discontinuation, changes in treatment regimen or treatment provider, and ongoing treatment (Fig. 1).

We evaluated post-treatment 12-week SVR rates in patients with RF_{2k/1b} and compared them to patients with GT2, GT1, and GT3. For the generalizability of our results, we undertook re-genotyping and sequencing in randomly selected samples from patients with unspecified GT2a/2c who failed to achieve SVR at other HCV elimination program provider centers.

Parameters assessed

Demographic and epidemiological characteristics were collected from patients' medical records and the National Hepatitis C Elimination Program online database. The degree of liver damage was assessed by non-invasive methods such as liver stiffness measurement with transient elastography (FibroScan; Echosens, Paris, France) and Fibrosis-4 (FIB-4) score. Only patients with FIB-4 score from 1.45 to 3.25 were eligible for FibroScan. We stratified patients into the following groups: patients without advanced chronic liver disease (ACLD) (FIB-4 < 1.45; FibroScan < 10 kPa), and patients with ACLD (FIB-4 > 3.25; FibroScan > 10 kPa), which includes patients with advanced fibrosis and compensated or decompensated cirrhosis. Additional parameters for calculation of Child-Pugh score were collected from patients' medical records. Hepatitis C virus RNA was assessed using a real-time polymerase chain reaction (PCR) HCV assay (Cobas 6800; Roche Diagnostics, Mannheim, Germany) with a lower limit of quantification and detection of 10 IU/mL. Hepatitis C virus genotype was determined using the VERSANT HCV Genotype 2.0 (VERSANT LiPA; Healthcare SIEMENS, Munich, Germany). For identification of RF_{2k/1b} samples, refinement of INNO-LiPA genotyping results for all patient samples assigned the unspecific HCV genotypes 2a/2c was carried out by partial sequencing of core and non-structural protein 5B (NS5B) genes.⁹ Labor Limbach (Heidelberg, Germany) carried out PCR, standard genotyping, and sequencing. Sustained

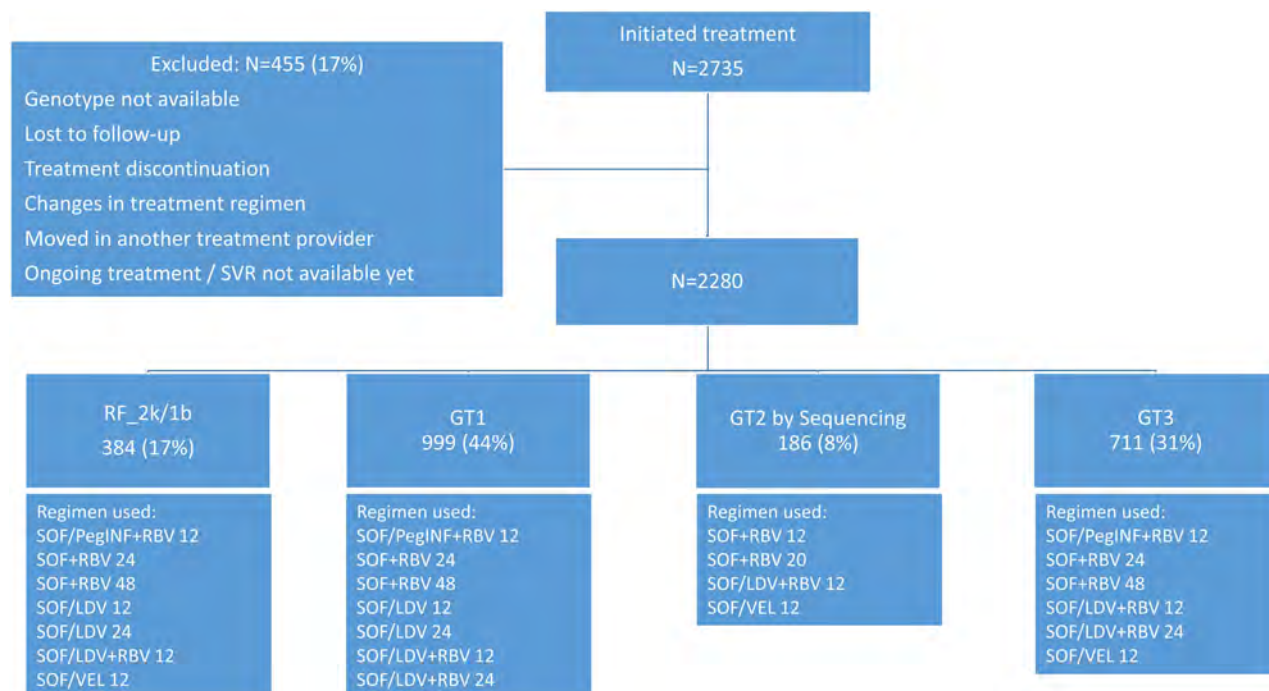


Figure 1 Flowchart of patient selection and treatment regimens according to hepatitis C virus genotypes among study participants. The number in the treatment regimen refers to the number of treatment weeks. GT, genotype; LDV, ledipasvir; PegIFN, pegylated interferon; RBV, ribavirin; RF, recombinant form; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

virologic response was defined as undetectable HCV-RNA 12 weeks after the end of therapy.

Hepatitis C virus therapy

Patients were treated with the following SOF-based regimens: SOF, 400 mg; SOF/ledipasvir (LDV), 400/90 mg; or SOF/velpatasvir (VEL), 400/100 mg. In some cases, regimens included weight-based RBV, in doses ranging from 1000 mg to 1200 mg daily, and PegIFN α -2b or α -2a. Treatment regimens were chosen according to the national HCV management guidelines, which were based on available medications, HCV genotype, liver disease severity, and interferon and RBV eligibility. The clinical committee, established within the framework of the elimination program, identified a high prevalence of patients with RF_2k/1b and suggested the most appropriate treatment regimens for these patients (Fig. 1). These suggestions were based on recommendations of international experts. After introduction of SOF/VEL in Georgia, in February 2019, patients with GT1 continued treatment with the SOF/LDV regimen.

Statistical analyses

Statistical analyses were undertaken using IBM SPSS Statistics 20 (IBM; Armonk, New York, USA). Bivariate associations were undertaken for the subset of patients with complete demographic and treatment results. $P < 0.05$ was used to define statistical significance.

RESULTS

A TOTAL OF 2735 patients started treatment at Medical Center Mrcheveli from May 2015 through December 2019. The most prevalent HCV GT by the standard genotyping system, VERSANT HCV Genotype 2.0 Assay (INNO-LiPA HCV 2.0) was GT1 ($n = 1175$; 43%), followed by GT3 ($n = 842$; 31%) and GT2 ($n = 670$; 22%). After sequencing of core and NS5B genes, 66% of GT2 samples and 16% of the total samples ($n = 444$) were confirmed RF_2k/1b (Fig. 2).

Treatment results were only assessed for those patients to whom HCV genotyping results were available and who had post-treatment PCR HCV-RNA results: a total of 2280 patients, including 384 patients with RF_2k/1b (Fig. 1).

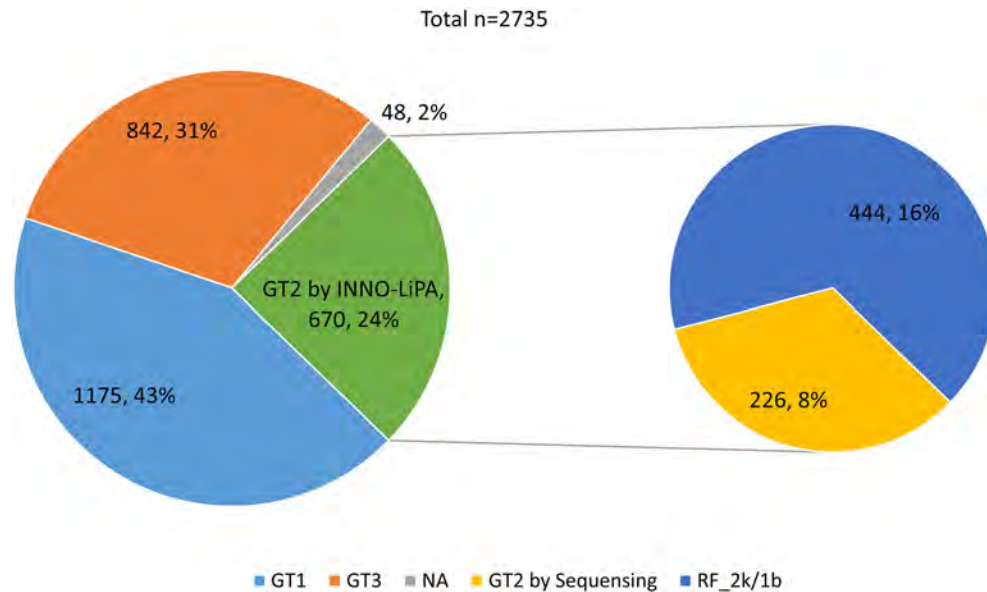


Figure 2 Distribution of hepatitis C virus genotypes among patients who started treatment at Medical Center Mrcheveli (Tbilisi, Georgia), May 2015–December 2019. GT, genotype; NA, not applicable; RF, recombinant form.

Analysis of baseline characteristics of patients with RF_2k/1b to patients with GT1, GT2, and GT3 showed that approximately one-third of patients had ACLD in both groups and a higher proportion of men were found in the RF_2k/1b group (82%/74%). Most patients (82%) from the non-RF_2k/1b group were from the capital of

Georgia, Tbilisi, and nearly 40% of patients with RF_2k/1b were from either the western or eastern parts of Georgia (Table 1).

The highest SVR (100%) was achieved in patients with RF_2k/1b treated with fixed dose combination medication (SOF/LDV or SOF/VEL), compared to patients treated with

Table 1 Demographic and clinical characteristics of patients with hepatitis C virus recombinant form (RF) 2k/1b ($n = 2280$)

Patient characteristic	GT1 ($n = 999$)	GT2 by sequencing ($n = 186$)	GT3 ($n = 711$)	Total GT 1 2 and 3 ($n = 1896$)	RF_2k/1b ($n = 384$)	P-value*
Gender, n (%)						
Male	650 (65)	129 (69)	623 (87.6)	1402 (74)	314 (82)	0.01
Female	349 (35)	57 (31)	88 (12.4)	494 (26)	70 (18)	
ACLD, n (%)	310 (31)	49 (26)	283 (39.8)	642 (34)	116 (30.2)	0.18
Mean baseline ALT level, n (range)	67.5 (10–528)	61 (6–345)	110 (13–583)	80 (6–583)	78 (15–391)	0.84
Treatment experience, n (%)						
Naïve	950 (95)	184 (99)	679 (96)	1813 (96)	361 (94)	0.10
PegIFN + RBV	49 (5)	2 (1)	32 (5)	83 (4)	23 (6)	
Geographic distribution, n (%)						
From capital (Tbilisi)	799 (80)	150 (81)	604 (85)	1553 (82)	229 (60)	<0.01
HBV co-infection, n (%)	7 (0.7)	2 (1)	11 (1.5)	20 (1)	4 (1)	0.96
Mean age, n (range)	47 (12–79)	50 (21–74)	44 (20–73)	46 (12–79)	46 (17–73)	0.29
Mean BMI, n (range)	27 (16–50)	28 (18–41)	27 (17–47)	28 (16–50)	26 (16–46)	0.33

Data are shown as n (%) or n (range).

*P value was calculated after comparison of two groups: RF_2k/1b and GT 1, 2 and 3.

ACLD, advanced chronic liver disease; ALT, alanine aminotransferase; BMI, body mass index; HBV, hepatitis B virus; PegIFN+RBV, pegylated interferon+ribavirin.

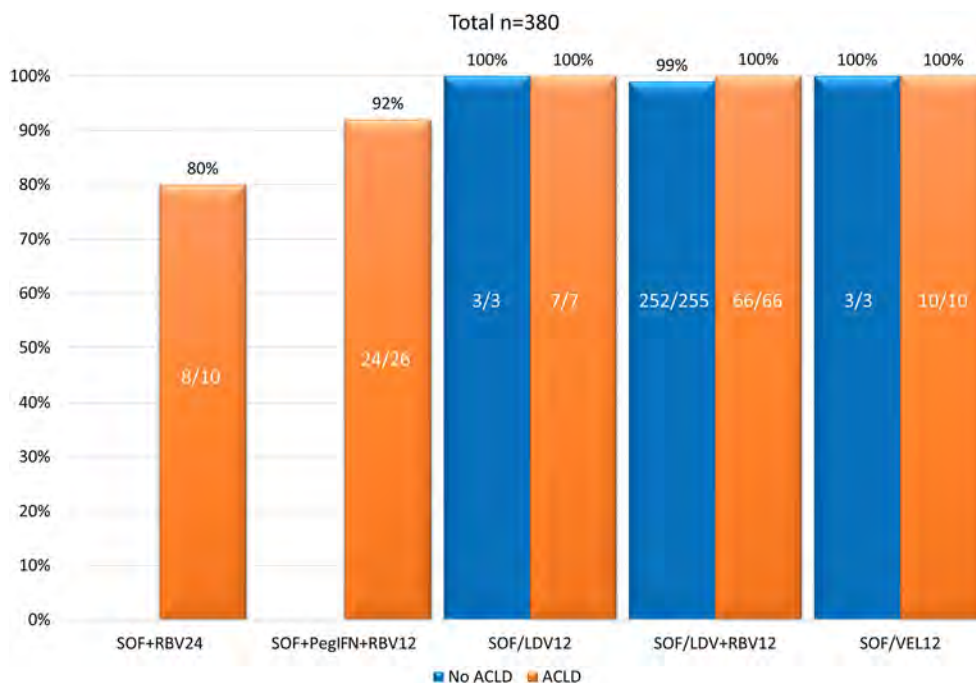


Figure 3 Treatment outcomes of patients with hepatitis C virus recombinant form 2k/1b treated with different sofosbuvir (SOF)-containing regimens. The number in the treatment regimen refers to the number of treatment weeks. ACLD, advanced chronic liver disease; LDV, ledipasvir; PegIFN, pegylated interferon; RBV, ribavirin; VEL, velpatasvir.

SOF + RBV and SOF + PegIFN + RBV regimens (80% and 92%, respectively) (Fig. 3).

The majority of patients with RF_2k/1b (83.5%; 321/384) were treated with the SOF/LDV + RBV regimen for 12 weeks. This regimen was available for a longer time compared to other regimens within the National Hepatitis C Elimination Program. The overall SVR rate in all patients with or without ACLD, treated with SOF/LDV based regimens with or without RBV, was high: RF_2k/1b, 330/333, 99%; GT1, 876/885, 99%; GT2, 152/157, 97%; and GT3, 529/533, 99% (Table 2).

From May 2015 until March 2016, SOF was only available in combination with PegIFN and RBV. During that period, four treatment provider centers were eligible to treat patients and because of the large number of patients awaiting antiviral treatment, only patients with ACLD were eligible. We treated patients with RF_2k/1b in a similar fashion to those with GT1 (SOF + PegIFN + RBV 12 weeks or SOF + RBV 24 weeks). In other HCV provider centers with limited capacity to identify the patients with RF_2k/1b, patients with unspecified GT2a/2c were treated with SOF/RBV for 12 or 20 weeks depending on the presence of cirrhosis. The patients with unspecified GT2a/2c had an SVR of 79% (351/446), compared with 96% (23/24)

among those with confirmed GT2 who were treated with the same regimen in our clinic ($P < 0.05$) (Fig. 4).

For identification the patients with RF_2k/1b, among unspecified GT2 treatment failures, 20 samples of 95 were randomly selected in order to undertake partial genome sequencing of core and NS5B regions. Sequencing was not carried out in one sample due to low viral load. Two of 20 samples appeared to be GT1 and GT3. All other 17 samples were RF_2k/1b.

Treatment with SOF + RBV for 24 weeks yielded a higher SVR of 80% (8/10) in patients with RF_2k/1b compared to SVR of 46% (24/52) in patients with GT1 ($P = 0.05$). A slightly higher SVR rate was observed in patients with RF_2k/1b compared to GT1 treated with SOF + PegIFN + RBV for 12 weeks, although the difference was not statistically significant (92% vs. 80%, $P = 0.159$) (Fig. 5).

After introduction of SOF/LDV within the program, the clinical management guidelines of the National Hepatitis C Elimination Program allowed treatment of patients with RF_2k/1b only with SOF/LDV + RBV, similar to the patients with GT2. We treated patients with SOF/LDV without RBV only in those cases where the patients were ineligible for RBV and did not have ACLD ($n = 10$). Despite the small number of patients, the SVR rate was

Table 2 Sustained virologic response rates among study participants treated with different sofosbuvir (SOF)-containing regimens ($n = 2280$)

Treatment regimen [†]	ACLD	RF_2k/1b	GT1	GT2 by sequencing	GT3
SOF/PegIFN + RBV for 12 weeks	All with ACLD	24/26 (92)	44/55 (80)	-	100/104 (96)
SOF + RBV for 12 weeks		-	-	15/15 (100)	-
SOF + RBV for 20 weeks		-	-	8/9 (89)	-
SOF + RBV for 24 weeks		8/10 (80)	24/52 (46)	-	47/53 (89)
SOF + RBV for 48 weeks		2/2 (100)	3/7 (43)	-	1/2 (50)
SOF/LDV for 12 weeks	With ACLD	7/7 (100)	136/138 (99)	-	-
	Without ACLD	3/3 (100)	685/689 (99)	-	-
SOF/LDV for 24 weeks	All with ACLD	2/2 (100)	15/16 (94)	-	-
SOF/LDV + RBV for 12 weeks	With ACLD	66/66 (100)	36/38 (95)	24/25 (96)	62/63 (98)
	Without ACLD	252/255 (99)	-	128/132 (97)	415/417 (100)
SOF/LDV + RBV for 24 weeks	All with ACLD	-	4/4 (100)	-	52/53 (98)
SOF/VEL for 12 weeks	With ACLD	3/3 (100)	-	-	7/8 (88)
	Without ACLD	10/10 (100)	-	4/5 (80)	9/11 (82)
All regimens	With ACLD	113/116 (97)	262/310 (85)	47/49 (96)	269/283 (95)
	Without ACLD	264/268 (99)	685/689 (99)	132/137 (96)	424/428 (99)
	Total	377/384 (98)	947/999 (95)	179/186 (96)	693/711 (97)

Data are shown as n/N (%).

[†]Chosen according to the national hepatitis C virus (HCV) management guidelines, which were based on available medications, HCV genotype (GT), degree of liver damage, and eligibility for interferon and ribavirin (RBV) therapy.

-, no cases; ACLD, advanced chronic liver disease; LDV, ledipasvir; PegIFN, pegylated interferon; RF, recombinant form; VEL, velpatasvir.

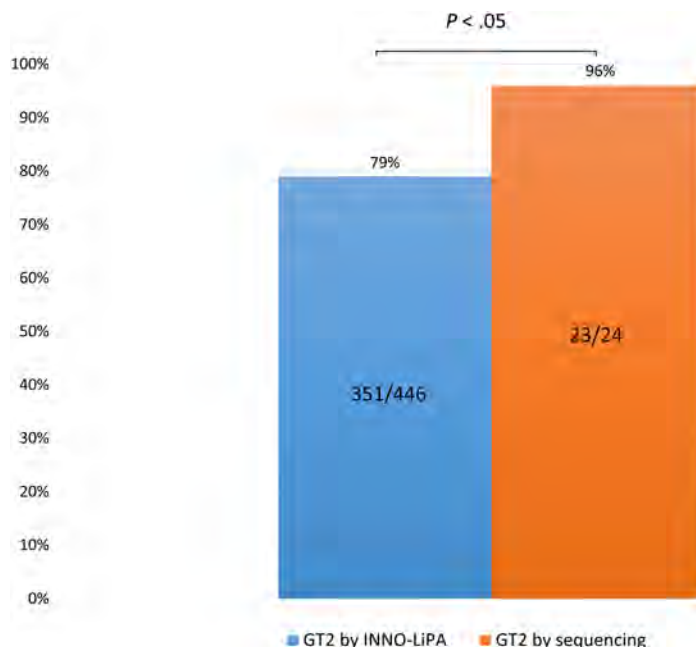


Figure 4 Comparison of sustained virologic response rates among patients with unspecified genotype (GT) 2 (by INNO-LiPA assay) and “pure” GT2 (by sequencing) hepatitis C virus (HCV), treated with sofosbuvir + ribavirin. All patients had advanced chronic liver disease. The patients with GT2 by INNO-LiPA ($n = 446$) were treated by other HCV treatment providers. This separate data was extracted from the national HCV elimination program database of Georgia.

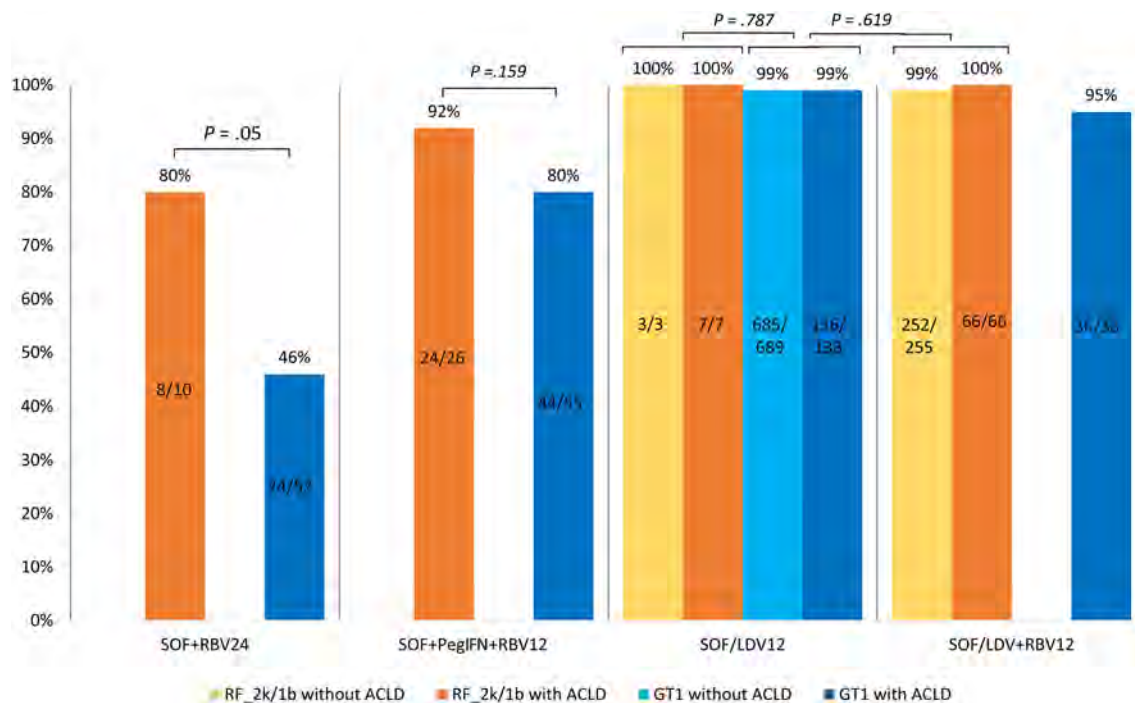


Figure 5 Comparison of sustained virologic response rates among patients with hepatitis C virus HCV recombinant form (RF) 2k/1b and genotype (GT) 1. The number in the treatment regimen refers to the number of treatment weeks. ACLD, advanced chronic liver disease; LDV, ledipasvir; PegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir.

highest and consistent with results for patients with GT1 (100% vs. 99%, $P = 0.787$) (Fig. 5).

Patients with GT2 were also treated with a non-standard regimen,¹² amended for the National Hepatitis C Elimination Program, of SOF/LDV + RBV for 12 weeks irrespective of presence of ACLD. The SVR rate was high (97%) and was not less than historical data of patients with GT2 treated with standard regimens (SOF/VEL and glecaprevir/pibrentasvir).

The SVR rates of patients with RF_2k/1b compared to patients with GT2 and GT3, treated with the SOF/LDV + RBV regimen, showed no significant differences between genotypes (Fig. 6).

DISCUSSION

HEPATITIS C VIRUS has substantial genetic diversity, classified into seven genotypes and many subtypes, with GT1 and GT3 dominating the European population.¹³ In 2002, Kalinina *et al.* reported a new circulating HCV strain in St. Petersburg, Russia, which was different from known genotypes.¹⁴ This genetic divergence was not due to mutations but the recombination of HCV genomes of different genotypes, which the authors called

“recombinant form.” Hepatitis C virus recombination is thought to be rare and to play a minor role in HCV evolution. Isolated cases have been reported in many other countries, which has not generally exceeded 3% among all HCV genotypes.^{15,16} Despite this, a recent journal article showed that the prevalence of this recombinant virus in Georgia is one of the highest reported worldwide.¹⁶

The key questions that arose after identification of high-prevalence RFs were: (i) how to best treat those patients? and (ii) is it necessary to differentiate RFs in the era of pan-genotypic DAAs?

The HCV genotype has long been considered a predictor of the outcome of antiviral therapy. All currently registered DAAs are active only against non-structural proteins (NS5B and NS5A) of HCV. It is already known that this part of RF1_2k/1b is similar to GT1b. So, it is suggested that patients with RF1_2k/1b should be provided the same treatment as patients with GT1b. An earlier study by Hedskog *et al.* suggested that the antiviral treatment outcome in patients with the HCV RF_2/1 with a 12- to 16-week course of SOF/RBV was closer to the response seen in patients with GT1 than in patients with GT2.¹⁰ In another study, published by Susser *et al.*, a very high rate of virologic relapse (93%) occurred in patients with

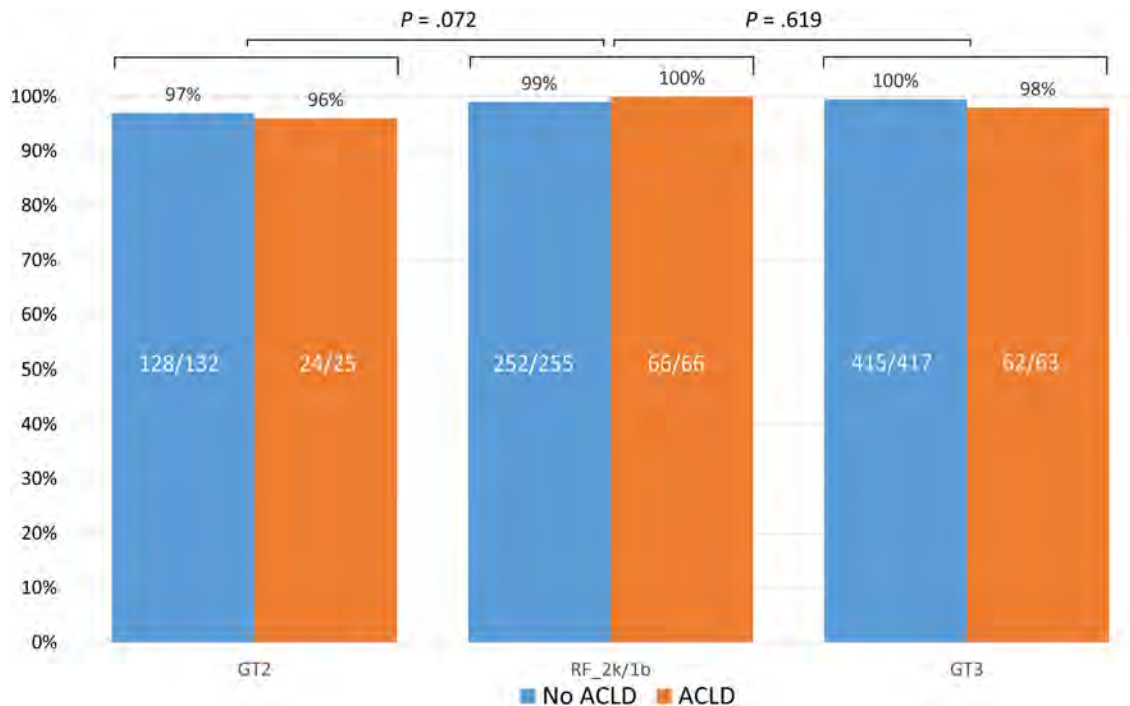


Figure 6 Comparison of sustained virologic response rates among patients with hepatitis C virus recombinant form (RF) 2k/1b, genotype (GT) 2, and GT3 treated with sofosbuvir/ledipasvir + ribavirin for 12 weeks. ACLD, advanced chronic liver disease.

RF1_2k/1b treated with a GT2 regimen. Nevertheless, excellent results were achieved when RF patients were either initially treated with a GT1 regimen (eight of nine patients achieved SVR) or were retreated after relapse (13 of 13 patients achieved SVR).¹¹

There are several case reports that detail the successful results of DAA treatment in patients with RF_2k/1b.¹⁷⁻¹⁹

The study published by Karchava *et al.* evaluated the SVR results of 103 Georgian patients with RF_2k/1b and concluded that the SOF/LDV + RBV regimen was better than the SOF + RBV regimen.²⁰

In 2015, the first PegIFN-free treatment regimen was introduced to patients with GT2: SOF + RBV for 12, 16, or 20 weeks.²¹ The SVR rates were between 83% and 100%. During the first year of the National Hepatitis C Elimination Program (May 2015–March 2016), when only SOF was available and only patients with ACLD were eligible for the treatment, we were concerned about the treatment outcomes for the group of patients with GT2, as it might have potentially included the high prevalence of patients with RF_2k/1b. Other HCV treatment provider centers in Georgia with a limited capacity to differentiate patients with GT2 from those with RF_2k/1b have observed lower SVR rates (79%) after treating with the standard SOF + RBV regimen for 12, 16, or 20 weeks. In our

center, after refinement of patients with GT2 from patients with RFs, we treated patients with RFs with the GT1 regimen (adding PegIFN), and received better viral cure results (SVR of 92%). To double-check this difference, we genotyped and sequenced randomly selected treatment failures from the other medical centers, checking those that were thought to be GT2, and confirmed that 17 of 20 patients were RF_2k/1b.

