Pre-exposure Prophylaxis (PrEP) for Prevention of HIV Infection

Accessible Version: https://youtu.be/R6Saff_u-xY
HIV Pre-exposure Prophylaxis: Preclinical Research in Animal Models

Walid Heneine, PhD
Surveillance, Antiretroviral Prophylaxis and Drug Resistance Team Lead
Laboratory Branch, Division of HIV/AIDS Prevention
NCHHSTP
Importance of Animal Models to Assess PrEP Efficacy

- Provide first *in vivo* evidence of protection from infection

- Assess relationship between efficacy and pharmacologic parameters
  - How well the drug prevents infection
  - How drugs are distributed systemically
  - How drugs are distributed at mucosal sites of HIV entry (e.g. vaginal, rectal tissue)
Importance of Animal Models to Assess PrEP Efficacy

- Help inform clinical trial designs in humans
  - Prioritization of PrEP regimens
  - Dose selection

- Identify most promising PrEP candidates for clinical trials in humans
  - ~$20-80 million
  - ~3-5 years to provide answers

CDC unpublished data
Repeat Exposure Macaque Model
- Macaques – preferred animal model for HIV infection
- Virus used - simian HIV (SIV or SHIV)
- Weekly rectal or vaginal exposure to SHIV
- SHIV dose within upper range of HIV infectious dose in humans

Exposures to virus repeated to mimic high-risk human exposures to HIV
- Better simulate HIV exposures in humans than do previous models with single high-dose virus challenge
- Protection evaluated against multiple exposure events
Protection measured over multiple exposures per animal
- Power to detect protective effect using smaller numbers of study animals

PrEP regimens that are equivalent to clinical drug exposures in humans

Inform potential PrEP efficacy trials in humans
Among marketed antiretroviral drugs for treatment of HIV-1 infected persons, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) considered because:

- Safe, well tolerated, and potent
- Reverse transcriptase inhibitors
- Co-formulated as single once-daily pill marketed as Truvada®
- Have long plasma (10 to 17 hours) and intracellular (40 to ≥60 hours) half-lives
  - Long half-life allows forgiveness for imperfect daily use
- Have even higher penetration in vaginal and rectal tissues
Design of PrEP Efficacy Study in Animals

- **Drug 1 week**
- **Drug and Weekly Rectal virus**
- **Drug 4 weeks**
- **Follow up**

**Group 1 (n = 18)**
Untreated controls

**Group 2 (n = 6)**
Daily oral TDF and FTC

**Group 3 (n = 6)**
Daily subcutaneous FTC and high-dose tenofovir

**Group 4 (n = 6)**
Daily subcutaneous FTC

Design of PrEP Efficacy Study in Animals

Drug 1 week

Drug and Weekly Rectal virus

Drug 4 weeks

Follow up

1

14

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Daily subcutaneous FTC

Daily PrEP Regimens Against Rectal SHIV in Macaques

- FTC/high dose tenofovir (subcutaneous, n = 6)
  [HR = 3.8, p = 0.02]
- TDF/FTC (oral, n = 6)
  [HR = 7.8, p = 0.008]
- FTC (subcutaneous, n = 6)
  [HR = 3.8, p = 0.02]
- Control (n = 18)

HR: Hazard ratio
TDF/FTC: tenofovir disoproxil fumarate and emtricitabine
Interpretation and Implications of Animal PrEP Efficacy Study

- Daily oral TDF/FTC provided substantial protection against rectal infection
  - Substantial reduction among oral TDF/FTC-treated compared to control animals

- Data informed advancement of oral PrEP into clinical trials in humans
Animal and Human PrEP Research

- Rectal and vaginal protection
- Drug dose and delivery modality
- Single drug and drug combinations
Evolving Evidence from Clinical Trials of HIV Pre-exposure Prophylaxis

Melanie Thompson, MD
Principal Investigator
AIDS Research Consortium of Atlanta
Disclosures

- All research funding is for clinical trials through AIDS Research Consortium of Atlanta; no funding paid directly to Dr. Thompson
- Site Principal Investigator for clinical trials from the following sponsors:
- Data Safety Monitoring Boards:
  - Janssen/Tibotec Therapeutics and Viiv Healthcare
Common Design Elements of Oral PrEP Trials

