

# INNOVATIVE TEST DEVELOPMENT AND EXPERT EVALUATIONS

## OVERVIEW

The U.S. Centers for Disease Control and Prevention (CDC) has a cadre of experts with the technical know-how and established track record in strengthening laboratory networks and surveillance systems to provide faster and more accurate diagnoses. Specifically, CDC provides critical technical expertise to PEPFAR-supported and CDC Global Tuberculosis (TB) priority countries to effectively reach UNAIDS' global targets to control the HIV epidemic, and the targets of the World Health Organization's (WHO) "End TB Strategy" and the Stop TB Partnership's "Global Plan to End TB." CDC develops, evaluates, and advises country laboratory programs on the performance characteristics of tests and their appropriate placement and use, including assays that are performed both in the clinical laboratory and in point-of-care (POC) testing sites. CDC also provides guidance on these HIV and TB tests to support maximum impact of diagnostic testing on patient care and promote universal quality monitoring and assurance.

## HIV INCIDENCE TESTING

With increasing HIV treatment coverage, HIV prevalence data is not enough to understand how the HIV epidemic is evolving. HIV incidence provides a true measure of transmission dynamics -- recent infections reveal the current status of HIV transmission. As the pool of HIV-infected individuals narrows, a case-based incidence surveillance system can capture recent infections to help detect and interrupt chains of HIV transmission. CDC is at the forefront of research to develop and transfer technology for unique assays to identify and distinguish recent from long-term HIV-1 infection, which is critical for tracking the leading edge of the epidemic to estimate HIV-1 incidence (rate of new infection, or recency) for impact assessment and targeted prevention.

CDC has developed three incidence assays – tools that will play an important role in understanding the success of HIV prevention programs and the spread of HIV, as the world works to reach zero new infections. The first is LAg-Avidity EIA, a laboratory-based test that distinguishes between recent and long-term HIV infections. This commercially available, field-evaluated assay performs similarly across HIV-1 subtypes and has been shown to accurately estimate HIV incidence in cross-sectional populations without expensive longitudinal follow-up. LAg-Avidity EIA played a central role in measuring the impact of PEPFAR by estimating incidence in more than a dozen countries as part of Population-based HIV Impact Assessment (PHIA) surveys. Currently, over 50 countries are using the LAg-Avidity EIA to monitor the status of the HIV epidemic nationally or in key populations. The assay will continue to play a critical role in monitoring the epidemic, identifying high-incidence populations, and assessing the impact of prevention programs.

CDC has also developed a simple rapid test for recent infection (RTRI) in lateral flow format that can simultaneously diagnose HIV infection and identify recent infection in 20 minutes. The test is now available as commercial kits from two manufacturers. Due to simplicity of this technology, the assay can be used in HIV Testing Service (HTS) settings, providing real-time information about recent transmissions among newly diagnosed cases. The RTRI is critical to detect and prioritize recent cases for partner testing to increase HIV case detection rates and interrupt the chains of HIV transmission. The assay has the potential to identify hot spots in real time to allow for targeted prevention efforts to achieve epidemic control. This assay is being implemented in more than 20 countries.

Recently, CDC also developed a bead-based multiplex incidence assay that can diagnose HIV infection (positive or negative), perform serotyping (HIV-1 or HIV-2), and distinguish recent from long-term infection, all in one test. Currently under evaluation, this assay will simplify surveillance by combining multiple layers of testing in one assay, reducing cost and labor. The flexibility of this approach provides opportunity to include additional biomarkers (e.g. syphilis) in the future in surveillance settings. CDC continues to advance incidence assay technologies by expanding the innovations in this area.

## HIV DRUG RESISTANCE TESTING

Lifelong treatment for HIV infection can lead to the emergence of drug-resistant strains of HIV. The development of drug resistance (DR) can be mitigated by testing populations receiving antiretroviral treatment (ART) and by following up with those who are newly infected with drug-resistant strains. A low-cost, broadly sensitive genotyping assay developed by CDC has reduced the reagent cost for HIV DR testing by 30 percent and accelerated HIV DR testing in PEPFAR-supported countries. The technology was transferred to Thermo Fisher Scientific, which developed HIV-1 Drug Resistance Genotyping Kits. The standardized kit has greatly simplified the procurement process, as well as streamlined and reduced technical

hands-on testing time. The assay's ability to genotype diverse HIV-1 group M viral strains from dried blood spot specimens has made nationwide HIV DR genotyping surveys a reality in many developing countries.