After introduction of the SOF/LDV regimen, the key concern was that patients with GT2 and GT3 would receive a non-standard regimen for those genotypes. To standardize our approach, the clinical committee of the National Hepatitis C Elimination Program, with the help of international experts, suggested to treat all genotypes, except GT1, with SOF/LDV + RBV. Only RBV-ineligible HCV patients with RF_2k/1b were allowed to be treated with only SOF/LDV for a prolonged treatment duration. Because of the similarity to GT1 within the non-structural region of the recombinant virus's genome,⁹ a 100% cure rate was achieved (10/10). A surprisingly high cure rate was observed among patients with GT2 and GT3 treated with the SOF/LDV regimens despite the presence of ACLD (97% and 99%, respectively).²²

Based on these retrospective data analyses, providing patients with RF_2k/1b the same treatment as patients with

GT1 was the appropriate treatment decision. We can also assume that when GT2 was considered the best genotype for a cure, the majority of treatment failures could have been patients with RF_2k/1b, at least in the country of Georgia.

The data showed that treatment of patients with RF_2k/1b with SOF/LDV or one of the pan-genotypic drugs (SOF/VEL) is extremely effective. We can also assume that other DAAs that are used for patients with GT1 and/or pan-genotypic drugs might be as effective.

Although the recent pan-genotypic DAAs are ultimately eliminating any concern related to the effect of genotype on treatment response, the availability of these expensive drugs is still currently limited. It is worth mentioning that six developing nations (China, Pakistan, Nigeria, Egypt, India, and Russia) account for more than half of HCV infections worldwide.²³

Continuous identification of recombinants could be helpful for making treatment choices until pan-genotypic medications become widely available and affordable. Identification of recombinants in high-prevalence areas might be reasonable for improving antiviral response rates, particularly in the context of HCV elimination worldwide.^{16,24}

In conclusion, identification of RF_2k/1b in treatment-naïve or PegIFN/RBV treatment-experienced patients, with or without liver cirrhosis, in countries where pan-genotypic drugs are available, is not necessary. However, in areas where pan-genotypic DAAs are not available or affordable, especially in low-income countries with a high prevalence of HCV infection, differentiating patients with GT2 from those with RF_2k/1b might be reasonable for choosing the most cost-effective treatment regimens.

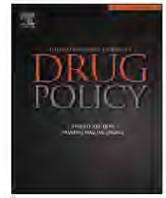
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Integration of hepatitis C treatment at harm reduction centers in Georgia—Findings from a patient satisfaction survey

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ABSTRACT

Background: Georgia launched national HCV elimination program in 2015. PWID may experience barriers to accessing HCV care. To improve linkage to care among PWID, pilot program to integrate HCV treatment with HR services at opiate substitution therapy (OST) centers and needle syringe program (NSP) sites was initiated. Our study aimed to assess satisfaction of patients with integrated HCV treatment services at HR centers.

Methods: Survey was conducted among convenience sample of patients receiving HCV treatment at 5 integrated care sites and 4 specialized clinics not providing HR services. Simplified pre-treatment diagnostic algorithm and treatment monitoring procedure was introduced for HCV treatment programs at OST/NSP centers which includes fewer pre-treatment and monitoring tests compared to standard algorithm.

Results: In total, 358 patients participated in the survey - 48.6% receiving HCV treatment at the specialized clinics while 51.4% at HR site with integrated treatment. Similar proportions of surveyed patients at HR sites (88.0%) and clinics (84.5%) stated that they did not face any barriers to enrollment in the elimination program. Most patients from HR pilot sites and specialized clinics stated that they received comprehensive information about the treatment (98.4% vs 94.3%; $p < 0.010$). 95% of respondents at both sites were confident that confidentiality was completely protected during treatment. Higher proportion of patients at pilot sites thought that HCV treatment services provided at facility were good compared to those from the specialized clinics (85.3% vs 81.0%). We found significant difference in the time to treatment, measured as average time from viremia testing to administration of first dose of HCV medication: 42.9% of patients at pilot sites vs 4.6% at specialized clinics received the first dose of medication within two weeks.

Conclusion: Quality of services and perceived satisfaction of patients receiving treatment, suggests that integration of HCV treatment with HR services is feasible.

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Introduction

Georgia, a country with high burden of hepatitis C virus (HCV) infection (Gvinjilia et al., 2016), launched an ambitious national hepatitis C elimination program in 2015 (Ministry of Labour Health and Social Affairs (MoLSHA), 2020; Mitruka et al., 2015) and has made substantial progress (Averhoff et al., 2019). Georgia has a large population of people who inject drugs (PWID); to achieve elimination, which Georgia defined as a 90% reduction in hepatitis C prevalence, efforts are needed to engage PWID, who are at high risk of HCV infection and may experience barriers to accessing hepatitis C care and treatment (Hagan et al., 2019). Provision of treatment for hepatitis C for PWID is effective particularly when delivered in an integrated and multi-disciplinary approach (Bajis et al., 2017; Bird, Socías & Ti, 2018; Eckhardt, Scherer, Winkelstein, Marks & Edlin, 2018; Stvilia et al., 2019). Integration of services may mitigate stigma and facilitate hepatitis C treatment access for PWID by creating a welcoming environment at familiar institutions, such as the harm reduction (HR) centers, that foster trust and support for this often-marginalized population.

It is estimated that 2% of the adult population in Georgia inject drugs (Stvilia et al., 2019). Since the launch of the national hepatitis C elimination program in the country, screening for HCV infection dramatically increased among PWID (Stvilia et al., 2019). However, among clients of needle and syringe program (NSP) that tested positive for active HCV infection, only 75.1% initiated treatment (Stvilia et al., 2019). To improve linkage to care and treatment among PWID, the Government of Georgia initiated a pilot program to integrate hepatitis C treatment with HR services at opiate substitution therapy (OST) centers and needle syringe program (NSP) sites. To assess acceptance of integration of hepatitis C treatment services at HR centers, patient satisfaction with OST/NSP participating sites was evaluated and compared to existing centers in Georgia that offer hepatitis C care and treatment without provision of HR services.

Methods

A patient satisfaction instrument was developed, and a survey was conducted among a convenience sample of patients receiving hepatitis C treatment services at 5 participating integrated care sites (hereafter “pilot centers”) and 4 specialized service centers treating HCV-infected patients but not providing HR services during May 2018 through September 2019. Clients of OST or NSP centers with active HCV infection (HCV RNA positive individuals) and low liver fibrosis level (FIB-4 score < 1.45) who were enrolled in the integrated hepatitis C treatment program at HR centers were surveyed (patients with advanced liver fibrosis [FIB4 ≥ 1.45] are referred to specialized treatment centers). Patients at specialized clinics were surveyed regardless of liver fibrosis stage. All study participants were enrolled in the study 1 month after initiation of treatment.

A simplified pre-treatment diagnostic algorithm and treatment monitoring procedure was introduced for hepatitis C treatment programs at the participating OST and NSP centers. Compared to the standard algorithm, the simplified version includes fewer pre-treatment (alkaline phosphatase (ALP), gamma-glytamyl transpeptidase (G-GT) and glucose tests were removed) and monitoring (HCV RNA test and complete blood count (CBC) on week 4, alanine aminotransferase (ALT) on week 8 and creatinine and bilirubin on week 12 of treatment were removed) tests.

The nine participating treatment centers included two OST centers in Tbilisi (the capital city), three NSP centers – one in Tbilisi and two in regional cities Zugdidi and Batumi, and four specialized service provider clinics in Tbilisi. The survey instrument was a self-administered questionnaire specifically designed for this study. The questionnaire asked for information about socio-demographic characteristics, perceived barriers faced during enrollment in the hepatitis C treatment program, convenience of location, satisfaction with conditions at the

treatment site, perceived attitude of providers including doctors and nurses, perceived concerns about confidentiality, length of time from first viremia testing to the administration of first dose of HCV treatment received, quality of information provided about the treatment and possible side effects of the drugs, and overall satisfaction about treatment services provided at the facility. Study participants were recruited using a convenience sample design at each study site. Participation in the survey was voluntary and participants signed informed consent. The study was approved by institutional review board of Health Research Union (IRB#00009520). The collected data were entered and analyzed in statistical software SPSS v.22.

Results

In total, we recruited 385 patients and 358 (92.9%) participated in the survey. A total of 174 (48.6%), received hepatitis C treatment at the specialized clinics while 184 (51.4%) received treatment at a HR site with integrated hepatitis C treatment. Compared to specialized clinics, pilot sites had more male participants (89.7% vs. 70.7%; $p < 0.0001$), more persons aged 30–50 years (62.1% vs. 47.1%; $p < 0.005$), and more persons unemployed (64.1% vs. 46.2%; $p = 0.001$). There were no differences in marital status (73.8% vs. 75.3%; $p = 0.100$), education (62.1% vs. 66% had university degree, $p = 0.200$) and place of residence (70.7% vs. 77.6% resided in Tbilisi, $p = 0.100$) between the HR and specialized clinic participants respectively.

OST/NSP centers were the primary source of information about the hepatitis C elimination program for the majority of patients (54.3%) treated at HR pilot sites with family members/relatives/friends being the second most common source of information (36.0%). For patients from specialized clinics, family members/relatives/friends were the most commonly reported source of information (34.5%), followed by healthcare worker (28.2%) and media (27.0%).

Similar proportions of surveyed patients at HR sites (88.0%) and specialized clinics (84.5%) stated that they did not face any barriers to enrollment in the elimination program ($p = 0.300$) (Table 1).

The location of the treatment facility was considered more convenient for patients treated at HR (97.3%) than at the specialized clinics (89.1%), ($p = 0.002$), although both scored highly. Conditions at the medical facility (98.4% vs. 91.4%; $p < 0.0010$) received higher scores from patients treated at the HR site compared to those treated at the specialized clinics, while the attitude of doctors (96.2% vs. 97.7%; $p = 0.300$) and nurses (94.5% vs. 98.8%; $p = 0.600$) were comparable and generally satisfactory by the participants at both the HR pilot sites and the specialized clinics, respectively. Most patients from HR pilot sites and specialized clinics stated that they received comprehensive information about hepatitis C treatment and side effects of medications (98.4% vs 94.3%; $p < 0.010$).

More than 95% of the respondents surveyed at both HR pilot sites, and specialized clinics were confident that their confidentiality was completely protected during treatment ($p = 0.200$).

We found a significant difference in the time to treatment, measured as the average time from the first viremia testing to administration of the first dose of hepatitis C treatment course: 42.9% of patients at pilot sites received the first dose of medication within two weeks after the first viremia testing, whereas only 4.6% of the patients at the specialized clinics received medication within two weeks ($p < 0.0001$).

A higher proportion of patients at pilot sites thought that hepatitis C treatment services provided at the facility were very good compared to those from the specialized clinics (85.3% vs 81.0%; $p = 0.030$). All study participants (100.0%) from both pilot sites and the specialized clinics would recommend their family members, relatives and/or friends enroll in the hepatitis C elimination program (data not shown). Among those receiving care at the pilot sites, 98.9% reported that integrated care was very convenient.

Table 1

Levels of satisfaction among patients treated for HCV infection at specialized treatment clinics not providing harm reduction services and integrated hepatitis C treatment sites providing opioid substitution therapy or needle/syringe program services, Georgia.

Characteristics	Pilot program centers providing OST/NSP services		Specialized clinics providing HCV care		p-value
	N	%	N	%	
Facing barriers regarding enrollment in hepatitis C elimination program					
No	162	88.0	147	84.5	0.300
Yes	22	11.9	27	15.5	
Convenience of the medical facility's location					
Convenient	179	97.3	155	89.1	0.002
Not convenient	5	2.7	19	10.9	
Conditions (building, waiting space, sanitary norms) at the medical facility					
Satisfactory	182	98.9	159	91.4	0.001
Partially satisfactory/Not satisfactory	2	1.1	15	8.6	
Attitude of doctor towards patient					
Satisfactory	177	96.2	170	97.7	0.300
Partially satisfactory	7	3.8	3	1.7	
Attitude of nurses towards patient					
Satisfactory	174	94.5	172	98.9	0.600
Partially satisfactory	10	5.5	2	1.1	
Received comprehensive information about hepatitis C treatment and side effects					
Yes, completely	181	98.4	164	94.3	0.010
Partially/No	3	1.6	10	5.8	
Protection of confidentiality during hepatitis C treatment					
Yes, completely	180	97.8	166	95.4	0.200
Partially/No	4	2.2	8	4.6	
Average time spent at the facility during the first visit for enrollment in hepatitis C elimination program					
10 min	92	50.0	39	22.4	0.400
20 min	48	26.1	63	36.2	
30 min	44	23.9	72	41.4	
Average time from viremia testing to the administration of the first dose of hepatitis C medication					
2 weeks	79	42.9	8	4.6	<0.0001
1 month	78	42.4	109	62.6	
2 months	20	10.9	39	22.4	
> 2 months	7	3.8	18	10.3	
Average time waiting to receive medication at medical facility					
15 min	173	94.0	161	92.5	0.400
30 min	10	5.4	13	7.5	
60 min	1	0.5	–	–	
Convenience of receiving hepatitis C treatment and OST/NSP services at the same facility					
Convenient	182	98.9	N/A	N/A	
Partially convenient	2	1.1	N/A	N/A	
Quality of hepatitis C treatment services at the facility					
Very good	157	85.3	141	81.0	0.030
Good	27	14.7	27	15.5	
Not good not bad	–	–	6	3.4	
Recommending family member/relative/friend to get enroll in hepatitis C elimination program?					
Yes	184	100.0	174	100.0	
No/Not sure	–	–	–	–	

Abbreviations: OST = opiate substitution therapy; NSP = needle syringe program.

Discussion

In countries where injection drug use is an important mode of HCV transmission, to eliminate hepatitis C and reduce transmission, it is critical to ensure access to treatment for PWID. However, globally, treatment rates remain low among this high-risk population (Day et al., 2019; Socías et al., 2019), in part due to barriers in accessing care and treatment services (Day et al., 2019; Socías et al., 2019). Integrating the provision of hepatitis C treatment with HR services can improve access to services for PWID (Bird et al., 2018; Socías et al., 2019). Our study found that care integration in HR decreased the time from diagnosis to receipt of the first dose of medication, which can reduce dropout and improve initiation of treatment (Mohamed et al., 2020). Satisfaction with treatment services was at least as good in the HR sites as in the specialized clinics.

An important consideration is that the surveyed populations differed significantly between the HR and specialized clinics. Aside from

demographics, all patients surveyed at HR pilot sites were PWID, a marginalized and stigmatized population, while at the specialized clinics, the population surveyed included patients who were not PWID. This may have limited the perceived satisfaction and impact of treatment receipt at HR sites; that is, specialized clinics may have had a lower satisfaction rate if the surveyed population was limited to PWID receiving services at those sites.

Taken together, our findings suggest that incorporating hepatitis C treatment into HR will improve treatment uptake.

This is the first study in Georgia assessing the satisfaction of patients receiving hepatitis C treatment at HR centers. The majority of surveyed patients at HR centers were satisfied with the convenience of the location, conditions of the facility, the supportive environment, the sense that confidentiality would be assured, and the quality of treatment. It is important to note that there was no difference in the level of satisfaction between the pilot program providing integrated care and treatment services and the specialized clinics.

This study has several limitations. First, we haven't randomized study participants and used convenience sampling. But we don't expect selection bias, because there are no predefined criteria of scheduling patients' appointments by specific days or times. Accordingly, patients visiting clinics for their regular elimination program visits, are not expected to be different. Also, participation rate was high (96% of those asked to participate in a survey). Second, integration of HCV treatment with harm reduction services is a pilot program in Georgia involving only limited number of HR centers. Accordingly, our findings cannot be generalized to all PWID in the country. Third, self-reported data can be associated with information bias.

The quality of service and perceived satisfaction of patients receiving treatment, suggests that this integration model could improve adherence and compliance, decrease dropout rates, and therefore, play a critical role in reaching elimination in Georgia. Integration of hepatitis C treatment with HR services is feasible. Ministry of Internally Displaced Persons from the Occupied Territories, Labor, Health and Social Affairs is planning to expand decentralization of hepatitis C treatment services and one of the key activities is the integration of treatment at HR centers throughout the country. The lessons from this study could facilitate treatment introduction in such settings, and are applicable to other countries with large numbers of PWID seeking to eliminate hepatitis C.

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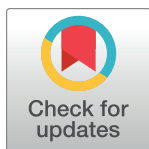
RESEARCH ARTICLE

Sensitivity and specificity of rapid hepatitis C antibody assays in freshly collected whole blood, plasma and serum samples: A multicentre prospective study

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Abstract

Background

This study evaluated performance of two hepatitis C virus (HCV) rapid diagnostic tests (RDTs) performed by intended users in resource-limited settings.

Methods

Testing was conducted at three facilities in two countries (Georgia, Cambodia) using matched fingerstick whole blood, plasma and serum samples. Investigational RDTs were compared with a composite reference standard (CRS) comprised of three laboratory tests, and a reference RDT.

Results

In matched samples from 489 HCV positive and 967 HCV negative participants, specificity with both investigational RDTs was high using either reference method ($\geq 98.4\%$ in all sample types). Sensitivity was lower in whole blood versus plasma and serum for both RDTs compared with the CRS (86.5–91.4% vs 97.5–98.0% and 97.3–97.1%) and reference RDT (93.6–97.8% vs 100% and 99.4%). Sensitivity improved when considering only samples with detectable HCV viral load.

Conclusion

Sensitivity was highest in serum and plasma versus whole blood. The World Health Organization prequalification criterion ($\geq 98\%$) was narrowly missed by both RDTs in serum, and one in plasma, possibly due to the intended user factor. Performance in whole blood was

whole blood, plasma and serum samples: a multicentre prospective study was published in Harvard Dataverse: <https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/W88BHP>.

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considered adequate, given potential roles of HCV infection history, improved sensitivity with detectable viral load and performance similarities to the reference RDT.

Introduction

World Health Organization (WHO) member states have committed to the elimination of viral hepatitis as a public health threat by 2030 [1]. Screening for hepatitis C virus (HCV), a pathogen that affects approximately 71 million people worldwide (2015 estimate), is critical to the success of these targets, especially as only an estimated 20% of infected people are aware of their HCV status [1]. According to WHO recommendations, screening should be performed through the detection of HCV-specific antibodies using a single quality-assured serological *in vitro* diagnostic test, which can be either a laboratory-based immunoassay or a rapid diagnostic test (RDT) [2]. A positive RDT test is followed by confirmatory testing for viraemic infection via detection of HCV viral load (VL) or core antigen [2].

Low- and middle-income countries (LMICs) have the highest burden of HCV, representing over 70% of the global total [3]. However, access to laboratory-based testing services in these settings is often limited by the absence of suitable equipment, stringent training requirements and sample or patient transportation challenges. RDTs, which can be used outside of the laboratory, are an attractive alternative due to their affordability, ease of use and feasibility of utilizing various sample types, including plasma, serum, fingerstick whole blood or oral fluid [2]. WHO prequalification status intends to indicate that an RDT is likely to have reliable performance in LMICs, as it requires the generation of performance data in LMICs in intended use settings by intended users, with at least a portion of these data generated using freshly collected samples [4]. However, of the many commercially available HCV RDTs, only four have obtained WHO prequalification status to date [5]. The scarcity of quality-assured RDTs is an important barrier to HCV screening in LMICs on a large scale [6].

A previous retrospective study evaluated the performance of 13 HCV RDTs in archived plasma samples [7]. In this study, the majority of RDTs exhibited performance in line with WHO criteria for selection of HCV diagnostics in samples from patients without human immunodeficiency virus [HIV] co-infection (sensitivity $\geq 98\%$ and specificity of $\geq 97\%$ in serum or plasma samples [8, 9]). Sensitivity was lower in samples from HIV infected participants compared with samples from HIV uninfected participants; interestingly, the majority of false negative HIV infected samples did not have detectable HCV VL/core antigen. However, the retrospective study was performed on archived samples by highly trained staff in evaluation laboratories, a setting that does not fully reflect the reality in which HCV RDTs are intended or likely to be used. In the field, HCV RDTs are most likely to be performed in primary care or screening facilities by staff with limited training, using whole blood by finger prick as the most common sample type. Data on RDT performance in whole blood is often limited or absent, particularly in comparison with matched samples of other types.

The objective of the current study was to evaluate the sensitivity and specificity of HCV RDTs in a real-world setting. Performance was assessed in fresh, matched whole blood, plasma and serum samples that were collected and tested in resource-limited settings by intended users, i.e. nurses and primary healthcare personnel.

Methods

Study design

This prospective, multicentre study (NCT04139941) assessed the performance of two HCV RDTs: the HCV-Ab Rapid test (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd,

Beijing, China) and the First Response HCV card test (Premier Medical Corporation Ltd., Mumbai, India). Operational characteristics of these tests are shown in [S1 Table](#). These RDTs were selected as they met WHO prequalification criteria in archived plasma samples in the previous study [7], and the manufacturers had demonstrated a commitment to seeking WHO prequalification status.

Testing was conducted at three primary healthcare facilities in two countries. These were: a general outpatient clinic at the Sihanouk Hospital Center of Hope (SHCH), a non-governmental hospital providing low-cost medical care in Phnom Penh, Cambodia; an HCV screening facility at the National Center for Disease Control and Public Health (NCDC) in Tbilisi, Georgia; and an opioid substitution treatment facility at the Centre for Mental Health and Prevention of Addiction (CMHPA), also in Tbilisi, Georgia.

RDTs were tested on three sample types: fingerstick whole blood, ethylenediaminetetraacetic acid (EDTA) plasma, and serum (matched samples), all collected and tested on the same day. Performance was compared with three WHO prequalified laboratory reference tests, of which two were enzyme immunoassays (EIAs; Murex Anti-HCV version 4.0, Fujirebio INNOTEST HCV Ab IV) and one was a line immunoassay (LIA; Fujirebio INNO-LIA HCV Score), using a previously described composite reference standard (CRS) that incorporated the results of all three reference tests [7]. The algorithm was based on WHO prequalification evaluation protocols, with the final decision being based on the LIA test result. A signal-to-cut-off ratio of ≥ 1 (based on the measured optical density) was used for the EIAs; interpretation of LIA results was performed according to manufacturer instructions. Performance of the two investigational RDTs was also compared with a reference RDT, the WHO prequalified SD Bio-line HCV test (Abbott Laboratories, Lake Bluff, USA; operational characteristics shown in [S1 Table](#)).

Reference testing was conducted at diagnostic reference laboratories (R. Lugar Center for Public Health Research, Tbilisi, Georgia and Biobaykhin Medical Analysis Laboratory, Phnom Penh, Cambodia) using plasma samples, collected and tested on fresh or non-frozen samples (stored at 4°C) within seven days of sample collection, in accordance with manufacturer instructions for use. Confirmatory testing to obtain HCV VL and genotyping information was performed on fresh plasma samples. Tests used for determination of HCV VL were the Real-Time HCV viral load assay (Abbott Laboratories, Lake Bluff, USA; limit of detection [LOD] 12 IU/mL) in Georgia and the AccuPid HCV Real-time PCR Quantification Kit (Khoa Thuong Biotechnology, Ho Chi Minh City, Vietnam; LOD 21 IU/mL) in Cambodia. Testing was performed between July 2019 and December 2019. Ethics approval for this study was obtained from the Cambodian National Ethics Committee for Health Research and the Georgian National Center for Disease Control and Public Health Institutional Review Board. Written informed consent was obtained from all study participants.

Participant recruitment

Participants providing samples were required to be aged ≥ 18 years, have no history of HCV treatment (past or present), and be willing to perform an HIV test. At SHCH in Cambodia, all individuals visiting the facility as outpatients were invited to participate in the study until the daily recruitment target (~ 10 participants/day) was met. At CMHPA and NCDC in Georgia, all individuals visiting the facility were invited to participate. Additionally, known HCV positive individuals from the site databases were contacted and invited to participate. Participant demographic and medical history information was collected, including age, HIV status, other medications and infections, and recent vaccinations. Counselling related to HCV test results was offered, and all participants received HCV confirmatory testing. Participants were

assigned to the HCV positive and HCV negative group based on the result of the composite reference standard. If positive, Cambodian participants were given free treatment; Georgian participants received treatment via the national HCV treatment programme. The HCV status of participants was not known to RDT testers.

RDT performance assessments

Every sample type was tested and interpreted once per RDT. Invalid results were repeated once, and plasma and serum samples were repeated in duplicate if the initial result was different to the reference RDT SD Bioline. Two lots of each RDT were used; the complete sample population was tested to approximately 50% with lot 1 and 50% with lot 2. Testers were nurses and primary healthcare personnel who are intended to perform RDT screening as per each countries' healthcare system. A number of different testers performed the tests at each site. The number of different testers for whole blood samples was 6, 2 and 4 at SHCH, CMHPA and NCDC, respectively. The corresponding numbers of testers for plasma and serum were 3, 2 and 3.

Data capture

Participant demographic, medical history, RDT and LIA results were initially captured on paper case report forms. Viral load and genotype results, as well as EIA results were captured in electronic format on the respective analyses platforms. All data were subsequently entered into the electronic databased Open Clinica v4.0.

Outcome measures

The primary outcome was the estimates of sensitivity and specificity of the two RDTs in each of the three sample types, compared with the CRS. Sensitivity and specificity compared with the reference RDT SD Bioline was a secondary outcome. For both outcomes, sensitivity and specificity were calculated for the overall sample set, by country and in the subset of samples with detectable HCV VL. Furthermore, statistical difference in performance between the sample types was assessed for both outcomes. Additionally, a multivariate analysis was performed to evaluate the impact of different demographic factors on RDT sensitivity in whole blood.

Statistical analyses

For sample size calculations, sensitivity and specificity was assumed to be 90% for whole blood and 95% for plasma and serum samples. However, using these assumptions, the minimum sample sizes to achieve 80% power with a 95% CI of $\pm 5\%$ were lower than WHO Technical Specification Series-7 (TSS-7) requirements of 400 HCV positive and 1000 HCV antibody and RNA negative samples for diagnostic assessments of HCV RDTs [4]. Therefore, the TSS-7 values were used, with a 10% increase to account for sample exclusion due to indeterminate HCV status with the CRS (based on experience from the previous study [7]). Final sample size targets were 440 HCV antibody positive (HCV positive) and 1,100 HCV antibody negative (HCV negative) samples.

Point estimates with 95% confidence intervals based on Wilson's score method, were calculated for sensitivity and specificity. A performance comparison was performed using Pearson's chi-square test with Bonferroni adjustment to estimate statistical differences in RDT performance between sample types and by sample type between the two countries. Statistical analysis was performed using R (version 3.6).

Covariates included in the multivariate logistic regression were age, gender, presence of detectable viral load, HCV genotype and country. The model was applied separately for each

of the two investigational RDTs and the two reference methods (CRS and reference RDT SD Bioline). Estimates of coefficients and p-values were calculated using glm function with binomial logit specification in R.

Results

Population and sample characteristics

Of 1,540 individuals recruited, 11 were excluded, thus 1,529 samples of each type were provided in total. Characteristics of the individuals who provided samples are shown in Table 1. Mean age ranged from 40.3 years at CMHPA to 51.8 years at SHCH. Of the 1,529 samples, 489 were HCV positive, 966 were HCV negative, and 74 were excluded due to indeterminate results on the CRS (Fig 1). The number of HCV positive individuals encountered at NCDC in Georgia was higher than expected, thus more HCV positive participants were recruited than was anticipated in the predefined site enrolment targets.

HCV VL was detectable in 63% of HCV positive samples. HCV genotype 1, 1a and 1b were the most common, followed by genotype 3 and genotype 6. However, there were no genotype 3 samples from Cambodia, and no genotype 6 samples from Georgia (Table 2).

Sensitivity and specificity versus composite reference standard

When compared with the CRS, specificity in the overall sample set was high ($\geq 98.4\%$ for both RDTs in all three sample types), with no differences observed across sample types (adjusted $p = 1.0$) (Table 3). Sensitivity was lower in whole blood for the HCV-Ab Rapid test (86.5%) and the First Response HCV card test (91.4%), versus plasma (97.5% and 98.0%, respectively, adjusted $p < 0.001$) and serum (97.3% and 97.1%, adjusted $p < 0.001$ for the HCV-Ab Rapid test and adjusted $p = 0.005$ for the First Response HCV card test). Sensitivity was higher in the subset of samples with detectable HCV VL ($> 95.4\%$ for both RDTs) for all sample types compared with the overall sample set.

Sensitivity in whole blood was considerably lower in Cambodia than Georgia for both RDTs (76.6% vs 94.2% for the HCV-Ab Rapid test and 85.0% vs 96.4% for the First Response HCV card test; adjusted $p < 0.001$; Table 4). The majority of whole blood false negative samples with detectable VL from Cambodia were of genotype 1b, while those from Georgia were found

Table 1. Study population characteristics.