- Community consultation
  - To assess trial feasibility, acceptability and implementation
- Random assignment to placebo or intervention groups receiving either TDF/FTC or TDF
- Daily dosing of study medication in oral arms of all studies
- Data and safety monitoring board
  - Periodic expert panel reviews to ensure data quality and participant safety

TDF/FTC: tenofovir disoproxil fumarate and emtricitabine
TDF: tenofovir disoproxil fumarate
Common Design Elements of Oral PrEP Trials

- Symptom assessment and laboratory tests for safety monitoring (e.g. liver enzymes and renal function)
- HIV testing, risk reduction and adherence counseling, adherence assessments at every visit
- Additional follow-up, viral resistance testing, and linkage to HIV care for participants who seroconvert during trial
- Efficacy determined by modified intention-to-treat (mITT)
  - mITT - analysis based on the initial treatment assignment
  - Modified to exclude persons found to be acutely infected with HIV at the time of enrollment in the study
# Randomized, Controlled PrEP Efficacy Trials

<table>
<thead>
<tr>
<th>Trial (Sponsor)</th>
<th>Sample Size</th>
<th>Intervention vs. Placebo</th>
<th>Population</th>
<th>Location</th>
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<tbody>
<tr>
<td>iPrEx (NIH; Gates)</td>
<td>n=2499</td>
<td>Oral TDF/FTC</td>
<td>MSM, transgender women</td>
<td>Peru, Ecuador, S Africa, Brazil, Thailand, US</td>
</tr>
<tr>
<td>Partners PrEP (Gates)</td>
<td>n=4747 couples</td>
<td>Oral TDF/FTC, Oral TDF</td>
<td>Heterosexual serodiscordant couples</td>
<td>Kenya, Uganda</td>
</tr>
<tr>
<td>TDF2 (CDC)</td>
<td>n=1200</td>
<td>Oral TDF/FTC</td>
<td>Sexually active adults</td>
<td>Botswana</td>
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<tr>
<td>Bangkok Tenofovir (CDC)</td>
<td>n=2413</td>
<td>Oral TDF</td>
<td>Injection drug users</td>
<td>Thailand</td>
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<tr>
<td>VOICE (MTN-003)</td>
<td>n=5029</td>
<td>Oral TDF/FTC, Oral TDF, Vag 1% tenofovir gel</td>
<td>Heterosexual women</td>
<td>Uganda, S Africa, Zimbabwe</td>
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Grant et al. NEJM 2010; 363 :2587-2599
Baeten et al NEJM 2012;367:399-410;CROI 2014: Abstract 43
Thigpen, et al. NEJM 2012;367:423-34
Marazzo et al. CROI 2013: Abstract 26LB
## Results of PrEP Efficacy Trials

Detection of Tenofovir Levels in Blood Associated with Greater Efficacy

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- **Study drug:** Oral TDF/FTC
- **Enrollment:** 2,499 MSM and transgender women
- **Sites:** Peru, Ecuador, South Africa, Brazil, Thailand, USA

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61
TDF/FTC: tenofovir/emtricitabine
MSM: Men who have sex with men
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*TDF vs TDF/FTC not significantly different*

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**Study drug:** Oral TDF/FTC, Oral TDF  
**Enrollment:** 4,747 heterosexual serodiscordant couples  
**Sites:** Kenya, Uganda

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Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61  
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*TDF vs TDF/FTC not significantly different*

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**Bangkok Tenofovir Study**

- **Study drug:** Oral TDF
- **Enrollment:** 2,413 Injection drug users
- **Sites:** Thailand

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61

Baeten et al. CROI 2014: Abstract 43
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<td>TDF2</td>
<td>TDF/FTC</td>
<td>0.62 (0.22 – 0.83)</td>
<td>50% among HIV infected</td>
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<td></td>
<td></td>
<td></td>
<td>80% among not infected</td>
</tr>
</tbody>
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% Pts with Detectable Drug