With the development and use of a new class of antiretroviral drugs (integrase inhibitors), CDC has also developed a method to test for HIV resistance to this new class of drugs that shows promising preliminary results. This assay will be evaluated in the field to determine its performance in clinical samples from individuals on integrase inhibitor-containing regimens. As new classes of drugs become accessible globally, CDC is contributing to new methods and tools to detect resistance to these drugs.

#### TB DIAGNOSTIC TESTS

TB is the leading cause of death among HIV-positive individuals worldwide, and those living with HIV are 20 to 30 times more likely to develop active TB disease than those without HIV. However, traditional TB diagnostic tests have had long turnaround times and poor sensitivity in HIV-positive individuals and children, making TB detection a challenge that can lead to delays in treatment, particularly for drug-resistant forms of the disease. To strengthen rapid TB diagnostic services, CDC works with Ministries of Health to introduce and evaluate the impact of new TB detection and drug susceptibility testing technologies, such as the near-POC Xpert MTB/RIF assay. By providing customized technical assistance and guidance to more than 30 countries, CDC works to collaboratively assess: (i) new test placement, quality, and utilization, (ii) diagnostic sensitivity of novel specimen types, such as stool and nasopharyngeal aspirates, for HIV-positive and pediatric patient populations, and (iii) national TB diagnostic algorithms and strategic policies to improve TB diagnostic networks.

#### HIV DIAGNOSTICS, RAPID TESTING, AND EVALUATIONS

To ensure the use of high-quality rapid HIV tests, CDC conducts technical evaluations to certify HIV rapid tests for PEPFAR-funded procurement. As part of the approval process shared by CDC and the U.S. Agency for International Development (USAID), CDC independently evaluates HIV rapid test kits for USAID approval for potential use in the PEPFAR program. Approval of HIV test kits has contributed to the expansion of HIV testing from 1.9 million tests in 2004 to more than 88.5 million tests in 2017. HIV rapid tests make diagnoses widely accessible by having test results available on the same day. The tests do not require refrigeration, are easy to transport, and can be performed by non-laboratory personnel (nurses, counselors and other personnel) with proper training.

From 2006-2016, CDC received requests from biotech manufacturers to evaluate 56 unique HIV rapid test kits. The evaluation process includes a dossier review and technical evaluation. Of the 48 test kits evaluated, 22 kits (46 percent) met the rigorous performance requirements (sensitivity >99 percent and specificity >98 percent) to qualify for inclusion in USAID's procurement waiver list and potential use in PEPFAR programs. CDC also conducts technical evaluations as part of the WHO prequalification process. All test kits undergo rigorous performance testing as part of this process. CDC will continue to evaluate new technologies to ensure high quality HIV test kits are used in PEPFAR-supported countries.

#### EARLY INFANT DIAGNOSIS FOR EARLY ACCESS TO CARE AND TREATMENT

CDC is a leader in expanding lower-cost early infant diagnosis (EID) dried blood spot testing procedures and supports the development of training tools and quality assurance programs to advance the accurate and early diagnosis of infants born to HIV-positive mothers. Early diagnosis of HIV in infants provides a critical opportunity to strengthen follow-up of HIV-exposed infants, enable early access and initiation of ART for infected children, aid evaluation of Prevention of Mother to Child Transmission (PMTCT) programs, and increase capacity to use laboratory and POC technologies. Infants can be diagnosed as early as four to six weeks after HIV exposure with nearly 100 percent accuracy using these nucleic acid amplification-based tests. CDC works with WHO on evaluating new viral load and EID instruments and assays as part of the WHO pre-qualification process. CDC's evaluation of the first two POC assays for EID showed results comparable to current laboratory technology. These assays currently are being implemented in over 15 countries in Africa.