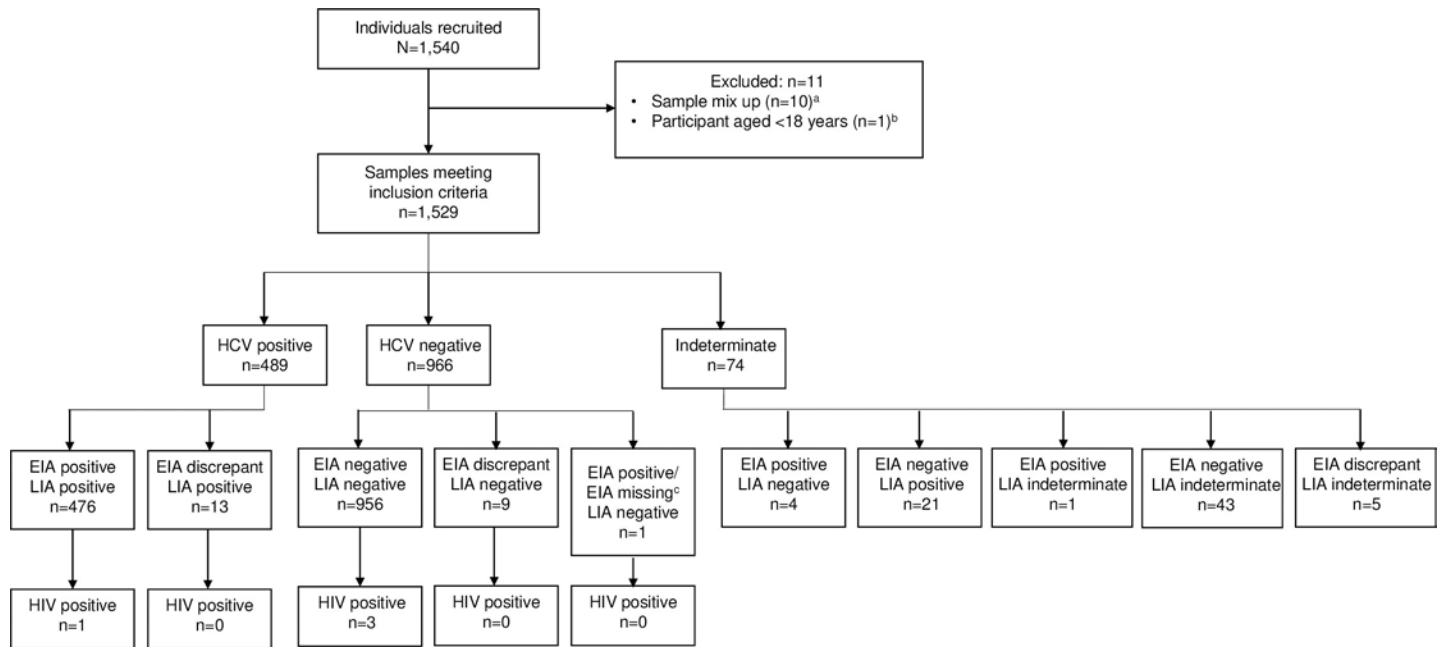
	SHCH Cambodia (N = 770)	CMHPA Georgia (N = 439)	NCDC Georgia (N = 320)
Male, n (%)	269 (34.9)	360 (82.0)	153 (47.8)
Mean age, years (range)	51.8 (± 13.7)	40.3 (± 10.5)	42.6 (± 13.6)
HCV positive on CRS, n (%)	214 (27.8)	209 (47.6)	66 (20.6)
HIV positive, n (%)	4 (0.5)	0	0
On ARV, n (%)	2 (0.3)	0	0
On other medication ^a , n (%)	375 (48.7)	259 (59.0)	49 (15.3)
Other infections ^{a,b} , n (%)	43 (5.6)	13 (3.0)	8 (2.5)
Recent vaccination ^{a,c} , n (%)	46 (6.0)	18 (4.1)	23 (7.2)

^aAll self-reported

^bHepatitis B virus, syphilis, hepatitis A virus, hepatitis D virus, influenza, measles, tuberculosis

^cIn the past 12 months; includes vaccination against hepatitis B virus, influenza, tetanus, rabies, human papillomavirus, measles-mumps-rubella, yellow fever. ARV, antiretroviral therapy; CMHPA, Centre for Mental Health and Prevention of Addiction; CRS, composite reference standard; HIV, human immunodeficiency virus; NCDC, National Center for Disease Control and Public Health; SHCH, Sihanouk Hospital Center of Hope.

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^aA mix up of the serum and plasma samples collected from these participants occurred during the procedure of aliquoting into pre-labelled tubes.
^bParticipant age (16 years) was not noted until review of participant demographics and date of birth.
^cEIA test result missing for 1 of 2 EIAs; classed as negative as the available EIA and the LIA test were negative.
 HCV, hepatitis C virus.

Fig 1. Number of samples by HCV status.

<https://doi.org/10.1371/journal.pone.0243040.g001>

across all genotypes (S2 Table). No significant differences in sensitivity between the two countries were observed for plasma or serum, and no significant differences in specificity were observed between countries for any sample type (adjusted $p > 0.215$).

Sensitivity and specificity of the reference RDT SD Bioline compared with the CRS are shown in S3 Table. Performance of this test was similar to the investigational RDTs in plasma

Table 2. HCV VL and genotype status of HCV positive samples.

	SHCH Cambodia (N = 214)	CMHPA Georgia (N = 209)	NCDC Georgia (N = 66)
HCV VL status, n (%)			
HCV VL undetectable	79 (36.9)	81 (38.8)	23 (34.8)
HCV VL detectable	135 (63.1)	128 (61.2)	43 (65.2)
Samples per HCV genotype, n (%)			
1, 1a, 1b	63 (46.7)	33 (25.8)	22 (51.2)
2	11 (8.1)	11 (8.6)	6 (14.0)
3	–	60 (46.9)	9 (20.9)
4	–	–	–
5	–	–	–
6	59 (43.7)	–	–
Mixed	–	20 (15.6)	6 (14.0)
Not determinable	2 (1.5)	4 (3.1)	–

SHCH, Sihanouk Hospital Center of Hope; CMHPA, Centre for Mental Health and Prevention of Addiction; NCDC, National Center for Disease Control and Public Health; HCV, hepatitis C virus; VL, viral load.

<https://doi.org/10.1371/journal.pone.0243040.t002>

Table 3. Investigational RDT performance versus composite reference standard in the overall sample set.

	TN, n	TP, n	FN, n	FP, n	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Point estimates						
Whole blood (all samples)						
HCV-Ab Rapid	958	423	66	8	86.5 (83.2, 89.2)	99.2 (98.4, 99.6)
First Response HCV	964	447	42	2	91.4 (88.6, 93.6)	99.8 (99.2, 99.9)
Whole blood (samples with detectable VL)						
HCV-Ab Rapid	—	292	14	—	95.4 (92.5, 97.3)	—
First Response HCV	—	301	5	—	98.4 (96.2, 99.3)	—
Plasma (all samples)						
HCV-Ab Rapid	951	477	12	15	97.5 (95.8, 98.6)	98.4 (97.5, 99.1)
First Response HCV	963	479	10	3	98.0 (96.3, 98.9)	99.7 (99.1, 99.9)
Plasma (samples with detectable VL)						
HCV-Ab Rapid	—	304	2	—	99.3 (97.6, 99.8)	—
First Response HCV	—	304	2	—	99.3 (97.6, 99.8)	—
Serum (all samples)						
HCV-Ab Rapid	955	476	13	11	97.3 (95.5, 98.4)	98.9 (98.0, 99.4)
First Response HCV	964	475	14	2	97.1 (95.3, 98.3)	99.8 (99.2, 99.9)
Serum (samples with detectable VL)						
HCV-Ab Rapid	—	303	3	—	99.0 (97.2, 99.7)	—
First Response HCV	—	303	3	—	99.0 (97.2, 99.7)	—
Performance comparison (all samples), p-values						
Sample type	Sensitivity			Specificity		
	HCV-Ab Rapid	First Response HCV		HCV-Ab Rapid	First Response HCV	
Whole blood vs plasma	<0.001	<0.001		1.0	1.0	
Whole blood vs serum	<0.001	0.005		1.0	1.0	
Plasma vs serum	1.0	1.0		1.0	1.0	

CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive; VL, viral load

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and serum (sensitivities of 95.1% and 93.9%, respectively), and even slightly lower in whole blood (90.4%). However, contrary to the other tests, no differences between sensitivity in whole blood samples and plasma or serum were observed for the reference RDT (adjusted p-value >0.160 for sensitivity and specificity across different sample types).

Sensitivity and specificity versus RDT reference SD Bioline

When the RDT SD Bioline was used as a reference for comparison, specificity in the overall sample set was high for both investigational RDTs in all three sample types ($\geq 96.8\%$), with no differences observed across sample types (adjusted $p > 0.099$) (Table 5). For both investigational RDTs, sensitivity in whole blood increased when using the SD Bioline RDT as a reference (93.6% for the HCV-Ab Rapid test and 97.8% for the First Response HCV card test) and further increased in samples with detectable HCV VL (97.3% and 99.3%, respectively). Sensitivity in plasma and serum was also slightly increased when the RDT SD Bioline was used as a reference to evaluate performance ($> 99.4\%$ for both sample types and RDTs). Sensitivity was considerably lower for both RDTs in whole blood compared with plasma (adjusted $p < 0.001$ for the HCV-Ab Rapid test and adjusted $p = 0.060$ for the First Response HCV card test), and for the HCV-Ab Rapid test in whole blood compared with serum (adjusted $p < 0.001$).

Table 4. Investigational RDT performance versus composite reference standard by country.

	TN, n	TP, n	FN, n	FP, n	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Point estimates						
Cambodia: whole blood						
HCV-Ab Rapid	510	164	50	5	76.6 (70.5, 81.8)	99.0 (97.7, 99.6)
First Response HCV	515	182	32	0	85.0 (79.7, 89.2)	100 (99.3, 100)
Georgia: whole blood						
HCV-Ab Rapid	448	259	16	3	94.2 (90.8, 96.4)	99.3 (98.1, 99.8)
First Response HCV	449	265	10	2	96.4 (93.4, 98.0)	99.6 (98.4, 99.9)
Cambodia: plasma						
HCV-Ab Rapid	503	210	4	12	98.1 (95.3, 99.3)	97.7 (96.0, 98.7)
First Response HCV	512	211	3	3	98.6 (96.0, 99.5)	99.4 (98.3, 99.8)
Georgia: plasma						
HCV-Ab Rapid	448	267	8	3	97.1 (94.4, 98.5)	99.3 (98.1, 99.8)
First Response HCV	451	268	7	0	97.5 (94.8, 98.8)	100 (99.2, 100)
Cambodia: serum						
HCV-Ab Rapid	505	208	6	10	97.2 (94.0, 98.7)	98.1 (96.5, 98.9)
First Response HCV	513	209	5	2	97.7 (94.6, 99.0)	99.6 (98.6, 99.9)
Georgia: serum						
HCV-Ab Rapid	450	268	7	1	97.5 (94.8, 98.8)	99.8 (98.8, 100)
First Response HCV	451	266	9	0	96.7 (93.9, 98.3)	100 (99.2, 100)
Performance comparison, p-values						
	Sensitivity			Specificity		
Cambodia vs Georgia	HCV-Ab Rapid	First Response HCV		HCV-Ab Rapid	First Response HCV	
Whole blood	<0.001	<0.001		1.0	1.0	
Plasma	1.0	1.0		0.541	1.0	
Serum	1.0	1.0		0.217	1.0	

CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

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RDT sensitivity in whole blood was lower in Cambodia than in Georgia for both tests (87.4% vs 97.8%, adjusted $p < 0.001$ for the HCV-Ab Rapid test and 95.1% vs 99.6%, adjusted $p = 0.022$ for the First Response HCV card test; Table 6). For both RDTs, specificity was lower in Cambodia compared with Georgia in plasma (94.5% vs 99.4%, adjusted $p < 0.001$ for the HCV-Ab Rapid test and 96.6% vs 99.6%, adjusted $p = 0.006$ for the First Response HCV card test) and serum (94.2% vs 99.6%, adjusted $p < 0.001$ for the HCV-Ab Rapid test and 96.2% vs 99.8%, adjusted $p < 0.001$ for the First Response HCV card test). There were no significant differences between study countries in specificity for whole blood for either test. The multivariable logistic regression analysis showed that country was the most significant covariate associated with sensitivity (S4 Table). Besides the country, only gender was associated with sensitivity (slightly higher in males). However, gender only passed the threshold of statistical significance in one case (HCV Ab Rapid compared with the CRS).

Discussion

In this prospective study of RDT performance in freshly collected whole blood, plasma and serum samples, sensitivity of both the HCV-Ab Rapid test and the First Response HCV card test was high in plasma and serum, but lower in whole blood. The concentration of antibodies is likely to be lower in whole blood compared with plasma and serum, which could explain the

Table 5. Investigational RDT performance versus reference RDT in the overall sample set.

	TN, n	TP, n	FN, n	FP, n	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Point estimates						
Whole blood (all samples)						
HCV-Ab Rapid	1063	422	29	15	93.6 (90.9, 95.5)	98.6 (97.7, 99.2)
First Response HCV	1064	441	10	14	97.8 (96.0, 98.8)	98.7 (97.8, 99.2)
Whole blood (samples with detectable VL)						
HCV-Ab Rapid	—	293	8	—	97.3 (94.8, 98.6)	—
First Response HCV	—	299	2	—	99.3 (97.6, 99.8)	—
Plasma (all samples)						
HCV-Ab Rapid	1023	472	0	34	100 (99.2, 100)	96.8 (95.5, 97.7)
First Response HCV	1036	472	0	21	100 (99.2, 100)	98.0 (97.0, 98.7)
Plasma (samples with detectable VL)						
HCV-Ab Rapid	—	304	0	—	100 (98.8, 100)	—
First Response HCV	—	304	0	—	100 (98.8, 100)	—
Serum (all samples)						
HCV-Ab Rapid	1026	465	3	35	99.4 (98.1, 99.8)	96.7 (95.4, 97.6)
First Response HCV	1038	465	3	23	99.4 (98.1, 99.8)	97.8 (96.8, 98.6)
Serum (samples with detectable VL)						
HCV-Ab Rapid	—	302	1	—	99.7 (98.2, 100)	—
First Response HCV	—	302	1	—	99.7 (98.2, 100)	—
Performance comparison (all samples), p-values						
Sample type	Sensitivity			Specificity		
	HCV-Ab Rapid	First Response HCV		HCV-Ab Rapid	First Response HCV	
Whole blood vs plasma	<0.001	0.060		0.136	1.0	
Whole blood vs serum	<0.001	1.0		0.099	1.0	
Plasma vs serum	1.0	1.0		1.0	1.0	

CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive; VL, viral load

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lower sensitivity seen in this study. However, although variability in sensitivity of HCV RDTs in whole blood has been previously reported in some studies [10–13], those that directly compared performance to plasma and serum have reported similar sensitivities across sample types [14, 15]. Other aspects that may have affected sensitivity include the possibility that some patients participating in the study had cleared their HCV infections, as evidenced by the absence of detectable VL in around one third of samples, and the improved sensitivity in the subset of samples with detectable viral load. Other studies have noted declines in HCV antibody levels following treatment-induced or spontaneous HCV clearance [16, 17], and a recent study observed reduced sensitivity of an HCV RDT in subjects with treatment-induced clearance [18]. While this would have affected all three sample types, it may have had a larger impact on sensitivity in whole blood as antibody concentrations would have been closer to the lower LOD compared with plasma and serum. Notably, WHO prequalification criteria are specifically designed for evaluation of plasma samples; no guidance is provided on expected performance in whole blood [8]. Given the variability in sensitivity in whole blood with HCV RDTs seen in earlier studies, achieving lower but acceptable sensitivity in whole blood may be considered adequate performance for the two investigational RDTs evaluated here. Nevertheless, HCV screening programmes using these RDTs must take into account the potential for lower performance in whole blood in real-world versus laboratory settings, particularly given

Table 6. Investigational RDT performance versus reference RDT by country.

	TN, n	TP, n	FN, n	FP, n	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Point estimates						
Cambodia: whole blood						
HCV-Ab Rapid	575	159	23	13	87.4 (8.18, 91.4)	97.8 (96.3, 98.7)
First Response HCV	576	173	9	12	95.1 (90.9, 97.4)	98.0 (96.5, 98.8)
Georgia: whole blood						
HCV-Ab Rapid	488	263	6	2	97.8 (95.2, 99.0)	99.6 (98.5, 99.9)
First Response HCV	488	268	1	2	99.6 (97.9, 100)	99.6 (98.5, 99.9)
Cambodia: plasma						
HCV-Ab Rapid	536	203	0	31	100 (98.1, 100)	94.5 (92.3, 96.1)
First Response HCV	548	203	0	19	100 (98.1, 100)	96.6 (94.8, 97.8)
Georgia: plasma						
HCV-Ab Rapid	487	269	0	3	100 (98.6, 100)	99.4 (98.2, 99.8)
First Response HCV	488	269	0	2	100 (98.6, 100)	99.6 (98.5, 99.9)
Cambodia: serum						
HCV-Ab Rapid	539	196	2	33	99.0 (96.4, 99.7)	94.2 (92.0, 95.9)
First Response HCV	550	197	1	22	99.5 (97.2, 100)	96.2 (94.2, 97.4)
Georgia: serum						
HCV-Ab Rapid	487	269	1	2	99.6 (97.9, 100)	99.6 (98.5, 99.9)
First Response HCV	488	268	2	1	99.3 (97.3, 99.8)	99.8 (98.9, 100)
Performance comparison, p-values						
	Sensitivity			Specificity		
Cambodia vs Georgia	HCV-Ab Rapid	First Response HCV		HCV-Ab Rapid	First Response HCV	
Whole blood	<0.001	0.022		0.145	0.221	
Plasma	N/A	N/A		<0.001	0.006	
Serum	1.0	1.0		<0.001	<0.001	

CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

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that testing of fingerstick blood in non-laboratory settings is likely to be a common usage of these tests.

In our previous study using archived plasma samples [7], sensitivity of the investigational RDTs met the WHO prequalification sensitivity criterion of $\geq 98\%$ [8], when compared with the laboratory-based CRS. In the current study, this criterion was narrowly missed by both RDTs in serum, and one of two in plasma. Unlike the previous study, in this evaluation the RDTs were performed by nurses and primary healthcare personnel, to represent a real-world setting. As such, variability in conditions, such as low lighting when reading RDTs, and user factors such as differences in line interpretation for low positive samples where lines can be more difficult to identify, could have impacted test performance. Similar factors, as well as the added technical challenge of fingerstick blood collection, may also have been a contributing factor to the lower sensitivity in whole blood. The fact that specificity was high in all sample types and sensitivity was close to WHO prequalification criteria in plasma and serum samples, suggests that the RDTs perform well in real-world settings and are likely to be beneficial to HCV screening programmes.

Consistent with our previous study in archived plasma samples [7], in this analysis, false negatives mostly occurred in samples with undetectable HCV VL. However, in our previous

study this effect was more apparent in HCV and HIV coinfecting samples [7]. As only four participants in the current study were HIV positive, the effect of HCV VL on test performance in this study was not linked to HIV. Other studies have reported similar observations of improved HCV RDT performance in samples with detectable VL [19]. HCV VL testing is used to confirm viraemic infection in people who test positive for HCV antibodies [2], thus these samples represent participants who had active HCV infections. Because the sensitivity of the investigational RDTs was higher in samples with detectable VL compared with the overall sample set for all sample types, this provides some reassurance in the feasibility of using these RDTs to detect HCV in the people in need of treatment.

RDT test performance in Cambodia was considerably lower than in Georgia, in terms of sensitivity in whole blood compared with either reference test (CRS or reference RDT) and in terms of specificity in serum and plasma compared with the RDT reference. Differences in specificity when compared to the RDT reference might be explained by the lower sensitivity of the SD Bioline RDT in serum and plasma samples from Cambodia, resulting in a higher number of apparent false positives for the investigational RDTs.

The reason for the lower sensitivity of the investigational RDTs in Cambodia is not clear.

Although the majority of false negative samples with detectable VL from Cambodia were of genotype 1b, while those from Georgia were found across all genotypes, different methodologies were used at the different sites to determine HCV genotype, so it is difficult to determine whether this represents a meaningful difference. A prozone effect, whereby the ability of antibodies to form immune complexes is impaired at high concentrations, may also have resulted in false negatives, as has been shown with other RDTs [20]. Alternatively, it is possible that HCV positive participants from Cambodia with undetectable HCV VL had lower antibody titres, as suggested by the fact that proportionally, there were more true positives in samples with undetectable VL from Georgia compared with Cambodia (87.5% versus 50.6% for the HCV-Ab Rapid test and 92.3% vs 63.3% for the First Response HCV card test). Historically, the HCV epidemic in Cambodia has been largely driven through past unsafe medical practices [21, 22], whereas Georgia has an ongoing HCV epidemic in injection drug users [23]. Additionally, one of the two centres in Georgia was an opioid substitution treatment facility, thus a high proportion of Georgian participants would have been injection drug users. This suggests a possibility that the between-country differences in sensitivity may be due to Cambodian participants having generally cleared infections longer ago, while more Georgian participants had ongoing infections. Previous studies have shown that HCV screening tests can provide discrepant results in people with waning antibodies [24]. However, it was not possible to test this hypothesis in this study, as it was not designed to recruit participants to represent the proportionate occurrence of ongoing and past infections. Further research is needed to better understand sensitivity differences across different population groups or HCV endemic areas.

It is interesting to note that the WHO prequalified RDT SD Bioline, used as a reference RDT in this study, also had lower than expected sensitivity in whole blood in the overall sample set (including samples with and without detectable VL) when compared with the laboratory-based CRS. The quality of SD Bioline is well established [25, 26], thus this further highlights how regional and demographic differences in population can impact on RDT performance, even with established RDTs, and demonstrates the generally lower sensitivity of RDTs compared with laboratory-based immunoassays as antibody screening tests.

Specificity was high in all sample types for both investigational RDTs when compared with the CRS, meeting the WHO prequalification specificity criterion of $\geq 97\%$ for HCV serology RDTs in plasma or serum specimens [8]. Specificity also met this criterion when compared with a WHO prequalified reference RDT test, except for one of two tests in plasma and serum samples, for which specificity dropped just below the threshold.

A limitation of this study is the stringent CRS used, which led to 73 samples being excluded from the study. While this provides confidence in the accuracy of the characterisation of the samples used in the study, it is possible that inclusion of the excluded samples would have affected sensitivity and specificity estimates. Additionally, the number of testers was higher for whole blood than for plasma and serum at two out of the three study sites, which may have contributed to differences in performance across sample types. However, previous studies have suggested that provision of training substantially reduces user errors with RDTs [27]. Training was provided to all testers involved in this study, thus the impact of user variability is likely to have been minimal.

In summary, both investigational RDTs performed well in fresh plasma and serum samples. Although sensitivity in whole blood performance was lower, particularly in Cambodia, given the potential impact of variability in HCV infection history, population drivers, conditions and user factors, data from other studies evidencing variable performance in whole blood with quality assured tests, and the fact that performance was similar to that of the reference RDT, test performance can be considered adequate. Additionally, overall performance in whole blood for samples with detectable VL was high. Comparative studies in different sample types should be taken into consideration when selecting HCV RDTs for screening programmes, bearing in mind that whole blood performance in real-world settings may be different from expectations based on data generated in laboratory evaluations.

Supporting information

S1 Checklist. TREND statement checklist.

(PDF)

S1 Table. Investigational and reference RDT operational characteristics.

(DOCX)

S2 Table. HCV genotype of false negative whole blood samples by country.

(DOCX)

S3 Table. Performance of the reference RDT test SD Bioline compared with the composite reference standard.

(DOCX)

S4 Table. Multivariable logistic regression analysis for RDT performance in whole blood (p-values).

(DOCX)

S5 Table. Protocol deviations.

(DOCX)

S1 File. Clinical study protocol.

(PDF)

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Original Research

Hepatitis C treatment uptake among patients who have received methadone substitution treatment in the Republic of Georgia

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ABSTRACT

Objectives: There is a dearth of research on hepatitis C virus (HCV) treatment uptake among people who inject drugs (PWIDs) and receive methadone substitution treatment (MST) in Eastern Europe and Central Asia countries. This study contributed to addressing that gap. We examined and identified factors that may affect HCV treatment uptake among PWID who received MST in the Republic of Georgia.

Study design: The design of the study is retrospective cohort study.

Methods: We conducted HCV care cascade analysis by matching the data from the web-based national hepatitis C program registry (ELIM C) and the MST treatment database between January 1, 2015, and December 31, 2018. Using the World Health Organization's (WHO) Consensus HCV cascade of care (CoC) global instrument, we assessed the progress made toward the country's 2020 and WHO's 2030 hepatitis C elimination targets for the subpopulation of MST patients.

Results: Overall, 10,498 individuals have been dispensed methadone during the study period. A total of 6828 MST beneficiaries had HCV screening, of whom 5843 (85.6%) tested positive; 5476 (93.7%) were tested for HCV viremia, and 5275 (96.3%) were confirmed with chronic HCV infection. More than 75% (n = 4000) of HCV-infected MST patients initiated HCV treatment, and 3772 (94.3%) completed the treatment. Of those eligible for sustained virologic response assessment, 71.0% (2641/3715) were evaluated, and the reported cure rate was 96.1% (2537). The study found the odds of patients starting HCV treatment differed by the type of facility they were screened at and whether they were registered as PWID at the screening sites. The patients screened at centers with integrated HCV treatment services had higher treatment uptake rates than those screened at other centers.

Conclusions: As the cumulative HCV treatment uptake and cure rates among MST patients with HCV infection are high (75.8% and 96.1%, respectively), the MST patients might become the first micro-elimination target population in which hepatitis C elimination will be achieved in Georgia. The study found the type of screening facility and whether MST patients registered themselves as PWID or not had significant effects on MST patients starting HCV treatment. At the same time, the study did not find gender and age to be significant predictors of MST patients starting HCV treatment. MST patients used different types of health facilities to get screened for HIV. Many of them did not register themselves as PWID when screened for HIV. The existence of only a few harm reduction sites with integrated HCV treatment services, a high level of stigma, and the criminalization of drug use might have incentivized MST patients to self-navigate across the HCV care continuum with the rest of the population. The implementation of focused, harm reduction, integrated HCV treatment with good peer and professional adherence support at treatment sites could help reach the hepatitis C elimination goals among MST patients.

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Introduction

Approximately 269 million people worldwide (nearly 5.4% of the global population), aged 15–64 years, used drugs at least once in 2018. Of them, approximately 53 million people used mostly opioids and 29 million used mostly opiates or amphetamines and prescription stimulants.¹ In 2018, an estimated 35.6 million people suffered from drug use disorders.² The situation is particularly alarming in Eastern and Southeastern Europe, Central Asia, and South Caucasus, where the proportions of the populations aged 15–64 years who inject drugs are almost four times higher than the global average.³

Pharmacological maintenance therapy, which uses drugs such as methadone and buprenorphine to reduce the craving for and use of opioids, is recommended by the World Health Organization (WHO) and has become the mainstream treatment for opioid dependence in many countries.^{4,5}

The number of PWID is increasing in Georgia. According to integrated behavior and biomarker surveillance surveys (IBBSS) of 2015 and 2017, the estimated number of PWID has increased from 49,200 to 52,500. The opioid dependence last was measured using a brief 8-item measure, the Rapid Opioid Dependence Screen (RODS), within the IBBSS conducted in 2017. The RODS calculation revealed that 31.4% of those who used illicit opioid drugs (93% of the whole sample) experienced an active phase of opioid dependence. This amounts to about 16,000 opioid-dependent PWID living in Georgia.⁶

More than 70 million people lived with the hepatitis C virus (HCV) infection, and only approximately 19% (13.1 million) of them knew their diagnosis in 2017.⁷ The prevalence of bloodborne infections, including HCV infection, remains high among the global drug user population. More than half of them live with hepatitis C, and approximately one in every eight people live with HIV.^{1,2} In 2017, the HIV prevalence among PWID was 2.3% (95% confidence interval [CI] 1.63–3.12) in Georgia, with no change since 2015 when HIV prevalence was 2.2% (95% CI 1.53–2.99).⁶ In 2015, hepatitis C prevalence in Georgia was considerably higher than the European average. An estimated 150,000 persons (5.4% of the adult population) lived with chronic HCV infection in the country at the time.⁸ It exceeded the estimated HCV prevalence of other countries of the Eastern Europe and Central Asia region except Uzbekistan and Ukraine (6.5% and 8% accordingly).⁹

In April 2015, with the support of the U.S. Centers for Disease Control and Prevention, Gilead Sciences, the WHO, and other partners, the Government of Georgia initiated one of the world's first Hepatitis C Elimination Programs with the ambitious goal of 90% reduction in chronic HCV prevalence by 2020.¹⁰ As of December 31, 2019, more than 1.9 million adults (67% of the adult population) have been screened with anti-HCV rapid diagnostic tests at over 1200 facilities countrywide, with an overall 6.7% anti-HCV antibody positivity rate in Georgia,¹¹ which fully corresponded to the national estimate for anti-HCV antibody prevalence based on the national seroprevalence study of 2015.⁸ The screening facilities list included 14 drop-in centers and eight mobile ambulatories of the Needle and Syringe Program (NSP).^{12,13}

An important direction of the National Hepatitis C Elimination Strategy is the identification of persons with chronic HCV among the general population, especially among high-risk groups such as PWID, who were reached through the NSP or enrolled in opioid substitution treatment (OST) Program (methadone and buprenorphine substitution programs).¹⁰

Studies report a positive impact of retention in OST on HCV treatment outcomes. The longer retention in OST translates in the higher probability of achieving an HCV cure.^{14–21} Methadone substitution treatment (MST) was first introduced in Georgia in 2005

through the support of the Global Fund (GFATM) and is available in two different forms: (1) methadone maintenance program and (2) the program using combined preparation with buprenorphine and naloxone.²² In 2018, the number of MST patients reached 10,498, which corresponds to 19.9% of the estimated 52,500 PWID living in Georgia.^{6,23} Fig. 1 represents the overall MST capacity distribution in the country for the same period. More than two-third of MST patients (6265) were receiving treatment in Tbilisi, the capital city.

While HCV infection is a major public health problem worldwide, currently, only a small portion of infected persons have been tested and know their diagnosis. Furthermore, there is uncertainty in many countries, including Georgia, regarding optimal testing approaches and whom to prioritize for testing.²⁴

During the last decade, the uptake of HCV treatment and related barriers have been explored within the different studies conducted among PWID worldwide. Many of these studies have contradicted previous concerns over poor treatment adherence and higher rates of re-infection among PWID, and therefore WHO has recommended HCV treatment within this population.^{25–32} Modeling studies have shown that scaling up HCV treatment, in combination with improved OST coverage and NSPs, could lead to substantial reductions in disease incidence and prevalence.^{33–35}

A study conducted during 2016–2017 among the people who inject drugs (PWIDs) confirmed the high burden (between 48.8% and 63.2% of different geographic locations) of chronic hepatitis C infection in Georgia.⁶ The present study was conducted to analyze the cumulative HCV treatment uptake, estimation of annual treatment, and cure rates, as well as the identification of factors associated with HCV treatment uptake among individuals who continued using MST treatment or were newly enrolled in the state MST programs during 2018 in Georgia.

Methods

The MST program uses an electronic web-based real-time data collection tool. The clients' information that is regularly collected, among other variables, includes the client's (1) 11-digit personal identification number, (2) residency address, (3) date of birth, (4) gender, (5) date of program entry, and (6) hepatitis C status. Georgia's hepatitis C elimination program data, on the other hand, is managed by the hepatitis C information system (ELIMC) that records screening, laboratory diagnostics, and treatment data and enables monitoring of the HCV care cascade for all population groups based on personal ID.³⁶

To generate the data set used by this study, first, the MST program's database was searched for patients undergoing methadone substitution therapy and getting at least one dose of medicine during 2018. Next, the MST patients' data were cross-matched with ELIMC by personal ID to identify the number of MST patients screened on HCV infection, confirmed to have active HCV infection, and the number of patients who were enrolled and completed the treatment.

As the study dealt with sensitive information, the matched data were provided to the researchers with all personal identifiers of patients removed. The study was approved by the National Center for Disease Control and Public Health, Georgia Institutional Review Board on July 30, 2020, approval number N2020-049.

Both databases had built-in data quality checks. Also, MST and HCV screening services were reimbursed based on the databases' records and were subject to regular monitoring for completeness and accuracy. We excluded all duplicates, as well as all observations for which the program entry date was missing, in total, 261 records. For anti-HCV screening, we used the facility name for the most recent HCV antibody test.

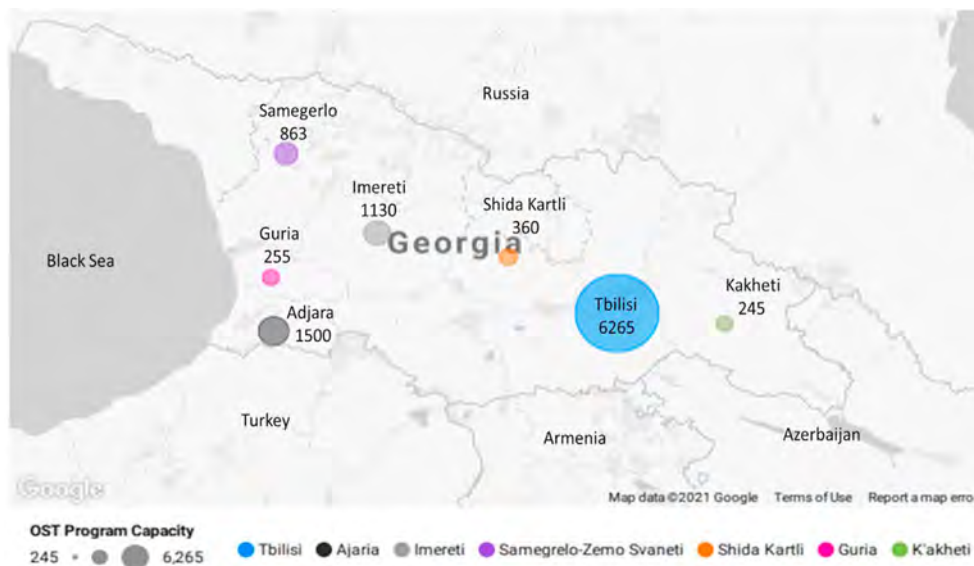


Fig. 1. The geographic distribution of the OST program capacity in Georgia. OST, opioid substitution treatment.

The study used the Consensus HCV cascade of care (CoC) global instrument of WHO to assess the progress toward the country's 2020 and WHO's 2030 hepatitis C elimination targets. The suggested WHO cascade includes (1) the estimated number of people with chronic HCV infection, (2) the number of people who received anti-HCV testing, (3) the number of people who received confirmatory HCV-RNA, (4) the number of people who enrolled in HCV treatment, and (5) the number of people who achieved a sustained virologic response (SVR; undetectable HCV-RNA) at least 12 weeks after therapy (SVR12). The proportion achieved for each step of the care cascade was calculated using the preceding step's nominator value as the denominator. The MST patients' HCV care cascade data were compared with the national HCV care cascade data to see the differences in the results for each step of the cascade.

In addition, the study examined the relationships between the outcome variables of the CoC and patient characteristics, such as age groups, gender, HCV antibody testing site, and whether the MST patient reported to be a drug user at the anti-HCV screening. In particular, the study used logistic regression to regress these characteristics on starting treatment. The study used StataCorp. 2019, Stata Statistical Software: Release 16, College Station, TX: StataCorp LLC to conduct statistical analysis.

Results

Of 10,498 patients who received at least one dose of methadone during 2018 and were registered in the state MST database, 6828 (65%) were tested for hepatitis C antibodies during 2015–2018 and were registered in the National Hepatitis C Testing and Treatment database—ELIMC.

Most MST program beneficiaries 74% ($n = 5051$) were between 30 and 49 years of age, 17.2% ($n = 1177$) were from 50 to 59 years old, and beneficiaries aged <25 and >60 years accounted for 3.4% ($n = 235$) persons. The median age of study participants was 41 years. Of them, 99.4% ($n = 6790$) were male.

Half of the MST program beneficiaries ($n = 3441$) had their most recent anti-HCV screening conducted at the National Center for Disease Control and Public Health (NCDC) central and regional laboratories with a positivity rate of 94.7%. Nine hundred seventy-seven (14.3%) beneficiaries were tested at hospitals during hospitalization for various clinical needs with a 67.7% anti-HCV antibody

positivity rate. In addition, 526 (7.7%) were tested at specialized clinics for drug addiction treatment, with a 67.3% anti-HCV antibody positivity rate, and 455 (6.7%) were tested at NSP sites with a 95% anti-HCV antibody positivity rate. The HCV service site in Tbilisi and HCV specialized treatment centers countrywide tested 505 (7.4%) of MST program beneficiaries with an anti-HCV positivity rate of 88.5% (see Fig. 2). The overall HCV prevalence in the study sample was 85.6%. The anti-HCV positivity rate was highest (93%) among 40- to 59-year-olds. The largest shares (28% [$n = 1901$] and 30% [$n = 2049$], respectively) of MST patients were tested in 2016 and 2017, but the percentages of patients tested decreased to 20% in 2018.

Of those MST patients who were tested on anti-HCV antibodies, 79% did not report being a drug user and were registered as a general population group in the ELIMC. Fourteen percent (982) of MST patients got registered as PWID, which included the 5% (370) who were tested outside of specialized addiction treatment clinics or harm reduction program facilities.

Among the 5843 anti-HCV-positive persons, 5476 (93.7%) had viremia testing, and 5275 (96.3%) were confirmed with chronic HCV infection. More than 75% ($n = 4000$) of HCV-infected MST patients initiated HCV treatment, and 3772 (94.3%) completed the treatment. Of those eligible for SVR assessment, 71.0% (2641/3715) were evaluated, and the reported cure rate was 96.1% (2537; see Fig. 3).

Confirmation of chronic HCV infection diagnosis among MST patients

We found a total of 5275 MST patients with positive HCV viremia test results in the ELIMC database, representing 96.3% of the entire sample with positive HCV antibody test results. Of those, 5239 (99.2%) were male. The majority of them (74.5% $n = 3988$) were aged between 30 and 49. Nearly 60% ($n = 3216$) of MST patients with chronic HCV infection had partaken in anti-HCV screening at the NCDC laboratories, whereas 10.9% (575) had been screened at hospitals.

HCV treatment uptake

The analysis of the ELIMC data showed that 4000 MST patients (75.8% of the patients with chronic HCV infection) were enrolled in

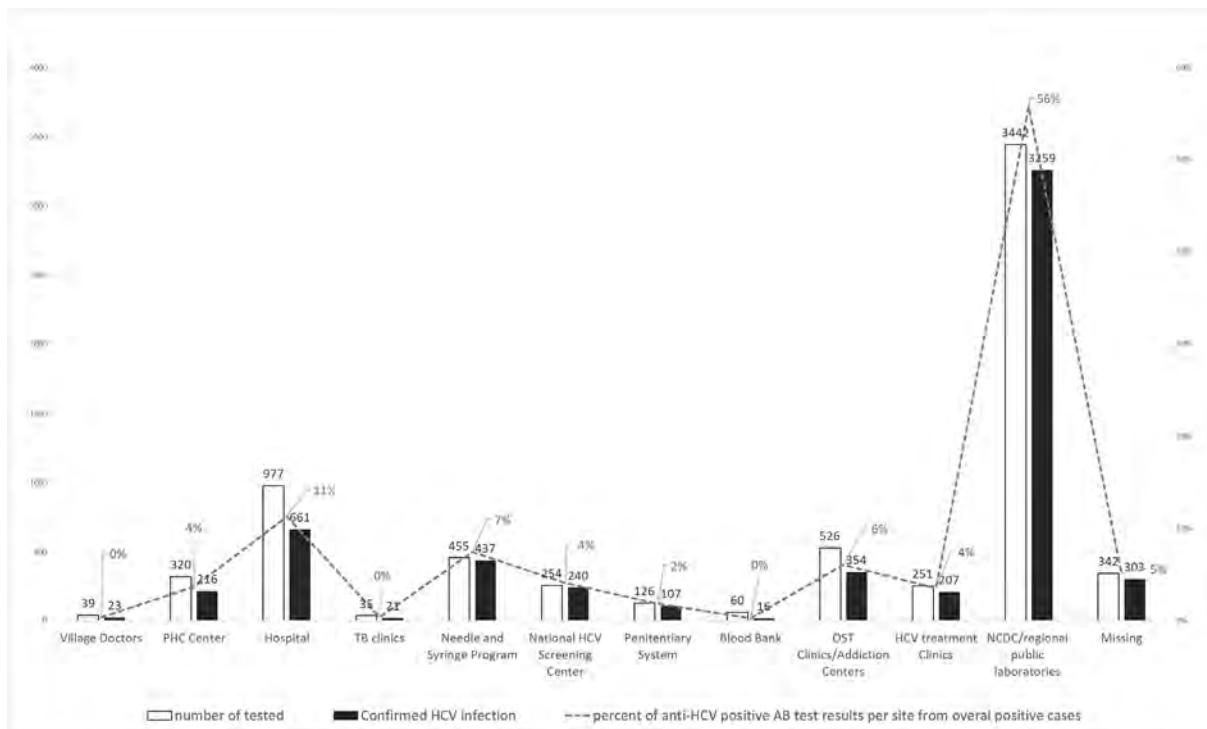


Fig. 2. HCV antibody screening of methadone substitution treatment patients by screening sites and percent positive (n = 6828) between 2015 and 2018. HCV, hepatitis C virus; OST, opioid substitution treatment; NCDC, National Center for Disease Control and Public Health; PHC, primary health care; TB, tuberculosis.

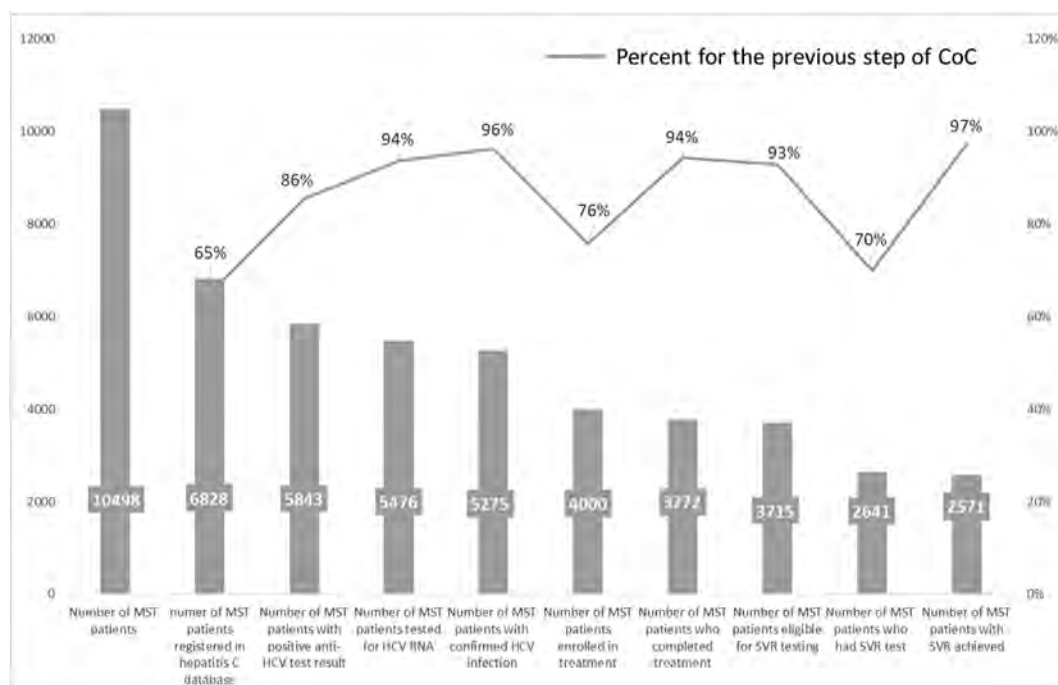


Fig. 3. HCV care cascade for MST patients between 2015 and 2018, n = 6828. Coc, cascade of care; HCV, hepatitis C virus; MST, methadone substitution treatment; SVR, sustained virologic response.

the hepatitis C treatment program. As was the case with the HCV-positive confirmation results, most MST patients (75.3%, n = 3009) who started HCV treatment were also aged between 30 and 49 years.

Approximately one-third (63.7%, n = 2546) of MST patients who started HCV treatment were from the group of persons tested for anti-HCV antibodies at the NCDC laboratories (see Table 1).

The logistic regression analysis (model fit likelihood ratio: $\chi^2 = 210.44$; $P < 0.0001$; pseudo $R^2 = 0.03$; number of observations = 5.418) showed that the type of the facility where patients were screened at and whether they registered as PWID or not at the screening had statistically significant effects on the patients' odds of starting HCV treatment. The study did not find

Table 1
Descriptive characteristics and HCV cascade data of the MST patients' cohort (N = 6828) registered in ELIMC during 2015–2018.

Categories	Complete sample		Anti-HCV AB positive		Tested with confirmed test		Confirmed positive		Started treatment		Completed treatment		Achieved SVR	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total number (N)	6828		5843		5476		5275		4000		3772		2571	
Gender														
Male	6790	99.4	5843	85.6	5384	99.5	5239	99.3	3984	99.6	3759	99.6	2527	99.6
Age														
<25	57	0.8	22	0.4	22	0.4	19	0.4	15	0.4	14	0.4	9	0.4
25–29	365	5.4	197	3.4	179	3.3	154	2.9	119	3	113	3	61	2.4
30–39	2387	35	1891	32.4	1760	32.5	1725	32.7	1279	32	1197	31.7	766	30.2
40–49	2664	39	2451	42	2280	42	2263	42.9	1730	43.3	1648	43.7	1136	44.8
50–59	1177	17.2	1124	19.2	1032	19	972	18.4	759	19	711	18.8	502	19.8
>60	178	2.6	158	2.7	151	2.8	142	2.7	98	2.5	90	2.4	63	2.5
Type of facility														
Unknown	342	5	301	5.2	279	5.1	271	5.1	199	5	185	4.9	118	4.7
Village doctors	39	0.6	23	0.4	25	0.5	24	0.5	19	0.5	17	0.5	10	0.4
PHC centers	320	4.7	216	3.7	179	3.3	173	3.3	108	2.7	97	2.6	62	2.4
Hospitals	977	14.3	661	11.3	592	10.9	575	10.9	348	8.7	312	8.3	174	6.9
TB clinics	35	0.5	21	0.4	19	0.4	18	0.3	9	0.2	8	0.2	3	0.1
Needle and syringe program	455	6.7	437	7.5	350	6.5	339	6.4	219	5.5	203	5.4	131	5.2
National HCV screening center	254	3.7	240	4.1	226	4.2	219	4.2	184	4.6	179	4.8	129	5.1
Prisons	126	1.9	107	1.8	75	1.4	72	1.4	57	1.4	54	1.4	25	1
Blood banks	60	0.9	16	0.3	16	0.3	15	0.3	12	0.3	11	0.3	6	0.2
OST clinics/addiction centers	526	7.7	354	6.1	279	5.1	270	5.1	177	4.4	163	4.3	95	3.7
HCV specialized treatment centers	251	3.7	207	3.5	180	3.3	173	3.3	121	3	111	2.9	58	2.3
NCDC and public laboratories	3441	50.4	3259	55.8	3204	59.1	3126	59.3	2546	63.7	2432	64.5	1726	68

HCV, hepatitis C virus; NCDC, National Center for Disease Control and Public Health; OST, opioid substitution treatment; PHC, primary health care; SVR, sustained virologic response; TB, tuberculosis.

gender and age to be significant predictors of MST patients starting HCV treatment. Furthermore, the omnibus tests of two-way interactions between the model's variables were not statistically significant at $P = 0.05$ level (Table 2).

In particular, patients screened at NCDC laboratories, the National Hepatitis C Screening Center, and prisons had significantly higher odds of starting treatment than patients screened at other facilities. MST patients who were screened by hospitals, primary

Table 2
The logistic regression model of starting HCV treatment (model fit likelihood ratio: $\chi^2 = 210.44$; $P < 0.0001$; pseudo $R^2 = 0.03$; number of observations = 5.418; significant relationships are in italic and boldface).

Category	OR	SE	Z	$P > z$	95% CI	
Gender (male)						
Female	0.51	0.19	-1.81	0.070	0.24	1.06
Age (<25)						
25–30	0.88	0.44	-0.26	0.796	0.33	2.32
31–39	1.09	0.52	0.19	0.852	0.43	2.75
40–49	1.22	0.57	0.42	0.677	0.48	3.07
50–59	1.08	0.51	0.16	0.871	0.43	2.74
>59	0.69	0.35	-0.74	0.461	0.26	1.84
Type of facility (NCDC and public laboratories)						
Unknown	0.65	0.09	-3.01	0.003	0.50	0.86
Village doctors	0.84	0.40	-0.37	0.708	0.33	2.11
PHC clinics	0.40	0.06	-5.76	0.000	0.29	0.54
Hospitals	0.37	0.04	-10.36	0.000	0.31	0.45
TB clinics	0.23	0.11	-3.15	0.002	0.09	0.58
NSP sites	0.55	0.08	-4.01	0.000	0.41	0.74
National HCV Service Center	1.13	0.20	0.70	0.484	0.80	1.60
Prisons	0.93	0.26	-0.26	0.798	0.54	1.61
Blood bank	0.84	0.49	-0.31	0.758	0.27	2.63
OST clinics/addiction centers	0.49	0.07	-5.29	0.000	0.37	0.64
HCV treatment clinics	0.53	0.09	-3.84	0.000	0.38	0.73
PWID (No)						
Yes	0.76	0.08	-2.53	0.011	0.61	0.94

CI, confidence interval; HCV, hepatitis C virus; NCDC, National Center for Disease Control and Public Health; NSP, Needle and Syringe Program; OR, odds ratio; OST, opioid substitution treatment; PHC, primary health care; PWID, people who inject drug; SE, standard error; TB, tuberculosis.

health care clinics, and tuberculosis (TB) clinics were the least successful in initiating HCV treatment (Table 3). Furthermore, MST patients who did not register as PWID at the screening had statistically significantly higher odds of starting treatment than patients who registered as PWID (Table 2).

As reported by Averhoff et al. in their 2020 article, the overall hepatitis C care cascade for Georgia for the end of December 2018 showed reasonable national progress in the anti-HCV screening of the population.³⁷ A comparison of the hepatitis C care cascade of MST patients with the national HCV care cascade shows considerably better coverage of MST patients with HCV viremia testing than the overall public (93.7% vs 81.6%), higher rates of chronic hepatitis C among MST patients (96.3% vs 83.1%), slightly lower rates for initiating treatment (75.8% vs 78.2%), and marginally higher rates of treatment completion (94.3% vs 92.1%; see Fig. 4). For the remaining part of the cascade, the percentages for MST patients are slightly lower than for the country's overall care cascade: 92.9% vs 95.8% for SVR testing eligibility, 70.0% vs 74.8% for SVR testing, and 96.1% vs 98.7% for cure rates.

Discussion

With the availability of newer direct-acting antiviral (DAA) medicines, modeling studies based on European populations, including Georgia, have shown that the increase in HCV diagnosis and treatment rates over time would decrease HCV prevalence and HCV-related morbidity and mortality.^{34,38,39} The effective planning of screening programs as of the initial step for HCV diagnosis and prioritization of populations for screening are critically important. A systematic review conducted by Schillie et al suggests that both integrated and non-integrated screening programs have their advantages and disadvantages, and they are complementary. If the integrated screening programs reach individuals who visit facilities for medical reasons and are less costly, non-integrated programs

Table 3
Statistically significant pairwise relationships between the values of facility type and the odds of starting treatment ($P < 0.05$).

Type of facility	Type of facility	Relationship	Odds ratio
NCDC and PLs	Unknown	Decreases	0.65
NCDC and PLs	PHC clinics	Decreases	0.40
NCDC and PLs	Hospitals	Decreases	0.37
NCDC and PLs	TB clinics	Decreases	0.23
NCDC and PLs	NSP sites	Decreases	0.55
NCDC and PLs	OST clinics/addiction centers	Decreases	0.49
NCDC and PLs	HCV treatment clinics	Decreases	0.53
Prisons	PHC clinics	Decreases	0.43
Prisons	Hospitals	Decreases	0.41
Prisons	TB clinics	Decreases	0.25
Prisons	OST clinics/addiction centers	Decreases	0.52
National HCV Service Center	Unknown	Decreases	0.58
National HCV Service Center	PHC clinics	Decreases	0.35
National HCV Service Center	Hospitals	Decreases	0.33
National HCV Service Center	TB clinics	Decreases	0.21
National HCV Service Center	NSP sites	Decreases	0.48
National HCV Service Center	OST clinics/addiction centers	Decreases	0.43
National HCV Service Center	HCV treatment clinics	Decreases	0.47
TB clinics	Unknown	Increases	2.08
Hospitals	Unknown	Increases	1.75
Hospitals	NSP sites	Increases	1.46
Unknown	PHC clinics	Decreases	0.61

HCV, hepatitis C virus; NCDC, National Center for Disease Control and Public Health; NSP, Needle and Syringe Program; OST, opioid substitution treatment; PHC, primary health care; PL, public laboratory; TB, tuberculosis.

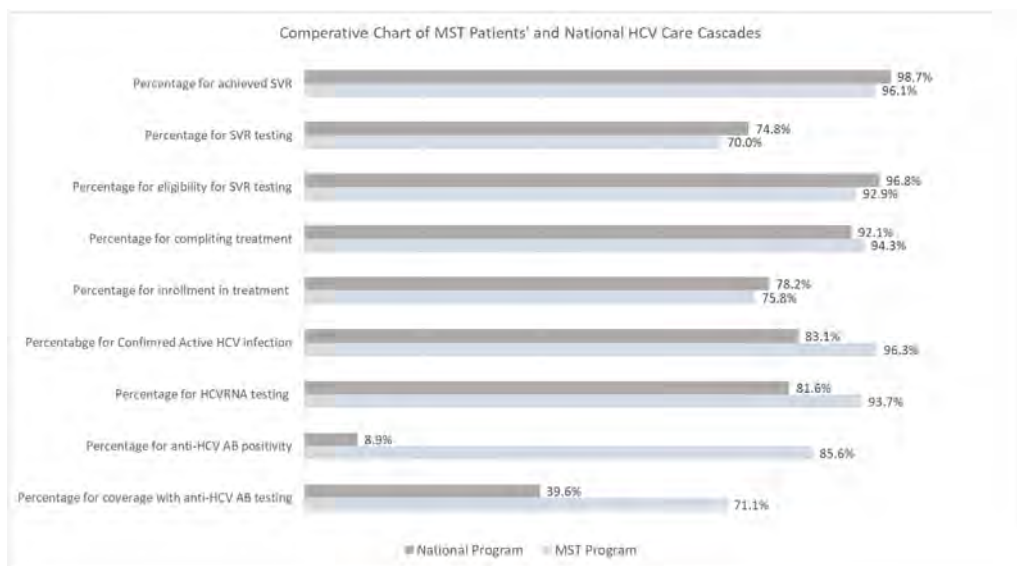


Fig. 4. Comparison of the MST patients HCV care cascade with the national hepatitis C care cascade for the end of 2018. AB, antibody; HCV, hepatitis C virus; MST, methadone substitution treatment; SVR, sustained virologic response.

are effective in the screening of populations with greater risk for HCV, such as PWID.^{39,40}

The rigorous HCV screening program of Georgia, that is, a mix of integrated and non-integrated screening interventions, has allowed for the rapid acceleration of HCV patients' enrollment in the treatment program. At the end of 2019, a total of 64,537 HCV-infected persons were enrolled in the treatment program. This falls short of the national target of treating 95% of people with chronic HCV infection but still corresponds to 50.3% of the target. It positions Georgia among the leading countries worldwide for hepatitis C elimination.³⁷ The country's sound achievements were possible because of the simplification of HCV diagnostics and treatment and the decentralization of HCV care at primary health care and harm reduction settings in 2018.^{41,42}

As the comparison with the national HCV care cascades showed, the indicative steps in the MST care cascades are considerably better than the national coverage for anti-HCV antibody testing and higher than the national rate for the confirmation of chronic HCV infection. For the rest of the cascade, the differences between the national cascade and MST patients' cascade are minimal. It shows that PWID enrolled in the MST program are well motivated to initiate HCV treatment and show good adherence and consequently high cure rates.

Although the government made SVR testing free of charge, the actual low uptake of SVR testing—70.0% for MST patients and 74.8% for national cascade—remains a challenge for both care cascades. Good adherence to treatment was demonstrated by HIV-positive PWID enrolled in antiretroviral therapy (ART) also. In Georgia,

78% of 1843 registered HIV-positive PWID were enrolled in ART with a high viral suppression rate of 84%.⁴³

Some prior studies in the literature reported low HCV treatment uptake among PWID and challenges associated with engaging them in HCV treatment.^{44,45} Our findings, however, are in line with studies that found PWID enrolled in MST programs could be motivated to initiate HCV treatment if access to integrated, community-based, and decentralized services is ensured and that ongoing drug use was not associated with decreased adherence to treatment.^{46–48}

The literature suggests that daily OST delivery in specialized HCV centers makes it difficult to follow HCV diagnostics and treatment steps. This concern can be addressed by establishing one-stop-shop MST and HCV treatment sites in Georgia as recommended by the literature and practiced in some countries.^{49–52}

Our findings showed that in the absence of MST-integrated HCV treatment sites, the MST patients prefer visiting the screening sites of the NCDC, National Hepatitis C Screening Center, and general medical facilities as ordinary patients over getting screened at harm reduction sites and registering in the hepatitis C program database (i.e. ELIMC) as drug users. The literature suggests that stigma and discrimination are significant barriers to HCV testing, and treatment access among PWID and health care facilities are reported as the common sites of such experiences by PWID.^{53–57} Strict drug law and a high level of stigma might be the main structural barriers preventing MST patients from revealing their drug dependence status at general health care facilities and getting additional adherence monitoring and support from HCV treatment service providers in Georgia.

A prior study conducted in 2018 in Georgia pointed to the importance of raising awareness of HCV infection and social support for HCV treatment. It showed that PWID who were treated for HCV and received peer support exhibited an exceptional treatment response (98% have completed HCV treatment and overall SVR was 84.8%) and good adherence.⁵⁸ According to our study, MST patients screened at the NCDC and regional public health laboratories, as well as patients who were registered at the National Hepatitis C Screening Center, had significantly higher odds of starting treatment than patients at other facilities (Table 3). The former group of facilities all have motivational and referral communication services in place, both of which might have contributed to their success.

Successful screening and treating patients with HCV infection during incarceration have shown to have both individual and public health advantages.^{59–62} A modeling study conducted in the United States demonstrated that scaling up DAA treatment in prisons can have a substantial impact on reducing HCV incidence and prevalence in communities.^{60,61} Our study's findings are consistent with the evidence from the literature confirming the importance of the availability of hepatitis C treatment in prisons, especially for the inmates with a history of injecting drug use and experience with methadone substitution treatment. DAA treatment creates a unique opportunity for imprisoned MST patients to initiate and complete HCV treatment. Our study found that the odds of imprisoned MSTs to start treatment were significantly higher than those of MST patients screened at PHC clinics, hospitals, TB clinics, or MST/addiction clinics (Table 3).

The study has a limitation. It examined only a limited number of MST patients' characteristics. Other variables of interest could be MST patients' adherence to substitution treatment, comorbidities (e.g. HIV and TB), awareness level, attitudes, and the socio-economic characteristics of the cohort. These variables might have affected the MST patients' health care seeking behavior and adherence to HCV treatment.

At the same time, the study used a large sample of MST patients, which increased the statistical power of the analysis. Furthermore, the study contributed to the knowledge of HCV treatment uptake among PWID in the Eastern Europe and Central Asia (ECCA) region, where the research on the subject is scarce.

Conclusion

The study's findings showed considerable progress in reaching MST patients with HCV diagnostics and treatment services, good adherence, and cure rates in Georgia. MST patients used different types of health facilities to get screened for HIV. Many of them did not register themselves as PWID when screened for HIV. We found that the type of screening facility and whether MST patients registered themselves as PWID or not had a significant effect on MST patients starting HCV treatment. At the same time, the study did not find gender and age to be significant predictors of MST patients starting HCV treatment.

The existence of only a few harm reduction sites with integrated HCV treatment services, a high level of stigma, and the criminalization of drug use might have incentivized MST patients to self-navigate across the HCV care continuum with the rest of the general population. The implementation of focused, harm reduction, integrated HCV treatment with good peer and professional adherence support at treatment sites could help reach the elimination goals among MST patients.

A future qualitative study that examines MST patients' health seeking behaviors, including their uptake of and adherence to HIV treatment, will complement the findings of the present study.

Author statements

Ethical approval

The study was approved by the National Center for Disease Control and Public Health, Georgia Institutional Review Board on July 30, 2020, approval number N2020-049.

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Competing interests

None declared.

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Article

Diagnostic Performance and Usability of the Genedrive[®] HCV ID Kit in Two Decentralized Settings in Cameroon and Georgia

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Abstract: Point-of-care diagnostics have the potential to increase diagnosis and linkage to care and help reach the WHO targets to eliminate hepatitis C virus (HCV) by 2030. Here, we evaluated the diagnostic accuracy of Genedrive HCV ID assay for the qualitative detection of HCV RNA in decentralized settings in two low- and middle-income countries using fresh plasma specimens from 426 participants. The Abbott RealTime HCV assay was used as the gold standard. Genedrive HCV ID assay was conducted by different users. Users also completed questionnaires to assess the usability of Genedrive. At detection thresholds of 12 IU/mL or 30 IU/mL, 1000 IU/mL, and 2362 IU/mL, the sensitivity was 96.2% (95% CI: 92.7–98.4), 100% (98.2–100), and 100% (98.2–100), respectively; the specificity was 99.5% (95% CI: 97.4–100), 99.5% (97.5–100), and 98.7% (96.1–100), respectively. All genotypes detected using the gold-standard assay were also detected with Genedrive. Users found Genedrive easy to use. Genedrive is a simple and accurate test to confirm chronic HCV infection in decentralized, real-life, resource-limited settings. This novel diagnostic tool could contribute to closing the current gap in HCV diagnosis.

Keywords: Hepatitis C; HCV RNA; diagnostics; point-of-care; Genedrive

1. Background

Hepatitis C virus (HCV) infection can lead to chronic disease that may progress for decades without being noticed until symptoms of advanced liver disease appear [1]. Approximately 71 million people worldwide are living with chronic HCV infection, and more than 80% of them are living in low- and middle-income countries (LMICs) [2]. The World Health Organization (WHO) has called for the elimination of HCV by 2030 [3]. Treatment for HCV is becoming more widely available worldwide, with the development of short-course oral direct-acting antiviral (DAA) regimens with higher tolerability and cure rates and the introduction of generic formulations [4–6]. However, access to treatment remains limited due to insufficient diagnostic services and poor linkage to care.

Nucleic acid testing for quantitative HCV RNA determination is mainly performed using high-throughput platforms in specialized laboratories. The cost of these assays is generally high, and turnaround times for results to reach patients can be several weeks in duration. More portable, affordable, and easy-to-use platforms that can be used in district hospitals or clinics may help decentralize and increase access to HCV testing in LMICs [7].

One HCV RNA assay that requires fewer technical skills to operate is the Genedrive[®] HCV ID Kit (Genedrive Diagnostics Ltd, Manchester, UK), henceforth referred to as Genedrive. This test meets most of the technical requirements for a virological test, as defined in the target product profile developed by FIND (Foundation for Innovative New Diagnostics) and WHO [8]. Genedrive detects HCV RNA in a small volume of plasma (30 µL) using reverse transcription polymerase chain reaction (RT-PCR). The system provides a simple, qualitative result without the need for specialist knowledge or data interpretation [9]. The Genedrive instrument is small and can be easily operated in a range of decentralized laboratory settings with limited requirements for ancillary equipment or test materials. The Genedrive HCV ID Kit comprises lyophilized PCR reagents packaged into a single-use, disposable cartridge, and the testing procedure consists of 12 manual steps [10]. The test turnaround time is about 90 min. It is intended to be a confirmatory test of current HCV infection following a positive HCV antibody test. The test is CE-marked [11] and WHO prequalified [12]. One study found Genedrive to have an analytical sensitivity of 2362 IU/mL, with 98.6% sensitivity and 100% specificity [13]. However, the performance was evaluated on leftover frozen plasma samples obtained from a research laboratory in Europe. The performance of Genedrive with freshly collected samples in real-world LMIC settings, operated by intended users, has not yet been assessed.

Genedrive has the potential to simplify testing requirements and decentralize HCV RNA testing for the confirmation of HCV viremia. The aim of this study was to evaluate the diagnostic performance and usability of Genedrive in laboratory-based real-life settings in Cameroon and Georgia.

2. Methods

2.1. Study Design

This cross-sectional study was performed and reported in accordance with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines [14]. The study was conducted in small laboratories in primary healthcare settings where, typically, HCV RNA testing is not available. Informed consent was obtained from participants in Georgia and Cameroon, who were then prospectively enrolled in the study. The study protocol was approved by the respective local ethics committees in Cameroon (N°2019/06/1166/CE/CNERSH/SP, 14 June 2019) and Georgia (N°8160-2/1, 1 December 2018). The diagnostic performance of Genedrive (index test) was evaluated against a gold standard (reference test), the Abbott RealTime HCV viral load assay (Abbott Molecular Inc., Des Plaines, IL, USA), henceforth referred to as Abbott HCV.

2.2. Study Population and Study Settings

Individuals who fulfilled the eligibility criteria were invited to participate in the study until the desired sample size was reached. Recruitment took place between June and October 2019. Three population groups were considered: “HCV risk,” “HCV seropositive,” and “HCV treatment.” The “HCV risk” group included individuals at risk of having HCV infection based on past and/or current exposure to risk factors, as defined in the WHO [15] and Centers for Disease Control and Prevention (CDC) guidelines [16]. The “HCV seropositive” group included individuals with a documented positive HCV serology result. Finally, the “HCV treatment” group included individuals diagnosed with chronic HCV infection who initiated or completed a course of DAA therapy and who presented at the clinical site for treatment monitoring or test of cure (i.e., sustained virological response).

Two sites per country were used for testing, one site for the index test and another for the reference test. In Georgia, recruitment and index testing was done at a Hepa Plus harm reduction site in Tbilisi, and reference testing was done at the National Center for Disease Control (NCDC). In Cameroon, recruitment and reference testing was conducted at the Centre Pasteur of Cameroon (CPC) in Yaoundé, and index testing was performed at the clinic “les Promoteurs de la Bonne Santé (PBS),” also in Yaoundé. Neither of the country index testing facilities had any prior experience in PCR-based assays and were blind to the

results of reference testing. At both sites, reference and index testing were carried out by different users, and no data were shared.

2.3. Testing Methods

Participants were asked to provide 8 mL of venous blood, collected in standard K₂ EDTA tubes. Plasma was aliquoted within 6 h of blood collection, and Genedrive testing carried out within 24 h, using 30 µL of plasma. The Genedrive testing procedure consisted of 12 steps, from sample input to result reporting. One plasma aliquot was used for testing with the Abbott HCV within 4 weeks of blood collection, using the m2000sp/m2000rt platform. Another aliquot of plasma was used for HCV genotype analysis, performed using Sanger sequencing in Cameroon and the Abbott RealTime HCV Genotype II Assay [17] in Georgia. The remaining aliquots were stored at −80 °C and used for repeat testing and resolution of discrepant results. All testing procedures were performed in accordance with the manufacturers' instructions.

2.4. Usability of Genedrive

All users received training on Genedrive from the manufacturer prior to the start of the studies. Two structured questionnaires, capturing ease-of-use, level of training received, problems encountered, and overall opinion of the technology were completed by each user based on their experience of the test system. Answers were rated using a 5-point Likert scale, from strongly agree to strongly disagree (Supplementary Material Table S1).

2.5. Statistical Analysis

Assuming a sensitivity and specificity of 95% and 97.5%, respectively, a power of 80%, and a significance level of 5%, it was calculated that a minimum sample size of 200 participants with detectable HCV RNA and 200 participants with no detectable HCV RNA was required.

The results of Genedrive were compared with those of the Abbott HCV to calculate sensitivity and specificity, along with 95% confidence intervals (CI). Sensitivity and specificity were calculated using different detection thresholds with the reference assay, namely: 30 IU/mL in Georgia [18] and 12 IU/mL in Cameroon; 1000 IU/mL based on recommendations from the European Association for the Study of the Liver (EASL) [19] and 2362 IU/mL based on Genedrive's lower limit of detection.

The rate of invalid results was estimated by calculating the total number of tests without a positive or negative result given by the Genedrive instrument, either because of an indeterminate result or a failed control. Invalid results were excluded from the diagnostic accuracy analyses. Descriptive statistics were used to describe the study population. All analyses were performed using the statistical software R (R Foundation for Statistical Computing, version 3.6).

3. Results

3.1. Characteristics of the Study Population

Among the 434 participants who met the inclusion criteria, 8 participants were excluded due to lack of consent, resulting in a total of 426 enrolled participants. The total number of participants classified according to HCV antibody status and HCV RNA is shown in Figure 1. The demographic characteristics of the participants are displayed in Table 1. Among all enrolled participants, the median age was 47 years, and 73.9% were male. In Georgia, 99.6% of participants had a history of injecting non-prescription drugs compared to none in Cameroon. Overall, 1.3% of participants in Cameroon were HIV-positive versus 1.1% in Georgia. Only 11.0% of participants had received HCV treatment, all from Georgia. Overall, 50.0% of participants had detectable HCV RNA levels. Of the samples with detectable HCV RNA, 93% had genotype data available, with genotype 1 being the most common (52.7%).

Table 2. Overall sensitivity and specificity of the Genedrive[®] HCV ID Kit compared with the sensitivity and specificity of the Abbott RealTime HCV Viral Load Assay at different detection thresholds.

		Abbott: 12–30 IU/mL Threshold		Total	Diagnostic Accuracy (95% CI)
		Target Detected	Target Undetected		
Genedrive [®] HCV ID assay	Positive	205	1	206	Sensitivity: 96.2% (92.7–98.4) Specificity: 99.5% (97.4–100)
	Negative	8	212	220	
	Total	213	213	426	
		Abbott: 1000 IU/mL threshold		Total	
		Target detected	Target undetected		
Genedrive [®] HCV ID assay	Positive	205	1	206	Sensitivity: 100% (98.2–100) Specificity: 99.5% (97.5–100)
	Negative	0	220	220	
	Total	205	221	426	
		Abbott: 2362 IU/mL threshold		Total	
		Target detected	Target undetected		
Genedrive [®] HCV ID assay	Positive	203	3	206	Sensitivity: 100% (98.2–100) Specificity: 98.7 (96.1–99.7)
	Negative	0	220	220	
	Total	203	223	426	

Abbreviations: IU: International Units; CI: Confidence interval.

In this study, all specimens that could be genotyped (with HCV viral loads >1000 IU/mL) had concordant results between Genedrive and Abbott HCV, showing a sensitivity of 100% (95% CI: 98.2–100) across all HCV genotypes tested. Among 426 plasma samples undergoing Genedrive testing, two were found to be “indeterminate” and five “control failed.” When repeated with remnant plasma samples, all seven tests were rendered valid. The overall invalid test rate was, therefore, 1.6% (1.9% in Cameroon and 1.5% in Georgia) (Table 3).

Table 3. Invalid test rate for Genedrive[®] HCV ID Kit by site.

Genedrive Result	Cameroon	Georgia	Total
Negative	69 (44.2)	146 (54.1)	215 (50.5)
Positive	84 (53.8)	120 (44.4)	204 (47.9)
Indeterminate	2 (1.3)	0 (0.0)	2 (0.5)
Control failed	1 (0.6)	4 (1.5)	5 (1.2)
Total tests	156 (36.6)	270 (63.4)	426 (100)
Invalid tests repeated	3 (1.9)	4 (1.5)	7 (1.7)
Negative	2 (66.7)	3 (75.0)	5 (71.4)
Positive	1 (33.3)	1 (25.0)	2 (28.6)
Total tests performed	159 (36.7)	274 (63.3)	433 (100)
Total invalid rate	3 (1.9)	4 (1.5)	7 (1.6)

Data are number (%) unless otherwise indicated.

3.3. Genedrive Usability

The results of the usability questionnaires are shown in Figure 2. Genedrive users in Georgia were two nurses who were not familiar with performing laboratory testing. In Cameroon, the users were three laboratory technicians who were not skilled in molecular testing, but who were familiar with general laboratory techniques. All users reported they found the Genedrive system easy to use. One user mentioned a need for initial training, stating that “training is really necessary before using the machine; it is true the instructions are clear but technical assistance is required for the first use.” All users strongly agreed with the statement that they received sufficient training on how to use the Genedrive. Answers relating to the ease-of-use of carrying out the 12-step testing procedure varied, with two users agreeing it was easy, one user strongly disagreed, and two had neutral views. The most frequently encountered issues were related to the optional printer, either due to the paper rolling up and jamming the printer or because of the connector to the instrument, which was loose and, therefore, easily disconnected from the printer. Users commented

to the printer and its occasional disconnection from the instrument due to the use of USB adapters.

One of the key benefits of Genedrive is the small volume of plasma needed for analysis (30 μ L); with the rapid development of new plasma separation devices, it should be possible to obtain this volume of plasma from finger-stick blood samples, obviating the need for centrifugation [22]. The test does not contain any hazardous chemicals, such as guanidinium thiocyanate, and with the small volume of reagent used (approximately 135 μ L), the test does not require any specific disposal measures other than standard bio-hazard waste disposal procedures. This could be an important advantage in decentralized LMIC settings, where access to high-temperature incinerators to dispose of toxic reagents can be problematic [23].

The Genedrive instrument has a small footprint, however, it requires an electrical power supply, thus limiting its placement to facilities equipped with the necessary electrical set up, which may exclude the device from being used at a lower level health facility not equipped with necessary wiring. Future developments will be required to equip the instrument with the battery, enabling several tests to be performed without the need for an uninterruptible power supply in settings where power cuts are commonplace.

Another technology with a small footprint that is already available on the market is the GeneXpert platform (Cepheid, Sunnyvale, CA, USA), which uses a self-contained cartridge for the quantitative measurement of HCV RNA [24]. The advantage of GeneXpert is its capability to run a wide range of disease-specific tests [25,26], whereas the Genedrive is currently limited to testing for HCV, mitochondrially encoded 12S rRNA (MT-RNR1), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). GeneXpert HCV VL Fingerstick test also has a smaller number of manual steps and a shorter turnaround time. The Genedrive HCV ID Kit costs between USD \$25 and \$30, including shipping costs, import duties, and distributor margins [27], which is slightly higher than that of the Xpert HCV viral load assay (USD \$21.64) [28]. The cost of the Genedrive instrument is about USD \$5000, making it more affordable than the one-module configuration GeneXpert Edge (USD \$8495). The choice of platform, therefore, depends on the type of setting and whether integration of diagnostic services is required.

The analytical sensitivity of Genedrive HCV assay is 2362 IU/mL using 30 μ L of plasma, which is lower than that of the Xpert HCV viral load (10 IU/mL using 1 mL plasma) and Xpert HCV VL Fingerstick test (100 IU/mL using 100 μ L capillary blood) [29]. However, the optimal limit of detection for an HCV point-of-care test to diagnose 97% of HCV-infected people is 1318 IU/mL, as determined by an analysis of a large, global dataset [30]. According to this dataset published by Freeman et al. [30], the limit of detection of 3000 IU/mL will allow detecting at least 95% of all HCV RNA-positive cases.

Currently, the need for plasma for Genedrive testing requires centrifugation of EDTA whole blood, which necessitates a basic laboratory setting to perform HCV testing. The future use of direct capillary blood would greatly enhance the use of Genedrive in remote settings, particularly in settings such as services for people who inject drugs, where individuals could be tested using a finger-stick blood sample [31]. Notwithstanding its limitations, the arrival of Genedrive on the market is expected to bolster competition and contribute to closing the current diagnostic gap in HCV diagnosis.

Decentralization of testing through point-of-care testing has the potential to support increased access to HCV diagnostics and improve linkage to care [32]. Indeed, many countries implementing HCV elimination programs experienced difficulties in identifying infected individuals, following an initial phase of treatment scale-up with pre-identified patients [33]. Near point-of-care solutions like Genedrive could support case-finding activities in decentralized settings; however, further implementation research is needed to confirm these assumptions.

This study has several limitations. First, the performance of Genedrive was assessed for diagnostic purposes, with most participants being treatment-naïve and only 40 participants who had received treatment in Cameroon were included in the study. Therefore,

the performance of Genedrive to assess sustained virological response (SVR) could not be determined because most participants had undetectable viral loads. It is important to note that the GeneDrive HCV ID assay is not intended to be used as a test of cure. A second limitation of the study is the difference in recruitment and Genedrive testing between the sites. In Georgia, the recruitment and Genedrive testing were performed at a harm reduction site, and the plasma aliquots were then sent to a reference laboratory. In Cameroon, the recruitment and reference testing were both carried out at a reference center, and then the plasma samples were sent to a private clinic for Genedrive testing. Although the transport of plasma samples to the Genedrive testing site in Cameroon took place under cold-chain conditions, we cannot exclude the possibility that this transportation may have impacted the accuracy of the test, as the sensitivity was slightly lower in Cameroon than in Georgia: 92.4% (95% CI: 84.9–96.8) versus 99.2% (95% CI: 95.5–99.9). Finally, the usability of Genedrive was only assessed among a small number of users. Although most answers were consistent across users, answers to the questions relating to the testing procedure varied. Therefore, future studies involving a larger number of users will be necessary to validate our findings.

5. Conclusions

In conclusion, this study contributes additional evidence of the potential of Genedrive. It can be used as a test for the confirmation of HCV viremia following a positive antibody test in decentralized settings in LMICs. Furthermore, Genedrive can be successfully used by staff with no previous experience in molecular testing.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/diagnostics11050746/s1>, Table S1: Detailed Genedrive System Usability Scale Questionnaire.

Author Contributions: E.I.R. and F.M.J.L. conceptualized the study and developed the study protocol. F.M.J.L. wrote first draft of the manuscript. E.I.R. and A.M. (Aurélien Mace). designed the data collection forms. F.M.J.L. and A.M. (Agnes Malobela) conducted site assessments and monitored the study. M.A., R.N., E.Y.M., N.B., M.A.-A., M.S. supervised local study procedures. M.C. conducted the statistical analysis. F.M.J.L. and E.F. drafted the manuscript; E.I.R., A.M. (Aurélien Macé), M.A., R.N. critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: The study was conducted according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

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Retreatment of Chronic Hepatitis C Infection: Real-World Regimens and Outcomes From National Treatment Programs in Three Low- and Middle-Income Countries

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Access to recommended second-line treatments is limited for patients who fail initial hepatitis C virus (HCV) therapy in low- and middle-income countries. Alternative regimens and associated outcomes are not well understood. Through a pooled analysis of national program data in Egypt, Georgia, and Myanmar, we observed SVR rates >90% for alternative retreatment regimens.

Keywords. hepatitis C; HCV; retreatment; treatment failure; low- and middle-income countries.

Achievement of hepatitis C virus (HCV) elimination in low- and middle-income countries (LMICs) relies upon a simplified public health approach and affordable generic direct acting antiviral (DAA) regimens. DAAs recommended as initial therapy combinations and available from generic manufacturers, such as sofosbuvir/daclatasvir (SOF/DCV), cure about 95% of those treated [1] and are available in over 100 countries [2]. Patients who fail initial treatments should be retreated with second-line therapy. Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is the only evidence-based retreatment option in resource-limited settings recommended by the World Health Organization (WHO), based on trials showing 96–98% sustained virologic response at 12 weeks (SVR12, ie, cure) in

patients previously treated with another DAA-based regimen [3]. However, SOF/VEL/VOX is not available as a generic formulation and is not widely accessible in LMICs [2, 4].

As access to HCV treatment in LMICs grows and more people are treated, the volume of patients requiring second-line therapy will increase. These patients need timely and effective retreatment to prevent progression of liver disease and secondary HCV transmission [5]. In the absence of recommended regimens (eg, SOF/VEL/VOX) for retreatment, clinicians in LMICs have utilized alternative therapeutic regimens and durations, typically based on SOF in combination with the NS5A inhibitors ledipasvir (LDV) or DCV for 12–24 weeks with or without the addition of ribavirin (RBV). Retreatment studies have been conducted with SOF/VEL+RBV and glecaprevir/pibrentasvir (G/P) in high-income countries for genotypes (GT)-1, 2, and 3 [6–9]. Studies of alternative options for HCV retreatment in LMIC settings are sparse [10–12].

Data are needed regarding the effectiveness of alternative and widely available retreatment regimens readily available in LMICs in achieving HCV cure among patients who initially failed treatment on a DAA-based regimen. The aim of this analysis was to pool de-identified program data across LMICs to assess the most common treatment regimens that have been used to retreat patients who failed initial DAA-based therapies and to determine SVR12 rates by treatment regimen and duration among patients who failed initial DAA-based therapies.

METHODS

Existing HCV treatment programs in LMICs were invited to participate in this study via partners in the Coalition for Global Hepatitis Elimination and Clinton Health Access Initiative country programs. A centralized, secure data portal was established for LMIC HCV treatment programs to share previously collected, de-identified data on HCV patients with failure of initial DAA treatment. Failure to primary DAA regimen was defined by a detectable HCV RNA at or after 12 weeks following the end of treatment course. Patients were not eligible for inclusion if suspected of having reinfection 1) as suspected by local clinicians, or 2) due to a negative HCV RNA at or after SVR12 time point followed by a positive HCV RNA at a later date.

Data included initial therapy and second-line therapy regimens and durations, patient demographic and clinical characteristics, and retreatment outcomes. Given that this retrospective analysis used de-identified data, this study was given a Non-Human Subject Research determination (Advarra IRB Pro00041396, Georgian National Center for Disease Control and Public Health IRB 2020-004). National

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programs from Egypt, Georgia, and Myanmar and clinical sites from Rwanda contributed data on initial therapy failures, retreatments with second-line therapy, or both; data from Rwanda (N = 37) included only initial therapy failures and were not included in the final analysis. All reported data from Georgia and Egypt were from the public sector, whereas data from Myanmar were from both public and private facilities. Descriptive statistics were used to assess patient demographic and clinical characteristics and second-line therapy regimens, as well as SVR12.

RESULTS

De-identified data on 1462 HCV infected patients with confirmed virologic relapse after initial DAA therapy and retreated with second-line therapy were shared from Egypt (N = 639), Georgia (N = 807), and Myanmar (N = 16) (Table 1). The median age of retreated patients was 53 (interquartile range [IQR]: 47–59) years, and 73.8% were male (N = 1079). Of retreated patients, 73.2% (N = 1061) were cirrhotic. The breakdown of genotypes for the 823 retreated patients in Georgia and Myanmar was as follows: GT-1: 50.8%, GT-2: 21.6%, GT-3:

Table 1. Patient Characteristics and Treatment Regimens Across Countries and SVR12 by Retreatment Regimen

	Egypt		Georgia		Myanmar		All Sites		SVR12 Achieved With Retreatment (All Sites)	
	N	%	N	%	N	%	N	%	n/N	%
Total N	639		807		16		1462		1004/1070	93.8%
Sex										
Female	258	40.4%	125	15.5%	0	0.0%	383	26.2%		
Age in years, median (IQR)	639	54 (47–59)	807	52 (46–58)	16	44 (40–49)	1462	53 (47–59)		
Known HIV-positive	103	16.1%	0	0.0%	16	100.0%	119	8.1%		
Known HBV-positive	2	0.3%	20	2.5%	0	0.0%	22	1.5%		
History of injecting drugs	82	10.2%	82	10.2%		
Genotype										
1	414	51.3%	4	25.0%	418	50.8%	217/229	94.8%
2	178	22.1%	0	0.0%	178	21.6%	115/120	95.8%
3	215	26.6%	8	50.0%	223	27.1%	97/111	87.4%
6	0	0.0%	4	25.0%	4	0.5%	0/0	N/A
Cirrhotic	495	77.5%	565	70.1%	1	25.0%	1061	73.2%		
Duration of initial treatment										
12 weeks	294	36.4%	14	87.5%	308	37.4%		
24 weeks	391	48.5%	2	12.5%	393	47.8%		
Other	122	15.1%	0	0.0%	122	14.8%		
Initial therapy										
SOF/LDV	0	0.0%	102	12.6%	0	0.0%	102	7.1%	39/46	84.8%
SOF/LDV+RBV	0	0.0%	144	17.8%	0	0.0%	144	10.0%	57/58	98.3%
SOF+RBV	384	62.5%	556	68.9%	0	0.0%	940	65.4%	678/719	94.3%
SIM/SOF	110	17.9%	0	0.0%	0	0.0%	110	7.7%	99/104	95.2%
SOF/DCV	55	9.0%	0	0.0%	16	100.0%	71	4.9%	51/55	92.7%
SOF/DCV+RBV	63	10.3%	0	0.0%	0	0.0%	63	4.4%	55/61	90.2%
Other	2	0.3%	5	0.6%	0	0.0%	7	0.5%	0/2	0.0%
Second-line therapy and duration selection										
12 weeks										
SOF/LDV+RBV	0	0.0%	77	9.5%	0	0.0%	77	5.3%	61/62	98.4%
SOF/DCV+RBV	79	12.4%	0	0.0%	0	0.0%	79	5.4%	71/77	92.2%
SOF+SIM+DCV+RBV	77	12.1%	0	0.0%	0	0.0%	77	5.3%	75/77	97.4%
Other ^a	34	5.3%	40	5.0%	4	25.0%	78	5.3%	56/57	98.3%
24 weeks										
SOF/LDV+RBV	0	0.0%	465	57.6%	0	0.0%	465	31.8%	266/291	91.4%
SOF/DCV+RBV	449	70.3%	0	0.0%	0	0.0%	449	30.7%	395/422	93.6%
SOF/VEL+RBV	0	0.0%	201	24.9%	3	18.8%	204	14.0%	64/68	94.1%
Other ^b	0	0.0%	24	3.0%	9	56.3%	33	2.3%	16/16	100.0%

Abbreviations: DCV, daclatasvir; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IQR, interquartile range; LDV, ledipasvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR12, sustained viral response at 12 weeks; VEL, velpatasvir.

^aAmong patients with SVR12 received.

^bOther regimens were as follows: SOF/VEL, SOF/DCV, SOF/LDV, SOF/LDV+RBV+PegIFN, SOF/VEL/VOX, SOF/VEL/VOX+RBV, SOF/PAR/OMB+RBV, SOF/SIM, SOF+RBV+PegIFN.

27.1%, GT-6: 0.5%. Genotype data were not available in Egypt. About 10% (N = 82) of retreated patients were persons who injected drugs (this variable was only collected in Georgia), 8.1% (N = 119) were known to be human immunodeficiency virus (HIV)-positive, and 1.5% (N = 22) were known to be hepatitis B virus (HBV)-positive. Of 823 patients in Georgia and Myanmar, 47.8% (N = 393) received 24 weeks of initial therapy, 37.4% (N = 308) were prescribed a 12-week regimen of therapy, and 14.8% (N = 122) were prescribed other initial treatment durations. The most common initial therapy regimens were SOF+RBV (65.4%) and SOF/LDV+RBV (10%). There was some use of SOF/LDV+RBV as first-line therapy for GT-2 (N = 30) and GT-3 (N = 99), despite this regimen not being recommended by WHO guidelines for these genotypes.

A total of 37.7% (N = 546) of retreated patients initiated second-line therapy within 6 months after completion of initial therapy. Of the 1462 patients retreated for HCV infection, the most common second-line therapy regimens and treatment durations were SOF/LDV+RBV for 24 weeks (31.8%), SOF/DCV+RBV for 24 weeks (30.7%), SOF/VEL+RBV for 24 weeks (14.0%), SOF/DCV+RBV for 12 weeks (5.4%), SOF/LDV+RBV for 12 weeks (5.3%), and SOF+simeprevir (SIM)+DCV+RBV for 12 weeks (5.3%). SOF/VEL/VOX or SOF/VEL/VOX+RBV was used for 11 patients (0.2%; all patients were in Myanmar).

At the time of analysis, 89.8% (N = 1313) of the 1462 retreated patients had completed second-line therapy. Of 1070 (81.5% of 1313) patients who completed retreatment and received SVR12 testing, the proportion of patients who achieved SVR12 was at least 91.4% for all regimens (range: 91.4–100%). Overall, 93.8% of the 1070 retreated patients who received SVR12 testing were cured. Cure rates were high for GT-2 (13/13; 100%) and GT-3 (39/40; 97.5%) patients treated with SOF/LDV+RBV, despite this not being a WHO-recommended regimen.

DISCUSSION

This retrospective analysis revealed that despite the unavailability of WHO-recommended regimens for HCV second-line therapy in 3 LMICs, alternative therapeutic regimens are available, are being used by clinicians, and resulted in over 93% of patients cured of HCV infection upon retreatment. The most commonly used second-line therapy regimens were SOF/LDV+RBV, SOF/DCV+RBV, and SOF/VEL+RBV for 24 weeks. Although the quality of this evidence is lower than that for the WHO-recommended regimen, these strategies of extending existing therapies to 24 weeks and/or adding ribavirin are consistent with commonly used practices in HCV treatment. All retreatment regimens used in Egypt and Georgia achieved SVR rates of more than 90%.

This analysis was limited by its observational, retrospective design. Direct comparison of SVR rates across retreatment regimens was not possible due to the potential for confounding

across regimens and settings. More than 20% of patients in the data set did not have SVR12 data reported, and these patients may have had a lower cure rate than that described here or may have experienced adverse events. Moreover, genotype data were not available from Egypt, although it has been well documented that the primary genotype in this population is 4a [13]. Most patients (65.4%) were initially treated with SOF+RBV, which is no longer the primary initial therapy in LMICs, and virologic failure after this regimen may be less likely to provoke NS5A resistance and possibly influence retreatment success. However, even when restricting analysis to only NS5A-containing initial regimens (SOF/LDV and SOF/DCV), SVR12 after retreatment was 89.1%, in line with the broader conclusions of the analysis. SOF/LDV+RBV was given to some genotype 2 and 3 patients as initial therapy, despite not being recommended by WHO guidelines. For these patients with SVR12 data, the retreatment outcomes were still favorable: GT-2: 100% cured; GT-3: 97.5% cured. No patients in this data set were treated with glecaprevir/pibrentasvir (G/P), as G/P is not currently widely available in LMICs. Retreatment outcomes may differ for failures of first-line regimens not included in this dataset.

Data on tolerability/adverse events were not systematically collected at all sites and therefore this topic was outside of the scope of this analysis. Additional data should be collected to assess the strengths and limitations of these second-line therapeutic options. For example, there are drawbacks of a ribavirin-based therapy, especially for 24 weeks, including a higher side effect profile, increased ribavirin monitoring needs, more challenges with adherence, and potential issues with availability of ribavirin. A prospective, randomized controlled trial in LMICs is needed to establish high-quality evidence on preferred second-line therapy regimens. Still, useful information may be gleaned by analyzing routinely collected, real-world data from active HCV programs in LMICs.

In the absence of a recommendation on affordable and accessible regimens for retreatment in international guidelines, clinicians in LMICs must use their own judgement based on second-line therapy options available or make the difficult decision to defer retreatment. Patients who defer retreatment may go on to develop advanced liver disease or primary liver cancer. These preliminary data suggest that currently available second-line therapy options have high cure rates. These alternative second-line therapy regimens are affordable at a cost as low as US \$28 for locally approved SOF/DCV and US \$63 for RBV for a 12-week treatment course [14, 15].

The World Health Organization set global targets for hepatitis elimination in 2030, and patients who experience initial therapy failures should not be forgotten on the quest to elimination.

Notes

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National Hepatitis C Elimination Program of Georgia

13

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13.1 HCV Epidemiology in Georgia

Georgia is a small Eastern European country (population: 3.7 million people) situated in the Caucasus between Russia and Turkey. The country has the fifth highest prevalence of hepatitis C in the world with an estimated 5.4% of adult population (150,000 persons) living with chronic HCV infection [1, 2]. Studies in various populations show that people who inject drugs have highest anti-HCV

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Table 13.1 Hepatitis C burden in various populations in Georgia

Population	Anti-HCV+ (%)	HCV-RNA+ (%)
General population of Georgia [1]	7.7	5.4
General population of capital city Tbilisi [3]	6.7	N/A
People who inject drugs [4]	68.8	N/A
People who inject drugs [5]	63.2	N/A
Men who have sex with men [6]	7.2	N/A
People living with HIV [7]	40.3	34.3
People living with tuberculosis [8]	20.9	N/A
Healthcare workers [9]	5.0	N/A

N/A not available

prevalence of up to 70%, followed by people living with HIV (40%), people living with tuberculosis (21%), and others (Table 13.1).

According to the latest estimates, genotype 1 accounts for 41% of HCV infections in Georgia, followed by genotype 3, 35%, and genotype 2, 24%. There have been temporal changes in genotype distribution over the last 15-year period with increase in genotype 3 infections, primarily attributable to injection drug use [10, 11]. Interestingly, sequencing studies indicate that majority (about 70%) of genotype 2 infections in Georgia are actually recombinant form (RF) 2k/1b and thus may account for up to 18% of all infections in the country [12, 13]. This chimera virus possesses genotype 2 sequence in the structural and genotype 1 sequence in the non-structural region of the virus affecting response to antiviral therapy [14].

13.2 National Elimination Program

Georgia had been laying groundwork toward elimination for a long time through developing strong human and technical capacities and through increasing access to HCV therapy. Over the years, the Government of Georgia substantially stepped up its efforts against hepatitis C by implementing national programs such as free of charge hepatitis C treatment for HIV/HCV co-infection patients (implemented in collaboration with the Global Fund to Fight AIDS, TB, and Malaria since 2011) and free of charge hepatitis C treatment in the penitentiary system (2013) and negotiating 60% price reduction on combination of pegylated interferon and ribavirin for general population (2013).

These efforts culminated with the launch of world's first hepatitis C elimination program in April 2015 in partnership with US Centers for Disease Control and Prevention (CDC) and commitment from Gilead Sciences to donate its direct-acting antivirals (DAAs) to treat all Georgian living with HCV infection free of charge [15, 16]. Georgia has been chosen as a first model country for eliminating hepatitis C for several reasons, including:

- High prevalence of hepatitis and a small size of the country
- Strong political will and public support
- Strong technical and human capacities
- Existence of effective systems for implementing large-scale health programs
- Best practice experience in ensuring universal access to HIV and TB treatments

Combination of these factors strengthened by international partnership translated into successful rollout of elimination program. Together with CDC, WHO, and other international partners, Technical Advisory Group (TAG), represented by world's leading experts, was established to guide implementation of the program. Based on TAG recommendations, Georgia developed comprehensive strategic plan covering all key direction needed for eliminating hepatitis C by 2020, including advocacy and awareness; surveillance; prevention of transmission through blood safety, infection control, and harm reduction; and screening, care, and treatment. All these activities are implemented through either donor support or national allocations representing an example of an effective public-private partnership.

While Georgia's approach builds on delivering comprehensive response to HCV, treatment remains the cornerstone of elimination program. The overall goal of the program is to eliminate hepatitis C primarily through identifying and treating all HCV-positive persons strengthened by effective prevention interventions.

Despite very high effectiveness of modern DAAs approaching 100% cure rates, complete eradication of HCV infection, similar to that of smallpox, is impossible, and therefore Georgia set the goal for eliminating and not eradicating HCV. Although classical definition focuses on incidence [17], Georgia's HCV elimination goal was defined as 90% reduction in HCV prevalence from 5.4% to 0.5% [18].

To achieve the goal, the strategy has set forth 90-95-95 targets to be reached by 2020: (a) 90% of people living with HCV infection know their status; (b) 95% of people aware of their status are treated for HCV infection; and (c) 95% of people treated for HCV infection are cured.

Georgia's elimination program envisages active case finding and treating all patients, regardless of degree of liver damage, in order to achieve maximum prevention effect. Also for achieving the elimination goal, all patients with virological failure are retreated.

Treatment component of the elimination program started in April 2015 with four specialty clinics delivering care in the capital city of Tbilisi, and after 3 years, this expanded to over 30 HCV care provider clinics countrywide. Decentralization process further continues through establishing HCV treatment capacities in primary healthcare clinics and harm reduction sites.

Successful treatment expansion was possible through dedicated human capacity strengthening program delivered by Liver Institute and Foundation for Education and Research (L.I.F.E.R.) and Project ECHO of the New Mexico University.

National treatment protocols are developed in collaboration with leading international hepatologists and support simplified diagnostic and monitoring approaches. During the first year of the program, sofosbuvir (SOF) was the only DAA available within the program, which was used in combination with ribavirin with or without pegylated interferon. Since March 2016, Gilead donates fixed-dose combination of

ledipasvir/sofosbuvir (LDV/SOF). Exclusive decision was made for the elimination program to recommend LDV/SOF for all genotypes including with or without ribavirin for genotype 1 and in combination with ribavirin for genotypes 2 and 3.

Development of electronic health information systems has been essential part of elimination program. In 2015 national HCV treatment database was established, which is now modern web-based health information system connecting all HCV care providers countrywide. The database collects comprehensive case-based information, including demographic, laboratory, and clinical data, on every person enrolled in elimination program using standardized protocol. Effective validation mechanisms are available to ensure that high-quality data are captured. The database is the key source for monitoring treatment on individual and programmatic level, as well as for conducting research and for informing policies. In 2017 HCV screening database was launched to collect data from all sites providing HCV screening services in Georgia. The next step is to create unified system for hepatitis C elimination program integrated into the national e-health management system.

13.3 HCV Cascade and Treatment Outcomes

Figure 13.1 describes HCV care cascade as of March 31, 2018. After 3 years of program implementation, 32.5% of estimated number of people with chronic HCV infection were diagnosed; 93% of those diagnosed started treatment, and more than 98% of those assessed for sustained virologic response (SVR) cleared the virus, thus already exceeding treatment related 95% targets.

This cascade shows that success of the elimination program primarily depends on ability of the program to identify 90% of people living with HCV infection. Georgia responded to this challenge by scaling up screening, including through healthcare-based and outreach activities. As of March 31, 2018, over 974 thousand persons were screened for HCV (35% of adult population of Georgia), and one-third of the HCV-infected population were diagnosed. Analysis of the data showed the yield of

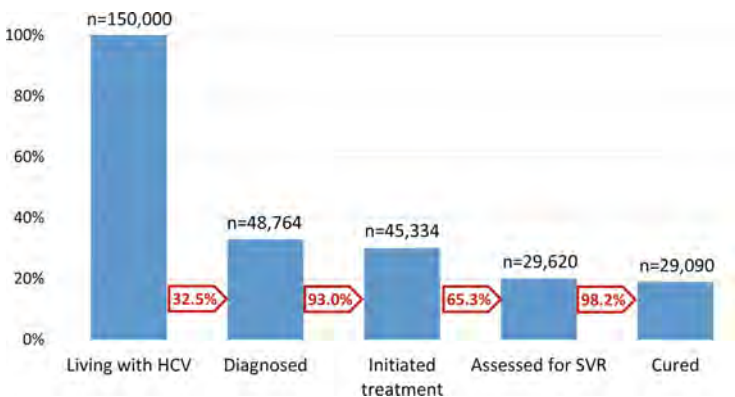


Fig. 13.1 HCV cascade as of March 31, 2018

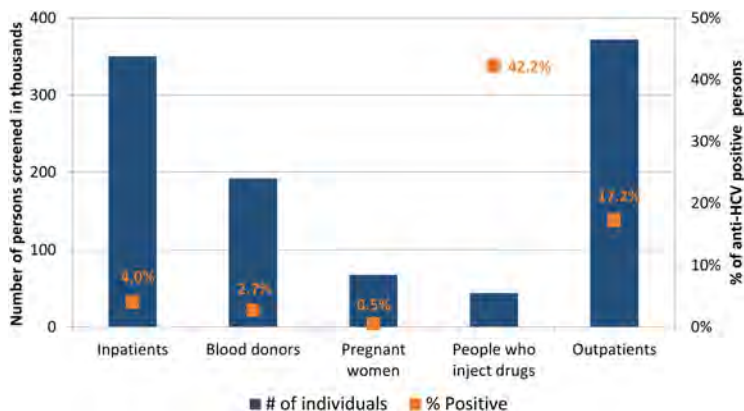


Fig. 13.2 HCV screening among different target groups

screening efforts differs between various populations: the highest rate of anti-HCV positivity of 42% was observed in harm reduction services for people who injected drugs, while only 0.5% tested positive in antenatal clinics (Fig. 13.2) [19]. This underlines the need for targeting services for those at highest risk of HCV infection. Together with international partners, the Ministry of Health of Georgia takes efforts to introduce innovative and high-quality strategies to increase awareness and improve access to screening.

During the initial year of the program, treatment was prioritized for patients with advanced liver damage (\geq F3 METAVIR fibrosis score or FIB-4 score $>$ 3.25). Treatment initiation criteria expanded in June 2016 to treat all patients regardless of liver damage status. This resulted in 300% increase in treatment initiation rates peaking with 4552 persons starting treatment only in August 2016. The rates declined afterward and flattened at monthly rate of around 1100 persons starting treatment in 2017 (Fig. 13.3). This reflects challenges in HCV case finding, with engagement in treatment services clearly outpacing the rate of new diagnosis.

With regard to treatment outcomes, SVR rate among persons starting SOF-based regimen was 82.1%, persons failing on SOF were retreated with LDV/SOF achieving 99.2% cure rates, and persons receiving LDV/SOF as initial treatment reached SVR of 98.4%. High overall cure rates were achieved in all patients with and without advanced fibrosis (97.3% and 98.7%, respectively, Fig. 13.4). Overall SVR rates did not differ by genotype—98.5% in genotype 1, 98.3% in genotype 2, and 97.7% in genotype 3 (Fig. 13.4). The most importantly, high cure rates have been achieved without newer generation DAAs and with only LDV/SOF with or without ribavirin.

High cure rate in genotype 1 patients in Georgian cohort is in line with previous findings from clinical trials and real-life studies demonstrating similar effectiveness of LDV/SOF [20–23].

LDV/SOF in combination with ribavirin proved to be highly effective in genotype 2 and 3 patients and can be considered as pangenotypic combination at least in Georgian settings. SVR rates shown in elimination program are comparable or even

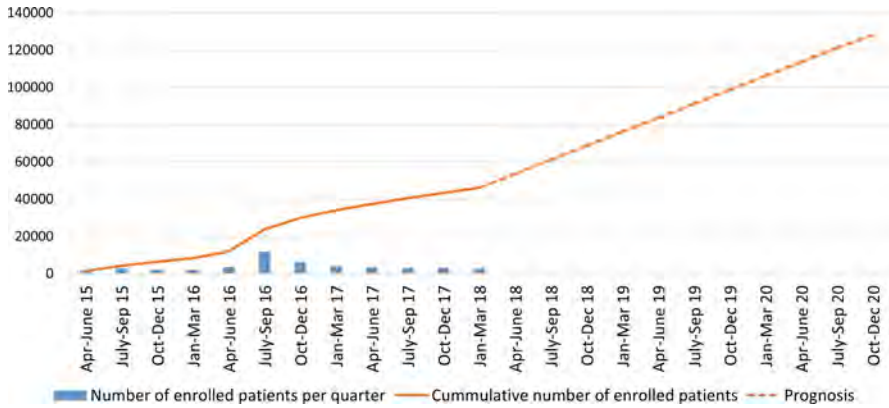


Fig. 13.3 Enrollment in HCV treatment

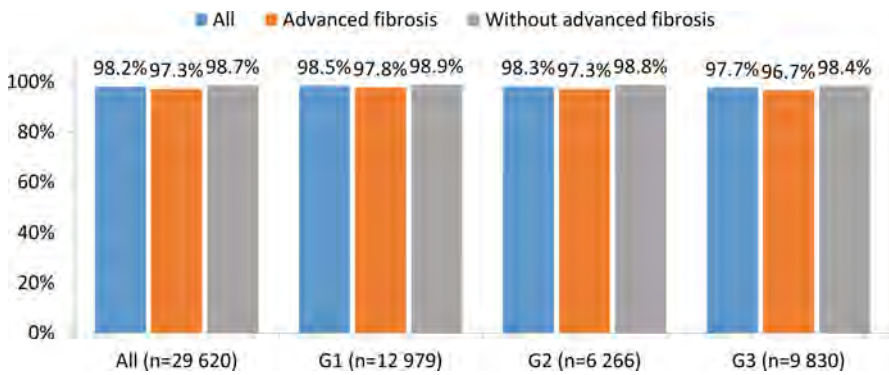


Fig. 13.4 HCV treatment outcomes by genotype and liver damage status among persons assessed for SVR, April 2015–March 2018

higher than those achieved with newer generation DAAs [24, 25]. Over 98% effectiveness of LDV/SOF in genotype 2 patients can be explained by high prevalence of RF_2k/1b recombinant form in Georgia, which has been shown to respond well to genotype 1 specific treatment options including LDV/SOF [26, 27]. Impressive results were obtained in genotype 3 patients with 97.7% SVR rate. International experience of using LDV/SOF in genotype 3 is very limited, and in the few published studies, SVR ranged between 78% and 91%, which is lower than Georgian experience [28–30].

13.4 Beyond Cascade

Georgia’s elimination program has made progress in all directions of the strategic plan of action.

- *Advocacy and awareness*: Massive awareness-raising campaign has been conducting utilizing variety of media strategies (TV ads, social media ads, internet platform, etc.), short text messaging, and distribution of public education materials. Special attention has been paid to fighting stigma through engaging people living with diseases and empowering local communities [31].
- *Prevent HCV transmission*: Primary HCV prevention is one of the major activities of the national strategy. This includes harm reduction services for people who inject drugs (PWID) such as needle/syringe exchange programs and opioid substitution treatment. Available data shows that 61% of estimated number of PWID had been reached with any prevention services and 48% had been screened for HCV infection [31]. Serious efforts had been made toward implementing infection control and prevention monitoring and evaluation in medical and non-medical facilities, as well as enhancing quality control mechanisms in blood banks.
- *Improve HCV laboratory diagnostics*: Essential steps toward improving laboratory diagnostics were implemented, including approval of regulatory documents for licensing laboratory service providers and implementation of national external quality assurance program [31].
- *Surveillance*: Monitoring progress toward HCV elimination requires a well-functioning surveillance system, and efforts are made to improve system's capacity to monitor/assess the burden and risk factors for HCV infection in the country. Special study to characterize the burden of HCV-associated hepatocellular carcinoma in Georgia is underway [31].

13.5 Achieving the Goal of Elimination

Georgian hepatitis C elimination program has made substantial progress since its initiation. Over the first 3 years, more than 48,000 persons were diagnosed, and over 45,000 of them initiated treatment achieving cure in 98.2% of those assessed for SVR. Mathematical modeling study showed that these efforts already averted 2500 HCV-related deaths and 5200 new HCV infections [32].

Along with accomplishments, formidable challenges remain, and first and foremost, this relates to HCV case finding. Most people living with HCV in Georgia still remain undiagnosed representing major obstacle for meeting 90-95-95 targets. In response, Georgia is ramping up screening services along with expanding access to treatment through decentralization and integration in primary healthcare and harm reduction services. This is key for securing access to services for all and particularly for those vulnerable, such as people who inject drug.

The important feature of Georgia's elimination program is that it not only hinges on seek, test, and treat strategy but also proactively supports primary prevention through better infection control practices, blood safety, and harm reduction. Such comprehensive approach puts the country on the right path to elimination goal. Continued governmental commitment, together with active engagement from civil society and productive international partnership, provides strong basis for sealing the

success. Georgia's hepatitis C elimination program will further evolve as innovative screening strategies, diagnostics, and prevention and treatment options are implemented, providing valuable lessons for the world [33].

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Hepatitis C core antigen test as an alternative for diagnosing HCV infection: mathematical model and cost-effectiveness analysis

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ABSTRACT

Background. The cost and complexity of the polymerase chain reaction (PCR) test are barriers to diagnosis and treatment of hepatitis C virus (HCV) infection. We investigated the cost-effectiveness of testing strategies using antigen instead of PCR testing.

Methods. We developed a mathematical model for HCV to estimate the number of diagnoses and cases of liver disease. We compared the following testing strategies: antibody test followed by PCR in case of positive antibody (baseline strategy); antibody test followed by HCV-antigen test (antibody-antigen); antigen test alone; PCR test alone. We conducted cost-effectiveness analyses considering either the costs of HCV testing of infected and uninfected individuals alone (A1), HCV testing and liver-related complications (A2), or all costs including HCV treatment (A3). The model was parameterized for the country of Georgia. We conducted several sensitivity analyses.

Results. The baseline scenario could detect 89% of infected individuals. Antibody-antigen detected 86% and antigen alone 88% of infected individuals. PCR testing alone detected 91% of the infected individuals: the remaining 9% either died or spontaneously recovered before testing. In analysis A1, the baseline strategy was not essentially more expensive than antibody-antigen. In analysis A2, strategies using PCR became cheaper than antigen-based strategies. In analysis A3, antibody-antigen was again the cheapest strategy, followed by the baseline strategy, and PCR testing alone.

Conclusions. Antigen testing, either following a positive antibody test or alone, performed almost as well as the current practice of HCV testing. The cost-effectiveness of these strategies depends on the inclusion of treatment costs.

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INTRODUCTION

Hepatitis C virus (HCV) is a major cause of liver disease and liver-related mortality (*Pawlotsky et al., 2018*). The World Health Organization (WHO) estimates that 71 million people worldwide are chronically infected with hepatitis C, and 400,000 people die from HCV every year, mostly due to cirrhosis and hepatocellular carcinoma. However, the majority of the HCV infected individuals are not aware of their infection (*WHO, 2021*). Effective hepatitis testing strategies and tools are needed to achieve the WHO target of eliminating HCV as a major public health threat by 2030 (*World Health Organization, 2016*).

Since 2014, Direct Acting Antivirals (DAA) form the standard HCV treatment. For successful DAA treatments, tests are needed to diagnose the infection and confirm the clearance of viral replication (*Pawlotsky et al., 2018; Tillmann, 2014*). Two types of tests are usually applied: serological assays that detect antibodies to HCV, and nucleic acid tests that detect HCV RNA genomes to confirm active infection (*Tillmann, 2014; Gretch, 2000*). The most commonly used testing protocol is to first use an antibody test, and if the result is positive, check the presence of the virus with a nucleic acid test (usually a polymerase chain reaction test, PCR) (*Tillmann, 2014; Gretch, 2000*). The sensitivity and specificity of PCR tests are high (*Gretch, 2000*). PCR testing requires time and trained laboratory personnel, which increases the costs. The cost of PCR is an important barrier for comprehensive testing, especially in low- and middle-income countries.

HCV-antigen test is a serological assay that directly detects a viral protein, giving a positive result as soon as the virus component is present. The test can be done on the same platform as the antibody test (*Tillmann, 2014*), is cheaper (*Cresswell et al., 2015*) and requires less special training than PCR testing. While antigen tests have a specificity of up to 100%, viral loads below 3,000 IU/ml may not be detected (*Tillmann, 2014; Bertisch et al., 2020*).

With a limited budget, replacing PCR by antigen testing could increase testing coverage, but people with very low viral loads may be missed. Using the country of Georgia as an example, we aimed to study the cost-effectiveness of different testing strategies using a mathematical model.

MATERIALS AND METHODS

Model structure and inputs

We developed a mathematical model for HCV disease progression, similar to a previously published model (*Sadeghimehr et al., 2019*). We simulated cohorts of patients from infection until death. The progression of HCV is represented by a directed acyclic graph of health states. In each state, the model samples when and to which state the patient will move next. The process is repeated until the patient reaches a terminal state (death). The patients progress along the stages of liver disease, course of HCV infection and cascade of care (*Fig. 1*). The liver disease stages are represented by the METAVIR scoring system

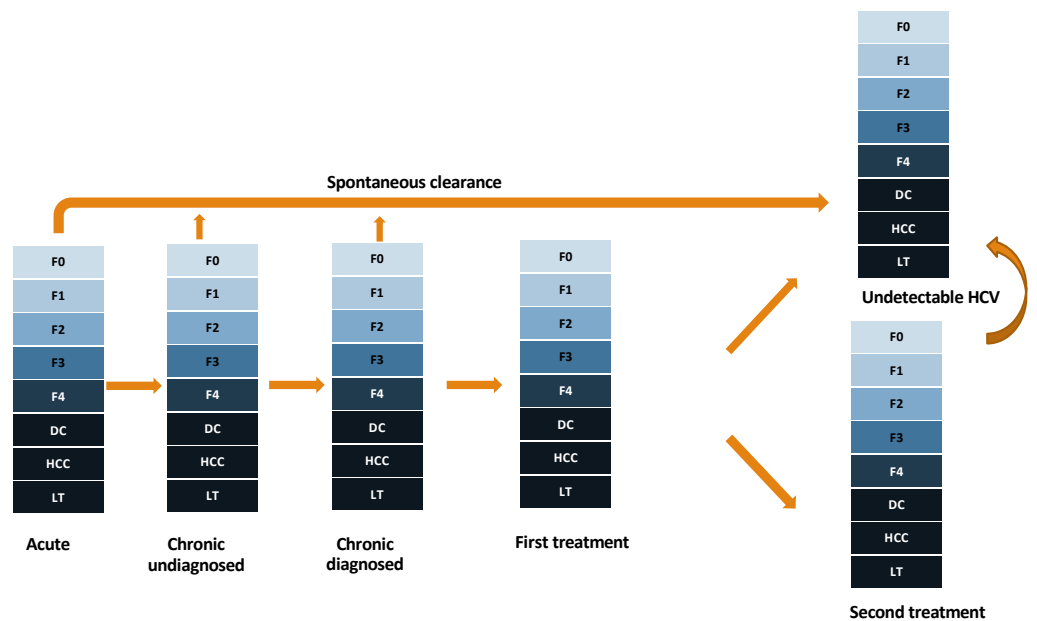


Figure 1 Structure of the simulation model. Individuals can progress vertically based on liver disease, and horizontally through the hepatitis C virus (HCV) infection and cascade of care. First and second treatments contain the treatment episode itself and, in case of treatment failure, the time after ending therapy. Death can occur at any state (not shown in the graph for simplicity). F0-F4, stages of fibrosis according to the METAVIR scoring system; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, Liver transplantation.

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(F0-F4), followed by decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and liver transplantation (LT). At the beginning of the simulation, patients are assigned the following characteristics: age at infection, year of birth, gender, HIV co-infection, level of alcohol consumption, and duration of intravenous drug use (IDU).

Many studies have shown that hepatitis C viral load is relatively stable in untreated patients with chronic infection (*Gretch, 2000; Nguyen et al., 1996*). We therefore assumed that viral loads remain approximately constant in untreated individuals. We used the viral load distribution among patients in the Swiss Hepatitis C Cohort Study (*Bertisch et al., 2020*) and assigned each patient a baseline viral load. Viral load values at the time of HCV testing were sampled from a log-normal distribution around the baseline viral load. We denote viral loads below 3,000 IU/ml as very low viral loads (VLVL) (*Tillmann, 2014; Bertisch et al., 2020*).

We considered the following testing strategies: HCV-antibody followed by PCR testing in case of a positive antibody test (baseline strategy); HCV-antibody followed by HCV-antigen testing in case of a positive antibody test (antibody-antigen strategy); HCV-antigen test alone; and PCR test alone. In all strategies, a second test (either PCR or antigen, whichever was used to confirm the diagnosis) was taken 12 weeks after treatment completion to confirm sustained virologic response (SVR). We assumed that all individuals were tested

Table 1 Baseline characteristics of the simulated patients.

Characteristics	Active IDU	Non-IDU	Source
Alcohol consumption			
Abstinent	37%	37%	<i>Butsashvili (2016)</i> , assumption
Moderate (on average 20–40 g per day)	37%	37%	
Excessive (on average >40 g per day)	26%	26%	
Gender			<i>National Hepatitis C Virus Elimination Progress Report (2018)</i> , <i>Butsashvili (2016)</i> , <i>Stvilia et al. (2006)</i>
Female	0.8%	47.2%	
Male	99.2%	52.8%	
HIV co-infected	2.3%	0.2%	<i>UNAIDS (2018)</i>
HCV prevalence	66.2%	5.4%	<i>Strategic plan for the elimination of Hepatitis C Virus in Georgia (2020)</i> , <i>Jülicher & Galli (2018)</i>

Notes.

IDU, injection drug user.

for HCV once during the years 2015–2018. In case of a negative test result, the individual was not retested.

We assumed that the sensitivity of the antibody test increases exponentially during the first year of the infection and stabilizes at 99% thereafter (*Thomson et al., 2009; Tang et al., 2017*). The sensitivity of the antigen test was assumed to be 33.0% for patients with VLVL, and 98.2% for everyone else (*Bertisch et al., 2020*). The PCR test was assumed to be 100% sensitive. The expected numbers of tests among HCV uninfected people were calculated from the HCV prevalence in the target population. We assumed 100% specificity for HCV-antigen and PCR tests. We assumed that all detected patients are treated with DAAs, and 98% of the treated patients achieve SVR (*Pawlotsky et al., 2018*).

We parameterized the model for Georgia, one of the first countries that aimed to eliminate HCV. Enlarged-scale HCV screening began in January 2015, and the elimination programme (*National Hepatitis C Virus Elimination Progress Report, 2018*) was launched in April 2015. Screening services continue to be provided free of charge in various settings. As of June 30, 2018, a total of 1,175,291 HCV screening tests had been done and 1,125,808 persons registered in the elimination programme, of whom 93,181 (8.3%) were positive for HCV antibody. Currently in Georgia patients without documented HCV serological status first undergo anti-HCV antibody testing. Patients with positive anti-HCV antibodies undergo PCR testing, or since December 2017 alternatively core antigen testing (*Ministry of Health of Georgia, 2020*). [Table 1](#), [Table S1](#) and [Figs. S1–S2](#) present the baseline characteristics of the simulated individuals, the model's parameters and assumptions. We assumed that HCV viral loads were not independently associated with fibrosis progression rates (*Heller & Seeff, 2005*). The simulated population included patients infected before 2019 who had not cleared the virus spontaneously or been treated before 2015, and had not been diagnosed by 2015.

Model outcomes

We estimated the number of diagnoses for each testing strategy and compared the number of people who experienced severe liver disease (F3), cirrhosis (F4), DC, HCC, and liver-related death.

We also compared the cost-effectiveness of the testing alternatives, conducting three analyses with different assumptions regarding costs. In analysis A1, we only considered the direct costs of the HCV tests, including also testing the HCV uninfected individuals not explicitly simulated. In analysis A2, we added the costs of HCV-associated consultations with clinical assessment, complete blood count and alanine aminotransferase test (*Ministry of Health of Georgia, 2020*) and the lifetime costs associated with liver disease. This analysis takes the perspective of the health care payer in situations like in the country of Georgia where treatment costs are covered by external donors. In analysis A3, we included all costs of HCV testing, liver disease and HCV treatment. We reviewed the literature, and contacted persons involved in the elimination project in the country of Georgia to interpret published data to obtain costs of HCV testing, DAA treatment and liver disease, and HCV- and liver-related utilities (*Table 2*) (*Jülicher & Galli, 2018; Ormechi et al., 2014; Cloherty et al., 2016*). We adopted life-time liver disease costs from Turkey for viremic individuals (*Ormechi et al., 2014*). We assumed that the costs of liver disease in stages F0-F3 decreased by 50% after achieving SVR. The quality of life of patients has been shown to improve substantially after SVR (*Dusheiko, 2017*). Moreover, the model does not allow liver disease regression, so patients modelled to be in an advanced stage of the liver disease with SVR may in reality have returned to a less severe stage (*Knop et al., 2016*). It should therefore be safe to assume that the costs of treating liver disease decrease substantially after achieving SVR. In all analyses, we calculated the incremental cost-effectiveness ratios (ICERs) between the strategies, comparing incremental costs with incremental gain in quality-adjusted life expectancy at time of infection. The results are presented per infected individual. We discounted all future costs and quality-adjusted life years (QALYs) at 3% per year.

Sensitivity analyses

We conducted sensitivity analyses to address the uncertainty around key parameters and generalize our findings to other settings (*Table S2*). First, we reduced the unit cost of either the PCR test (sensitivity analysis S1) or antigen test (sensitivity analysis S2). Second, we reduced the liver-related costs after SVR to zero for liver stages F0-F2 (sensitivity analysis S3). Third, we used an alternative estimate of liver disease costs from France (sensitivity analysis S4). Fourth, we calculated the results for a population consisting completely of non-IDUs with decreased HCV prevalence (sensitivity analysis S5), or an IDU population with increased HCV prevalence (sensitivity analysis S6). Finally, we decreased the cost of HCV treatment to generalize the results for settings that have access to treatment with substantially reduced prices (sensitivity analysis S7).

RESULTS

In the baseline scenario, 89,400 of 100,000 infected individuals were diagnosed during the four-year screening period. In the antibody-antigen strategy, fewer infected individuals were detected (86,100 per 100,000 infected individuals). For antigen test alone the number of diagnoses was 87,500 per 100,000 infected individuals. PCR test alone could detect

Table 2 Unit costs and health utilities.

Costs	Value	Source
Antibody test	\$2	
Antigen test	\$21	<i>Strategic plan for the elimination of Hepatitis C Virus in Georgia (2020), Chikovani et al. (2019)</i>
PCR test	\$40	
Physician visit and blood collection	\$13	
Treatment monitoring costs ^a	\$117	<i>Strategic plan for the elimination of Hepatitis C Virus in Georgia (2020)</i>
Treatment cost	\$50,674	<i>Scott John (2019)</i>
Average annual cost of liver disease		
Fibrosis stage F0-F2	\$447	<i>Ormechi et al. (2014)</i>
Fibrosis stage F3	\$447	
Fibrosis stage F4	\$578	
Decompensated cirrhosis	\$1984	
Hepatocellular carcinoma	\$2474	
Health-related utilities		
Fibrosis stage F0-F2	0.82	<i>Knop et al. (2016), Deuffic-Burban et al. (2018)</i>
Fibrosis stage F3	0.76	
Fibrosis stage F4	0.76	
Decompensated cirrhosis	0.60	
HCC	0.60	
F0-F1 after sustained virologic response	0.95	
F2-F4 after sustained virologic response	0.85	

Notes.

^aIncluding the cost of clinical assessment, complete blood count, ALT (AST, creatinine), patient service standard. HCC, hepatocellular carcinoma; F0- F4, fibrosis stages according to METAVIR scoring system.

91,000 individuals; the remaining 9% of infected individuals either died or spontaneously recovered before testing.

The proportion of patients who experienced severe liver disease was highest in the antibody-antigen strategy, and lowest for PCR testing alone (Fig. 2). In the baseline strategy, 22.5% of infected individuals experienced at least liver disease stage F3. The percentages of people who experienced at least liver disease stage F3 were 23.5%, 22.9%, and 21.7% for antibody-antigen, antigen test alone, and PCR test alone, respectively. The percentages of people who reached stage F4 ranged between 10.0% and 12.0% across all strategies. For DC, HCC, LT and liver-related death the corresponding ranges were 2.2%–3.0%, 1.4%–2.1%, 0.5%–0.6% and 3.7%–5.0%, respectively.

In analysis A1, considering only the cost of testing, antibody-antigen was the cheapest strategy with a total cost of \$215 per infected individual and a mean quality-adjusted life expectancy of 15.51 QALYs (Fig. 3A). The most cost-effective strategy compared with antibody followed by antigen was the baseline strategy, with a quality-adjusted life expectancy of 15.56 QALYs and an ICER of \$369/QALY gained. Antigen alone had higher costs than the baseline strategy. PCR alone, which had a mean quality-adjusted life expectancy of 15.60 QALYs, was the most effective strategy with an ICER of \$10,763/QALY gained compared with the baseline strategy.

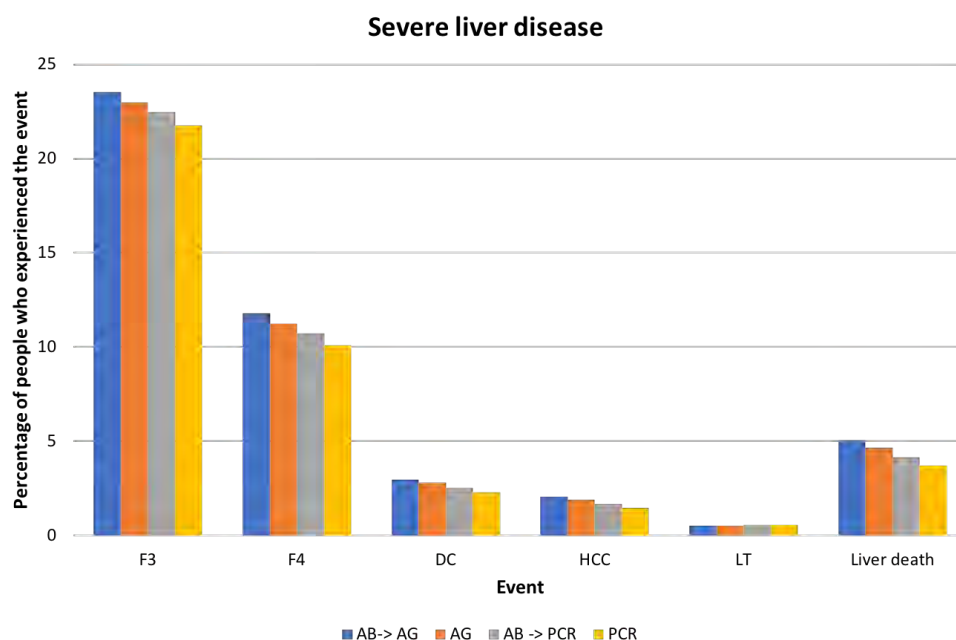


Figure 2 A comparison between different testing strategies: the proportion of infected individuals who experienced different stages of liver disease in their lifetime. F3–F4, stages of fibrosis according to the METAVIR scoring system; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, Liver transplantation.

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In analysis A2 including all costs except treatment (Fig. 3B), the baseline strategy was the cheapest, with a life-time cost of \$6,275. PCR test alone, the only strategy performing better than the baseline, had an ICER of \$9,281/QALY gained compared with the baseline scenario.

In analysis A3 considering all costs of testing, liver disease and treatment, antibody-antigen was again the cheapest strategy, with an average life-time cost of \$35,576 (Fig. 3C). Compared with antibody-antigen strategy, the baseline strategy was the most cost-effective, with an ICER of \$19,890/QALY gained. Compared with the baseline, the ICER of PCR testing alone was \$22,636/QALY gained.

Sensitivity analyses

Changing the input costs of diagnostic tests, liver disease or treatment did not change the patterns of cost-effectiveness substantially (Figs. S3–S7). The largest differences were in the analyses of the low- and high-prevalence populations. In a low-prevalence non-IDU population, the results of all three analyses were driven by the costs of testing uninfected individuals. Replacing the two-step testing (antibody-antigen, or baseline strategy) with antigen alone increased the costs of testing (analysis A1) by \$2,000, or with PCR alone, by \$4,000 per infected individual (Fig. S8). In the high-prevalence IDU population, the situation was reversed (Fig. S9). Considering the costs of testing only (analysis A1), antigen and PCR testing alone were slightly cheaper than their corresponding two-step procedures. If costs of liver disease were also included (analysis A2), PCR testing alone was the cheapest

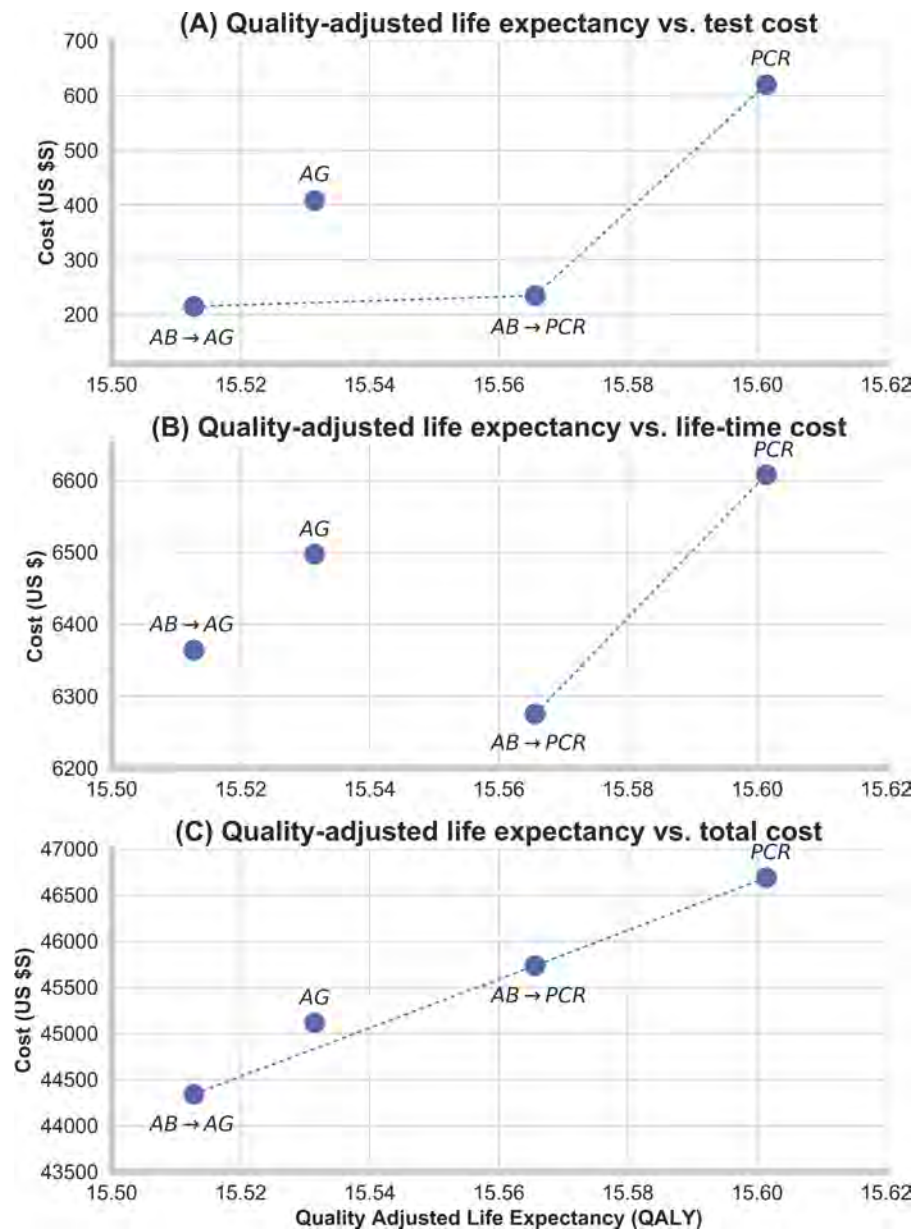


Figure 3 Quality-adjusted life expectancy *versus* cost. (A) Analysis 1: Cost of HCV testing *versus* the quality-adjusted life expectancy. (B) Analysis 2: Cost of HCV testing and life-time liver-related complications *versus* the quality-adjusted life expectancy. (C) Analysis 3: Cost of HCV testing, life-time liver related complications and HCV treatment *versus* the quality-adjusted life expectancy. All costs are measured per infected individual and include also costs of negative tests. Quality-adjusted life expectancy is measured per infected individual at the time of infection. All QALYs and costs are discounted by 3% per year. QALY, quality-adjusted life years; AB, antibody; AG, antigen.

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strategy. Considering all costs (analysis A3), antibody-antigen was again the cheapest scenario. Of the remaining strategies, antigen testing alone was most cost-effective with an ICER of \$12,265/QALY gained compared to the cheapest strategy.

DISCUSSION

Principal findings

Strategies using an antigen test to diagnose HCV infection performed reasonably well compared with the traditional PCR-based approach, but the cost-effectiveness of these strategies depends on the perspective taken. In situations like in the country of Georgia, where treatment is provided from external sources (*Ministry of Health of Georgia, 2020*), the current two-step testing procedure using antibody and PCR tests has the lowest costs from the healthcare system's point of view. Adding HCV treatment costs to our analysis made the two-step procedure with confirmation by antigen instead of PCR the cheapest, but also the least effective, strategy. However, the maximum difference in quality-adjusted life expectancy across all strategies was only one month. Antigen testing alone performed better than antibody followed by antigen, but not as well as the baseline strategy. PCR testing alone was clearly the most effective but also most expensive strategy. These additional costs could however be compensated by cost savings related to liver disease, if treatment costs were not considered.

Antigen testing alone is a potential alternative for the current two-step testing procedure. Both strategies miss some HCV infected individuals. In our study, antigen alone missed about 3% and the baseline strategy 2% of those infected. But the characteristics of the missed patients differ. The HCV antibody test can detect an infection only after about 35 days (*Ottiger, Gygli & Huber, 2013*). Strategies using antibody tests may lead to underdiagnosis in populations with ongoing transmission. In the Georgian HCV epidemic, where most infections were acquired during the first years after the collapse of the Soviet Union (*Walker et al., 2018*), this may be of limited relevance except for special groups such as IDU. Also, the antibody test may remain negative in immunosuppressed patients (*Medici et al., 2011*). The antigen test in turn misses around two thirds of individuals with VLVL (*Bertisch et al., 2020*). Antigen testing was less beneficial than the baseline strategy for two reasons: the number of VLVL patients was higher than the number of recently infected patients; and recently infected patients reach end stage liver disease later than VLVL patient on average. Antigen testing saved costs mainly by missing the individuals with VLVL and therefore reducing the number of treated patients. However, spontaneous cure is more frequent among VLVL individuals than other chronically infected patients (*Bertisch et al., 2020*), and the probability of onward HCV transmission may also be lower in persons with VLVL (*Bouvet, 2005*). A one-step simple test could also reduce the risk of loss to follow-up (LTFU). This may be highly relevant for a country like Georgia where, in 2015, more than 25% of anti-HCV positive individuals had no confirmatory testing and were considered LTFU (*National Hepatitis C Virus Elimination Progress Report, 2018*). A one-step simple test would also reduce the unnecessary anxiety among individuals with a false positive result or spontaneous cure.

Although PCR testing is more expensive than antigen testing, our analysis revealed some situations where the total costs may be lower with PCR based strategies. If treatment costs are not considered, the costs saved by preventing liver disease progression in a few patients could outweigh the additional costs needed for PCR testing. In addition to settings where treatment is covered by external sources, this may also be relevant for countries that have negotiated special agreements with treatment manufacturers. In the “subscription model” (*Trusheim, Cassidy & Bach, 2018; Moon & Erickson, 2019*), where the government pays a flat fee for treating all infected residents within a given time period, treatment costs do not depend on the number of treated patients and cost-effectiveness evaluations should focus on the costs of liver disease and diagnostics. PCR testing alone was used in our analysis as a theoretical best-case comparator: testing the population with this test costing more than \$40 is unlikely. However, in a setting with extremely high prevalence and ongoing transmission, such as active IDU, PCR testing alone could be cost-saving.

When comparing the current practice to the less expensive strategy using antibody followed by antigen testing, the ICER was \$19,600 per QALY for all costs including treatment, and the high costs were mainly caused by the increased need of treatment. This shows that in higher-income countries, the use of PCR as the confirmatory test can be justified from the financial point of view. However, in low-income settings, it may not be efficient to invest in PCR tests, in particular if individuals with low viral loads have a lower rate of HCV transmission and higher probability of spontaneous cure. It is notable that in low-income settings, government negotiations and other efforts towards HCV elimination may lead to lower price of DAA treatment and HCV RNA testing, but possibly also antigen testing. The formal cost-effectiveness analysis also does not consider factors such as budget restrictions. With a limited budget, less expensive tests allow to test more individuals, leading to more diagnoses and better clinical outcomes. Under some conditions, the use of antigen as a confirmatory test may thus be beneficial.

Strengths and limitations

Several studies have compared antigen and PCR testing and proposed the use of antigen testing (*Cloherty et al., 2016; Wang, Lv & Zhang, 2017; Alonso et al., 2016*). They were however limited to the costs of the diagnosis, or other short-term costs. Our study compares different HCV testing strategies on the life-time burden of HCV infection in a nationwide setting. Our study included the progression of both liver disease and HCV infection. We used different cost perspectives which makes the results of our study applicable for settings with differing financing systems and conditions. We used local programmatic data from Georgia and literature data to parameterize our model.

Our study is subject to limitations. First, HCV transmission was not included; thus, we ignored the additional disease burden and costs that each missed case might cause by onward transmission. Second, we did not consider HCV reinfection after SVR: we assumed that achieving SVR once will lead to a lifetime mitigation of liver related QALY loss and cost. Reinfection will reduce this benefit among people who are correctly tested positive and achieve SVR, which in turn will reduce the overall differences in QALYs and costs between the strategies. Third, we did not model any extrahepatic manifestations (EHM). EHM

could increase the overall life-time costs associated with HCV (Younossi *et al.*, 2016), which could further favour more effective testing. Fourth, we did not allow for HCV re-testing. Individuals at high risk of infection, such as active IDUs, are recommended to get retested at least once a year (Gretch, 2000). This is also the population with most acute infections. As antibody testing misses those recently infected, our model may overestimate the benefit of antibody testing for populations with many acute infections. Including re-testing could therefore favour the two-step testing procedures, as the patients who were tested negative during the acute phase of disease using an antibody test could be detected at the next testing round. Fifth, we did not consider some factors favouring the use of antigen testing, such as lower transmission risk and more spontaneous cure among patients with VLVL, and the potentially better retention of one-step testing strategies. Sixth, our analyses took the perspective of a health care payer. In the Georgian elimination program, the care is now free of charge for the patients. In settings where a considerable part of the costs is covered with out-of-pocket payments, the search for the most cost-effective strategy becomes more complicated.

CONCLUSIONS

A single antigen test can be a reliable and practical alternative for the current two-step procedure to diagnose HCV infection, but the cost-effectiveness of this strategy depends on various factors. In settings where the costs of treatment do not directly depend on the number of treated patients, the higher costs of PCR testing are likely compensated by savings in liver disease-related costs. However, a full consideration of treatment-related costs may favour simpler and easier tests such as antigen alone, or antigen after antibody testing. The change to a simple one-time test could offer advantages. In addition, the vast majority of individuals chronically infected with HCV have viral loads above 3,000 IU/ml, a level at which the diagnostic capacity of antigen tests does not differ from PCR. Replacing PCR test by antigen test to diagnose HCV can be considered as a safe option for settings with limited resources, although the associated cost savings may be limited.

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Competing Interests

The authors declare there are no competing interests. Sonjelle Shilton is employed by FIND, Geneva, Switzerland, Barbara Bertisch is employed by Checkin Helvetiaplatz and Maia Butsashvili is employed by Clinic Neolab.

Author Contributions

- Maryam Sadeghimehr and Janne Estill conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Barbara Bertisch and Olivia Keiser conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Francesco Negro, Maia Butsashvili, Sonjelle Shilton, Irina Tskhomelidze and Maia Tsereteli analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

The code is available at GitHub: https://github.com/maryamsadeghimehr/HCV_Antigen.

Supplemental Information

Supplemental information for this article can be found online at <http://dx.doi.org/10.7717/peerj.11895#supplemental-information>.

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Assessing cost-effectiveness of hepatitis C testing pathways in Georgia using the Hep C Testing Calculator

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The cost of testing can be a substantial contributor to hepatitis C virus (HCV) elimination program costs in many low- and middle-income countries such as Georgia, resulting in the need for innovative and cost-effective strategies for testing. Our objective was to investigate the most cost-effective testing pathways for scaling-up HCV testing in Georgia. We developed a Markov-based model with a lifetime horizon that simulates the natural history of HCV, and the cost of detection and treatment of HCV. We then created an interactive online tool that uses results from the Markov-based model to evaluate the cost-effectiveness of different HCV testing pathways. We compared the current standard-of-care (SoC) testing pathway and four innovative testing pathways for Georgia. The SoC testing was cost-saving compared to no testing, but all four new HCV testing pathways further increased QALYs and decreased costs. The pathway with the highest patient follow-up, due to on-site testing, resulted in the highest discounted QALYs (123 QALY more than the SoC) and lowest costs (\$127,052 less than the SoC) per 10,000 persons screened. The current testing algorithm in Georgia can be replaced with a new pathway that is more effective while being cost-saving.

Chronic hepatitis C virus (HCV) infection is a global health problem that affects about 71 million people worldwide¹. Of these, only 19% knew their infection status in 2017¹. In many countries, HCV-related disease burden and deaths have been steadily increasing, despite recent advances in HCV treatment¹. The highly effective direct-acting antivirals (DAAs) that became available from 2015 onwards can achieve high rates of sustained virologic response (SVR), a surrogate for cure². However, a huge majority—more than 80%—of HCV patients remain undiagnosed and therefore are unable to avail the benefits of improved survival and quality of life provided by DAAs¹.

The World Health Organization (WHO) recently launched a global strategy for elimination of HCV as a public health threat by the year 2030. This strategy aims to reduce HCV incidence by 80% and HCV-related mortality by 65%³. To reach this goal, the WHO estimates that by 2030 at least 90% of people with HCV need to be diagnosed, with a treatment rate of at least 80% among all treatment-eligible people with HCV³.

However, most countries do not have an HCV elimination strategy. In particular, for low- and middle-income countries (LMIC), which have limited resources but high HCV prevalence rates⁴, it is important to develop a cost-effective HCV elimination strategy. Given that the price of DAAs is low in most LMICs, the cost of testing can be a substantial contributor to the cost of HCV elimination⁵.

Georgia, a LMIC country, has a high HCV disease burden with prevalence of 5.4% in adults^{6,7}, and has launched a national program to eliminate HCV. The Georgian health care system is largely private, but the national HCV elimination program formed a partnership between private and public institutions with a cost sharing model—with treatment provided for free through a donation from Gilead⁸. However, a recent study concluded that to achieve the goal of eliminating HCV as a public health threat in Georgia, innovative, simple, and cost-effective strategies are needed to scale-up HCV testing^{9,10}. To help address this issue, the Foundation for Innovative Diagnostics (FIND) has proposed new testing pathways for HCV in Georgia.

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Parameter	Value
Age (median), years ¹⁵	39
Fibrosis score distribution⁶	
F0	38%
F1	32%
F2	13%
F3	10%
F4	7%
Sex distribution	
Male	50%
Female	50%
Virus genotype distribution^{6,7,16*}	
G1	40%
G2	24%
G3	34%
G4	2%

Table 1. Baseline population characteristics among HCV-infected persons in Georgia. *HCV* hepatitis C virus, *F* METAVIR fibrosis score, *G* genotype. *HCV genotypes 5 and 6 were not considered because of their rarity in Georgia. All the distributions in this table, including fibrosis score, sex and genotype were taken as independent of each other and assumed to have no dependencies.

The objective of this study was to evaluate the long-term cost-effectiveness of different HCV testing pathways in Georgia. We also developed an interactive online tool to assess and compare the health-related and economic outcomes of different pathways under different settings of HCV epidemic, patient flow and costs.

Methods

Overview. We utilized a state-transition model, MATCH (Markov-based Analyses of Treatments for Chronic Hepatitis C), which simulates HCV disease progression. Natural history outcomes from this model have been validated previously^{11–13}. We adapted this model to simulate the epidemiology of HCV in Georgia (MATCH-Georgia), and extended the model to evaluate the cost-effectiveness of several innovative HCV testing pathways for Georgia. The model was developed following the principles on economic analyses with respect to viral hepatitis recommended by the WHO¹⁴. Using the results from this model, we also developed an interactive online tool, the Hep C Testing Calculator (www.hepccalculator.org), that allows users to compare the cost-effectiveness of different testing pathways for Georgia by entering key model inputs as applicable to the local situation.

Baseline population characteristics. We ran the model for a general population cohort of 10,000 adults in Georgia, with an HCV antibody prevalence of 2% in the base case⁶, and the percentage of viremic infection among HCV antibody positive people of 75%. The baseline characteristics of HCV patients were determined by the different combinations of sex, HCV genotype, and METAVIR fibrosis stage observed in HCV patients in Georgia (Table 1). All HCV-infected patients were considered treatment-naïve because treatment coverage, until recently, had been very limited in Georgia. We assumed an average baseline age of 45 years. No human subjects were involved in this research.

Testing pathways. We simulated five testing pathways for HCV diagnosis and monitoring. Among these pathways, one represents the standard of care (SoC) in Georgia, whereas the other four represent innovative testing pathways proposed by FIND and initiated under the HEAD-Start Harm Reduction study¹⁷. Each pathway consists of several sequential testing stages including initial screening, confirmation of presence of HCV RNA, liver staging, and treatment response (Fig. 1). Pathways differ in the testing technologies used (including sensitivity and specificity of each test) and in locations where each test is performed—on-site, specimen collected on-site and then sent to a laboratory, or at another location that the patient must travel to. All pathways use on-site HCV-antibody rapid diagnostic testing for screening. Confirmation is done using either HCV-RNA testing or HCV core-antigen testing. Liver staging consists of two phases of testing using either Fibroscan or APRI/FIB4, and for some pathways phase 2 is completed only for patients with METAVIR fibrosis score of 4. Treatment is monitored using RNA or biochemical testing, and all pathways use RNA testing for SVR evaluation.

DAA treatment regimens and efficacy. Patients with viremic HCV infection who made it through the second liver-staging test in the pathway (or the first, if only one was done) were eligible to receive DAA-based treatment. The DAA regimens used in the model were determined by individual patient's liver fibrosis stage. Data about the regimens, including their efficacy in different scenarios, were obtained from clinical trials^{18–20} (Supplementary Table S1).

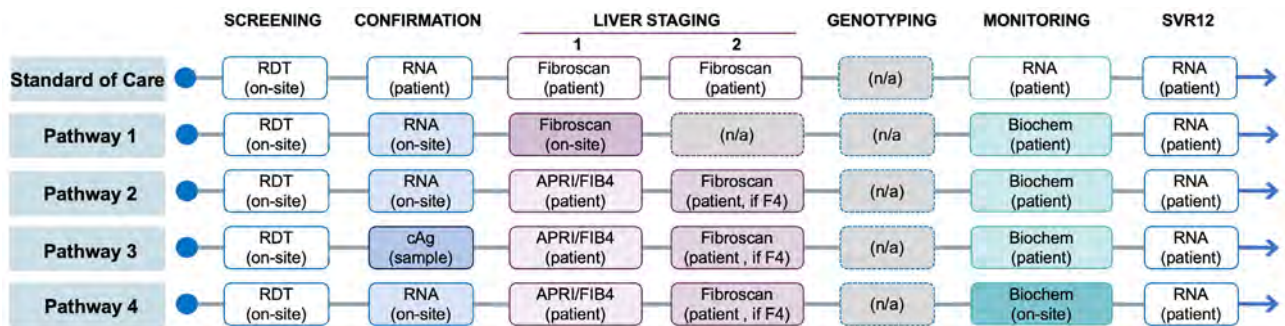


Figure 1. Patient flow under the current standard-of-care testing pathway and innovative hepatitis C testing pathways in Georgia. Abbreviations: RDT, rapid diagnostic test; RNA, ribonucleic acid test; cAg, core antigen test; APRI/FIB4, aspartate aminotransferase (AST)-to-platelet ratio index (APRI)/fibrosis-4 index; F4, METAVIR fibrosis score of 4.

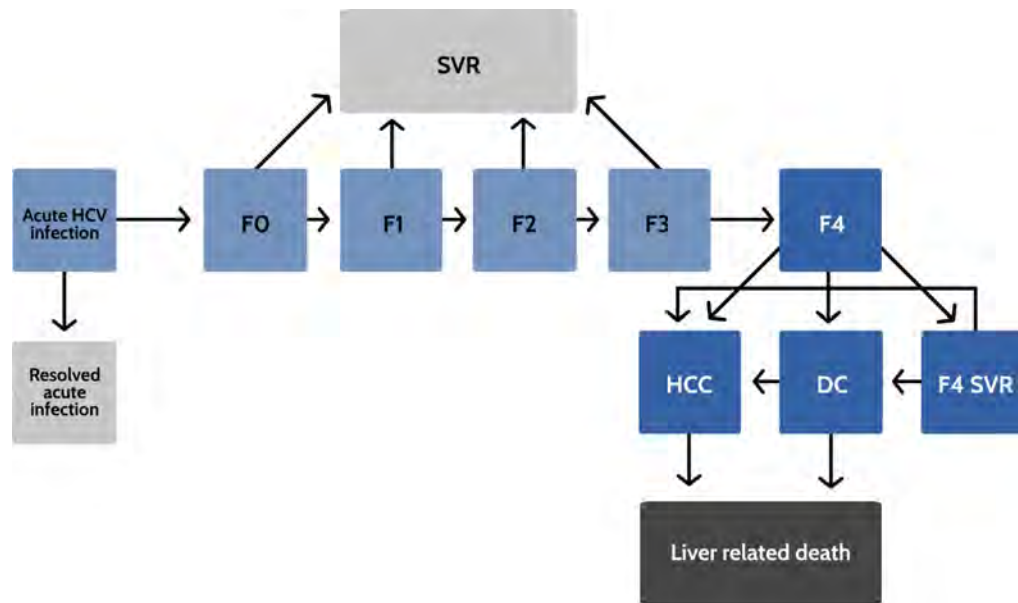


Figure 2. Model schematic of the natural history of hepatitis C virus in MATCH-Georgia model. Abbreviations: SVR, sustained virologic response; F0–F4, METAVIR fibrosis score; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; F4-SVR, sustained virologic response achieved at fibrosis stage 4.

Disease progression. Patients with HCV followed the natural history of HCV disease progression, defined as Markov health states in the MATCH-Georgia model (Fig. 2). Each patient started in a METAVIR liver fibrosis state of F0–F4. At the end of each simulation cycle (defined as one week), the patient could remain in the same state, progress into a more severe adjacent state of fibrosis, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), or liver-related death (LRD) or background mortality. Patients in the F0–F3 states who achieved SVR were considered cured and followed background mortality from that point on. However, patients who achieved SVR in the F4 state could still progress to DC, HCC and LRD states, though at a lower rate than F4 patients who had not achieved SVR²¹. Patients who fail treatment were assumed to continue to progress at the original rate. The fibrosis progression rates from F0 to F4 were based on a published meta-regression analysis²²; progression rates from cirrhosis to DC and HCC are from published observational studies^{23,24}. The liver-related mortality rates from DC and HCC were also derived from a published study²⁵. The model did not include liver transplantation as a state due to the rarity of this procedure in Georgia.

Quality of life weights. The model assigns quality-of-life (QoL) weights to each health state. All HCV-related QoL weights were derived from published studies^{26–28}. People without HCV were assigned QoL weights according to their sex and age, and for patients who achieved SVR, the QoL weights of the health states were assumed to be equivalent to that of the non-HCV-infected general population²⁶. However, if patients who achieved SVR progressed to DC or HCC, then the QoL weights of the corresponding state was applied. The adverse effect of anemia on quality of life during the treatment period was also considered, by applying an

anemia multiplier. All HCV-related and normal QoL weight values are summarized in Table 2. The use of QoL weights allows us to present health-related outcomes as quality-adjusted life years (QALYs).

Costs. The MATCH-Georgia model considered HCV diagnosis costs, DAA-based treatment costs and HCV disease management costs. All costs were considered from a healthcare payer's perspective.

The HCV testing costs consisted of the cost incurred at each step of the testing pathway, which included not only the costs for conducting laboratory tests, but also those for specimen shipment or of patient travel, as required, as these are integral parts of each testing pathway (Table 2). These costs were estimated from FIND HEAD-Start Georgia study²⁹. Patients who failed to follow up in the next testing stage no longer incurred any further testing costs and did not receive DAA treatment. Free DAA medicines are now available for Georgia HCV patients through contracts with the pharmaceutical companies³⁰, however we added \$100 per person treated as an operational expense.

We estimated annual healthcare costs associated with HCV disease management using the World Health Organization's CHOosing Interventions that are Cost Effective (WHO-CHOICE) tool³⁴ (Table 2). For that, we first extracted inpatient and outpatient primary costs from WHO-CHOICE and took the weighted average of cost per inpatient visit and cost per outpatient visit for each HCV-associated states in the United States; inpatient visits accounted for 38% of healthcare encounters for F0–F4 patients, 43% for compensated cirrhosis patients, 66% for DC patients, and 55% for HCC patients³⁵. We then estimated the ratio of the above costs in Georgia to United States and, finally, estimated Georgia-specific costs by multiplying this ratio with costs in the United States³⁵. To account for differences in medical practices between Georgia and the United States, we considered a wide range in costs in the sensitivity analysis.

Model outcomes. For each pathway, we projected average QALYs, total cost, and cumulative incidence of DC, HCC, and HCV-related deaths. We also estimated the testing costs per case treated and incremental cost-effectiveness ratio (ICER) of each pathway. A lifetime horizon was used, and all future costs and QALYs were discounted at 3% per year.

Interactive tool. We also developed an interactive online tool using R Shiny that allows users to change certain inputs and evaluated the comparative effectiveness and cost-effectiveness of different diagnostic testing pathways. In this tool, users can change the population cohort size, screening rate, prevalence rates (of anti-HCV antibody in the population and of viremia among HCV-seropositive persons), and patient/client follow up rate for each step in a testing pathway—with the ability to add custom testing pathways. The users can also change costs for DAAs, each diagnostic test, patient/client travel, and specimen shipment.

Once parameters are changed, the tool shows updated results for the total expected QALYs, costs, and disease burden for each of the testing pathways. It also calculates the ICERs of the testing pathways by comparing their QALYs and costs, to assist users in identifying the most cost-effective testing pathways. A screenshot of the interactive tool is provided in Supplemental Figure S1. The tool is still being expanded and can be accessed at hepccalculator.org.

Sensitivity analysis. We performed both deterministic and probabilistic sensitivity analyses to evaluate the effect of variations in model inputs on the cost-effectiveness of the testing pathways. These inputs included state transition probabilities, QoL weights, medical and disease management costs, diagnostic test costs, patient travel/sample shipping costs, and patient follow-up rates. Both the one-way and probabilistic sensitivity analyses also included HCV demographic parameters such as HCV prevalence and viremic rate in HCV antibody positive people. The ranges of all model inputs used for sensitivity analyses, and distribution used for the probabilistic sensitivity analysis, are defined in Table 2.

Results

Cost-effectiveness of HCV testing pathways. Compared with no screening, HCV screening under the SoC increased discounted QALYs by 333 per 10,000 people screened and decreased costs by US \$290,942 (Table 3). All the four new HCV testing pathways (*Pathways 1–4*; Fig. 1) further increased QALYs and decreased costs. *Pathway 1*—on-site rapid diagnostic test for HCV antibody followed by on-site HCV-RNA confirmatory test, on-site Fibrosan for liver disease staging of chronic HCV patients, sample transportation for genotype testing, and on-site HCV-RNA test for assessment of treatment response—resulted in the highest discounted QALYs of 169,753 (123 QALY more than that under the SoC) and lowest costs of \$142,939 (\$127,052 less than that under SoC) per 10,000 persons screened. Compared with other pathways, *Pathway 1* was cost-saving. The testing-related cost per HCV case treated for the SoC was \$289 and for *Pathway 1* was \$139. Pathways 2, 3, and 4 all had higher total costs as well as higher testing costs per patient treated.

Clinical efficacy of testing pathways. The diagnosis rate—defined as the percentage of people with viremic HCV who were eventually diagnosed—of the SoC was 79.2%; by contrast, the diagnosis rate of *Pathway 1* was 88%. Patients lost before initiating treatment accounted for a bigger difference between the percent of viremic patients treated, with only 64.2% of viremic patients treated in the SoC scenario but 88% of viremic patients treated in *Pathway 1*. Under SoC, 84 people needed to get antibody screening on average to diagnose one additional HCV-viremic case, while under *Pathway 1* this number was 76. All new HCV testing pathways improved the HCV diagnosis rate.

Parameter Name	Base Case	Low	High	Distribution
Testing pathway parameters (costs in USD)				
Antibody RDT test unit cost ²⁹	1.00	0.50	1.50	Gamma (18, 0.0556)
HCV-RNA on-site test unit cost (Genexpert) ²⁹	15.00	8.00	23.00	Gamma (17, 0.8824)
APRI test unit cost ²⁹	5.00	3.00	8.00	Gamma (14, 0.3571)
Fibroscan test unit cost ²⁹	33.00	17.00	50.00	Gamma (17, 1.9412)
Biochemical test unit cost ²⁹	10.00	5.00	15.00	Gamma (19, 0.5263)
Genotyping test unit cost ²⁹	51.00	26.00	77.00	Gamma (18, 2.8333)
HCV-RNA test by referral unit cost ²⁹	40.00	20.00	60.00	Gamma (18, 2.2222)
Core antigen (cAg) test unit cost ²⁹	12.00	6.00	18.00	Gamma (19, 0.6316)
Sample transportation cost ²⁹	0.37	0.19	0.56	Gamma (18, 0.0206)
Cost of treatment ³⁰	100.00	50.00	150.00	Gamma (19, 5.2632)
HCV antibody prevalence ⁶	2%	1%	3%	Beta (32, 1568)
Viremic rate in antibody-positive people	75%	50%	100%	Beta (19, 6.3333)
Target screening rate (assumption)	90%	75%	100%	Beta (38, 4.2222)
Confirmation test follow-up rate (Expert opinion ²⁹)	90%	75%	100%	Beta (38, 4.2222)
Liver staging-1 test follow-up rate (Expert opinion ²⁹)	90%	75%	100%	Beta (38, 4.2222)
Liver staging-2 test follow-up rate (Expert opinion ²⁹)	90%	75%	100%	Beta (38, 4.2222)
Monitoring test follow up-rate (Expert opinion ²⁹)	90%	75%	100%	Beta (38, 4.2222)
SVR12 RNA test follow-up rate (Expert opinion ²⁹)	90%	75%	100%	Beta (38, 4.2222)
Transition probabilities (annual)				
F0 to F1 ²²	0.117	0.104	0.130	Beta (285.98, 2158.26)
F1 to F2 ²²	0.085	0.075	0.096	Beta (239.77, 2581)
F2 to F3 ²²	0.120	0.109	0.133	Beta (351.88, 2580.45)
F3 to F4 ²²	0.116	0.104	0.129	Beta (304.4, 2319.73)
F4 to DC ²³	0.039	0.010	0.079	Beta (4.87, 120.08)
F4 to HCC ²³	0.014	0.010	0.079	Beta (0.64, 44.75)
Post F4-SVR to DC ²¹	0.008	0.002	0.036	Beta (0.87, 107.97)
Post F4-SVR to HCC ²¹	0.005	0.002	0.013	Beta (3.28, 653.57)
DC to HCC ²⁴	0.068	0.030	0.083	Beta (24.48, 335.51)
DC (year 1) to death from liver disease ²⁴	0.182	0.065	0.190	Beta (27.56, 123.89)
DC (1 + years) to death from liver disease ²⁴	0.112	0.065	0.190	Beta (11.29, 89.55)
HCC to liver-related death ²³	0.427	0.330	0.860	Beta (5.52, 7.41)
Health state costs (annual in USD)*				
F0–F2	62	31	123	Gamma (6, 10.3333)
F3	126	63	253	Gamma (5, 25.2)
Compensated cirrhosis	144	72	289	Gamma (6, 21)
Decompensated cirrhosis	1496	748	2993	Gamma (17, 88)
Hepatocellular cancer	2625	1413	5652	Gamma (17.17, 154.4118)
F4 post-SVR	72	36	144	Gamma (5, 14.4)
Health state quality-of-life weights				
Anemia multiplier ³¹	0.83	0.75	0.97	Beta (80, 16.3855)
F0–F3 ²⁶	0.93	0.84	1.00	Beta (40, 3.0108)
Compensated cirrhosis (F4) ²⁶	0.90	0.81	0.99	Beta (50, 5.5556)
DC ²⁶	0.80	0.57	0.99	Beta (12, 3)
HCC ²⁶	0.79	0.54	0.99	Beta (10, 2.6582)
Post-SVR ^{***}	1	0.92	1	Beta (3833.92, 3.84)
Test sensitivity and specificity				
Antibody RDT sensitivity ³²	98.0%	98.0%	100.0%	Uniform (0.98, 1)
Antibody RDT specificity ³²	100.0%	100%	100.0%	Uniform (1, 1)
HCV-RNA (lab) test sensitivity	99.8%	99.6%	100.0%	Uniform (0.996, 1)
HCV-RNA (lab) test specificity	99.7%	99.4%	100.0%	Uniform (0.994, 1)
cAg (lab) test sensitivity ³³	93.4%	90.10%	96.40%	Beta (150, 10.5996)
cAg (lab) test specificity ³³	98.8%	97.40%	99.50%	Beta (150, 1.8219)
Sex and age-based normal health utility values²⁶				
Female, age < 29	0.913	–	–	–
Female, age 30–39	0.893	–	–	–
Continued				

Parameter Name	Base Case	Low	High	Distribution
Female, age 40–49	0.863	–	–	–
Female, age 50–59	0.837	–	–	–
Female, age 60–69	0.811	–	–	–
Female, age 70–75	0.711	–	–	–
Male, age < 29	0.928	–	–	–
Male, age 30–39	0.918	–	–	–
Male, age 40–49	0.887	–	–	–
Male, age 50–59	0.861	–	–	–
Male, age 60–69	0.840	–	–	–
Male, age 70–75	0.802	–	–	–

Table 2. Model parameters used in the MATCH-Georgia model. *RDT* rapid diagnostic tests, *RNA* ribonucleic acid confirmation test, *APRI* aspartate aminotransferase to platelet ratio test, *FIB4* fibrosis-4 test, *cAg* core antigen test, *SVR* sustained virologic response, *F0–F4* METAVIR fibrosis score, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *F4-SVR* sustained virologic response achieved at fibrosis stage 4. *We estimated annual healthcare costs associated with HCV disease management using the World Health Organization's CHOosing Interventions that are Cost Effective (WHO-CHOICE) tool. ** For patients experienced anemia during treatment, quality of life was multiplied by this factor. ***For patients who achieved SVR, the QoL weights of the health states are assumed to be equivalent to that of the non-HCV-infected general population²⁶. For patients who achieve SVR at state F4 but further progressed to DC and HCC, their QoL weights were adjusted to those of DC and HCC, respectively.

	No screening	Standard of care	Pathway 1	Pathway 2	Pathway 3	Pathway 4
Total cost	\$560,933	\$269,991	\$142,939	\$225,122	\$251,769	\$225,389
Disease management	\$560,933	\$233,067	\$111,080	\$196,638	\$220,262	\$196,638
Testing	–	\$27,053	\$18,315	\$17,516	\$21,250	\$17,783
Treatment	–	\$9,871	\$13,544	\$10,968	\$10,257	\$10,968
QALYs (total cohort)	169,297	169,630	169,753	169,666	169,643	169,666
% viremic diagnosed	0.0%	79.2%	88.0%	88.0%	82.4%	88.0%
% viremic treated	0.0%	64.2%	88.0%	71.3%	66.7%	71.3%
Testing cost per treated pt	–	\$281	\$139	\$164	\$213	\$166
No. needed to screen to diagnose one HCV case		84	76	76	81	76
No. needed to screen to prevent one LRD		556	333	456	526	456
Disease Burden						
Decompensated cirrhosis	48	20	9	17	19	17
Hepatocellular carcinoma	30	13	6	11	12	11
Liver-related deaths (LRD)	41	23	11	19	22	19

Table 3. Comparison of health-related outcomes and economic outcomes of the five screening pathways vs. no screening per 10,000 persons screened. *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *LRD* HCV-caused liver related death. *The cost for no screening represents the cost of management of HCV sequelae.

The new pathways also improved clinical outcomes. Compared with the SoC, screening 10,000 people under *Pathway 1* would reduce the number of DC cases by 11, HCC by 7, and liver-related deaths by 12 in the lifetime horizon. The number of people needed to be screened (for antibody) to avoid one liver-related death for the SoC was 556, for *Pathway 1* was 333, for *Pathway 2* and *Pathway 4* was 456, and for *Pathway 3* was 526.

Sensitivity analyses. *Pathway 1* remained cost-saving irrespective of the changes in model parameters. Figure 3 shows the 20 parameters that the model is most sensitive to, including QoL after achieving SVR, QoL of patients in F1–F4 states, probability of disease progression from F4 to DC, and costs of managing DC and HCC. One-way sensitivity analysis results for all parameters are shown in Supplement Table S2. Parameters related to the testing pathways, such as costs of different tests or of patient travel or sample shipping and patient/client follow-up rates had less marked influence on the cost-effectiveness of the testing pathways. For the probabilistic sensitivity analysis, *Pathway 1* is the preferred cost-saving option in all scenarios, which is illustrated by the cost-effectiveness acceptability curve (Fig. 4).

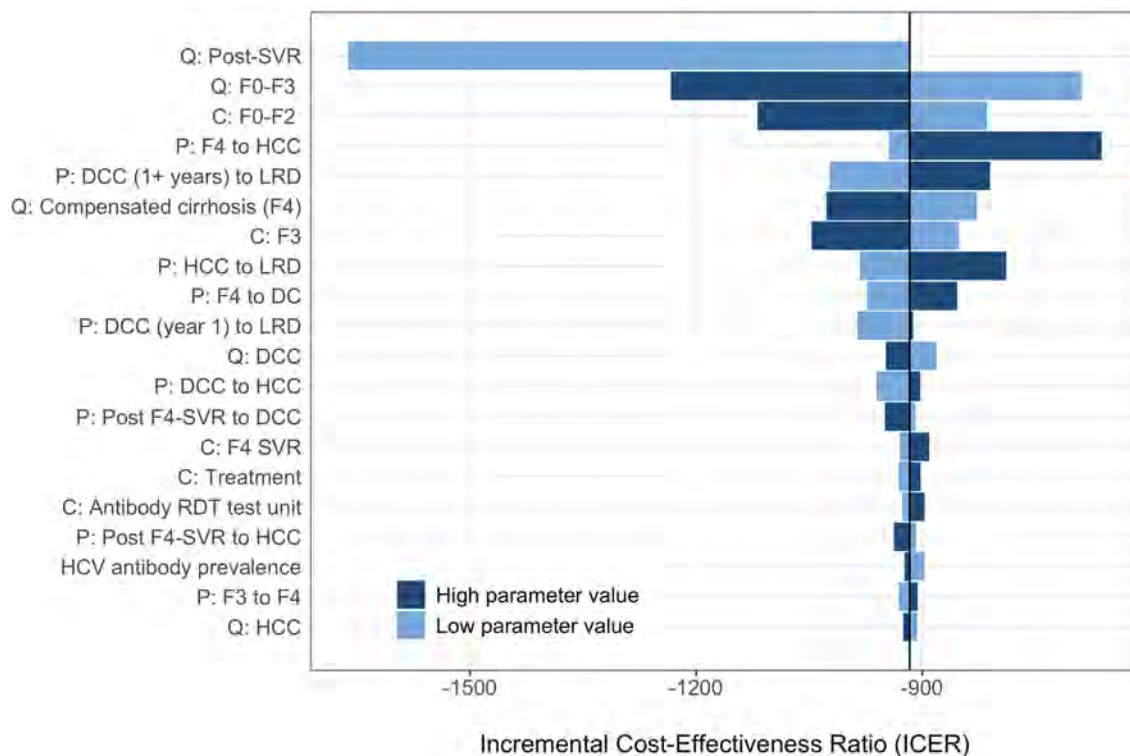


Figure 3. Tornado diagram for one-way sensitivity analysis of incremental cost-effectiveness ratio of *Pathway 1* versus *no screening* strategy. Horizontal bars show the variation in incremental cost-effectiveness ratio (ICER; in USD/QALY) with variation in the value of the parameter. In the parameter names, the prefix ‘C’ represents cost of a health-state, ‘Q’ the quality-of-life weight and ‘P’ the transition probability from one state to the other. Values of ICER below 0 indicate that the treatment is cost-saving. Abbreviations: SVR, sustained virologic response; F0–F4, METAVIR fibrosis score; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; F4-SVR, LRD, liver related death.

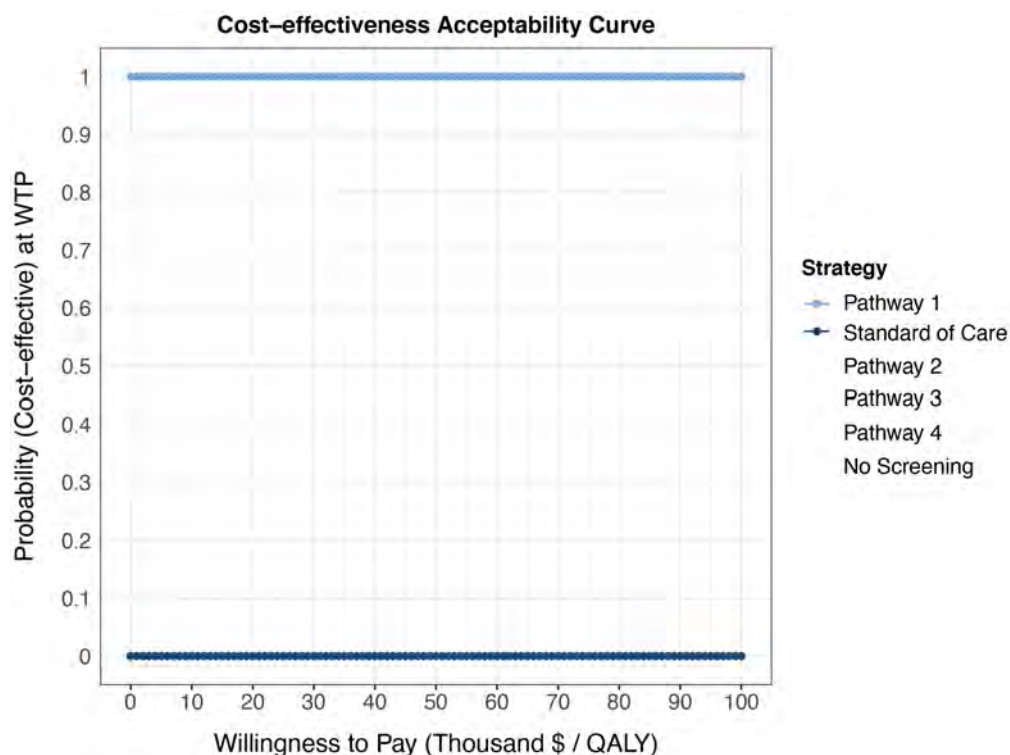


Figure 4. Cost-effectiveness Acceptability Curve of all pathways and *no screening* strategy.

Discussion

The availability of highly effective yet low-priced HCV treatment in LMIC offers an unprecedented opportunity to eliminate HCV as a public health threat. However, the majority of HCV patients remain undiagnosed and hence are not in a position to avail the benefits of new treatments. In this study, we evaluated the cost-effectiveness of five different testing pathways to diagnose and monitor HCV during treatment in Georgia. We found that the pathway using on-site HCV-antibody rapid diagnostic test and HCV-RNA testing, followed by on-site Fibrosan was cost-saving—this pathway would save US \$127,052 per 10,000 individuals tested (compared with the current standard), while increasing rates of diagnosis and linkage to successful treatment. This pathway would cost \$139 per HCV case treated and could diagnose 88% of the viremic cases if scaled-up at the population level.

As pointed out by a recent study, substantial scaling-up of HCV testing and treatment are needed to eliminate HCV in Georgia^{9,10}. However, that study did not evaluate what testing strategies would be cost-effective in Georgia. Therefore, our study fills an important evidence gap. We found that the preferred cost-effective strategies may depend on locally-determined factors, such as the HCV disease epidemiology, costs of different testing methodologies, patient follow-up rates following each visit or procedure, and the on-site availability of diagnostics such as Fibrosan and genotyping, leading to need for patient or specimen transport. We therefore also developed an interactive online-based tool that allows users to change several parameters in the model and identify the cost-effective testing pathway for their localized settings.

As the cost of DAAs has fallen below \$100 per treatment in Georgia (and other LMICs), the diagnostic cost per HCV case constitutes a substantial portion of HCV care expenses. The cost of diagnosing one HCV case exceeds the cost of HCV treatment in Georgia, which could also be true for many LMICs where low-cost DAAs are available. All countries must domestically finance for these HCV testing and treatment efforts, as there is no global funding mechanism for HCV elimination. This contrasts with HIV, TB, and malaria, for which the Global Fund provides substantial budget annually³⁶. Hence, it is very important for LMICs to identify HCV testing pathways that are cost-effective or cost-saving.

Interactive models such as this diagnosis pathway tool and our previously-developed *Hep C Treatment Calculator*¹³ are important tools to help aid countries, in particular LMICs, in understanding how to best use their existing domestic resources. Since the epidemiology of HCV varies geographically, having a tool that can be fed with location-specific epidemiology and cost inputs could provide countries with the context-specific cost-effectiveness estimates needed for their decision making. Our interactive tool takes this one step further. Even within a country, delivery of HCV services to different population groups may require different modes of service provision³⁷. This tool can aid in tailoring testing pathway approaches that programs may seek to implement to reach various groups, such as PWID, MSM, age cohorts, regional groups, and others, with differing HCV prevalence and viremia rates, and cost of delivery of each test in specific settings. Hence, our tool could help the public health community to identify and implement the most effective and cost-effective strategy in different settings.

Lastly, it is important to note that the lost-to-follow-up rate remains an important consideration for country-level decision makers and program managers. Our analysis shows that the lost-to-follow-up rate has a limited impact on the incremental cost-effectiveness ratio when comparing several testing pathways—however this could be because the pathways have similar set-ups in terms of follow-up rate. An increase in lost-to-follow-up rates will have a similar negative impact on all pathways simultaneously. However, our analysis does not diminish the importance of the lost-to-follow-up rate in HCV testing practice, but rather shows that this issue needs addressing irrespective of the testing pathway chosen.

Our study has some limitations. First, our analysis did not account for continued HCV transmission. Therefore, the benefits of HCV testing, which serves to guide treatment and cure leading to reduced risk of transmission, could be even higher and the optimal pathway could result in even higher cost-savings. Second, since Georgia-specific QoL weights are not available, we used QoL weights from other countries. Our analysis also does not account for different QoL or mortality for specific populations within Georgia, such as people who inject drugs. However, sensitivity analysis suggests that the results remain robust to a wide range of input parameters and that QoL estimates did not change the conclusion of the study. Third, we note that the cost of DAAs in Georgia is negligible due to the contract made with major pharmaceutical companies, a situation that does not apply to most other countries.

In conclusion, our study identified a novel testing pathway to diagnose HCV and monitor its treatment in Georgia with greater effectiveness and found that such a testing pathway would result in cost-savings over the SoC pathway. Our online interactive tool can provide optimal HCV testing pathway under different settings of HCV epidemiology, costs of different tests, patient follow-up rates, and the on-site availability of diagnostics.

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Study concept and design: M.A., Y.Z., H.Z., R.A., S.S., J.C. Statistical analysis: M.A., Y.Z., H.Z., T.Z., H.Z. Interpretation of data: all authors. Drafting of manuscript: M.A., Y.Z., S.S., J.C. Critical revision of the manuscript for important intellectual content: all authors.

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Competing interests

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Additional information

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