TDF vs TDF/FTC not significantly different

### Study Drug:
Oral TDF/FTC

### Enrollment:
1,200 sexually active adults

### Sites:
Botswana

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61
Baeten et al. CROI 2014: Abstract 43
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<td>FEM-PrEP</td>
<td>TDF/FTC</td>
<td>Stopped due to futility</td>
<td>&lt; 40% among all participants</td>
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</tr>
<tr>
<td>VOICE</td>
<td>TDF/TDF/FTC</td>
<td>Stopped due to futility</td>
<td>&lt; 30% among all participants</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Showed no efficacy</td>
<td></td>
<td></td>
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</table>

- Poor adherence, as measured by detectable drug levels, was a major factor in lack of efficacy in both studies
- Self reported adherence was very high and was not predictive of outcome except when patients said that they did not take drug
- In VOICE, no behavioral measures correctly predicted adherence as measured by drug concentration in the blood

**Futility:** stopping clinical trial when interim results suggest that it is unlikely to achieve statistically significant differences between treatment arm and placebo/control arm

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61
Baeten et al. CROI 2014: Abstract 43
van der Straten, et al. CROI 2014: Abstract 44
Safety of Tenofovir-based PrEP in Clinical Trials

- No significant differences in serious adverse events, renal function markers or deaths among patients taking study drug compared to those taking placebo.

- Adverse events more common on TDF or TDF/FTC than placebo in any study included:
  - Short-duration nausea, vomiting; dizziness
  - Back pain; decreased weight
  - Mild elevation in liver enzymes; mild neutropenia (more with TDF/FTC than TDF)
  - Small but statistically significant decreases in bone mineral density; no difference in atraumatic fractures

- Among women who became pregnant, study drug was not associated with increased pregnancy complications.

References:
- Grant et al. NEJM 2010; 363:2587-2599
- Thigpen, et al. NEJM 2012;367:423-34
- Groshkopf et al. JAIDS 2013;64:79–86
- Baeten et al NEJM 2012;367:399-410
HIV Resistance and PrEP

- Viral resistance occurs when mutations arise in genetic material of HIV that help it to survive in presence of an antiretroviral drug.

- Resistance means that a drug no longer works optimally, or at all, to suppress HIV.

- Resistance to one antiretroviral drug can result in cross-resistance to others that have never been taken.

- Persons who acquire HIV while taking TDF/FTC, or who have HIV before taking TDF/FTC for PrEP, are at risk for viral resistance that may limit treatment options.
HIV Resistance in PrEP Trial Participants

- Among persons with undetected acute infections before starting medication, resistance mutations found in
  - 8 of 30 persons randomized to TDF/FTC or TDF

- Among persons infected after enrollment
  - None randomized to TDF/FTC or TDF had TDF-resistant viruses (0 out of 263)
  - 5 had FTC-resistant viruses (1 in VOICE, 4 in FEM PrEP)

- In IPrEx and Partners PrEP, among persons infected after enrollment
  - 6 out of 99 randomized to TDF/FTC or TDF had low levels of minor resistance mutations, found using more sensitive research assays
  - Clinical implications unknown

- Viral resistance risk is highest if starting PrEP when already HIV infected, especially those recently infected

- HIV testing before and during use is critical

Grant et al. NEJM 2010; 363 :2587- 2599;
Lieber et al. JID 2014;
Thigpen, et al. NEJM 2012;367:423-34

Baeten et al NEJM 2012;367:399-410
Lehman et al. CROI 2014 590LB
Parikh et al. CROI 2014 Abstract 594
No Evidence of Increased Risk Behavior Seen in Clinical Trials

<table>
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<th>Trial</th>
<th>Risk Behavior Assessed</th>
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<tr>
<td>iPrEx</td>
<td>• Episodes of receptive anal sex declined</td>
</tr>
<tr>
<td></td>
<td>• Condom use during receptive anal sex increased</td>
</tr>
<tr>
<td></td>
<td>• No difference in condom use by perceived treatment group</td>
</tr>
<tr>
<td>US MSM Safety Study</td>
<td>• Number of partners and percent reporting anal sex without condom declined</td>
</tr>
<tr>
<td></td>
<td>• Episodes of anal sex without condom remained stable</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>• HIV uninfected participants reported declines in sex without condom use</td>
</tr>
<tr>
<td>TDF2</td>
<td>• Reported number of sex partners declined</td>
</tr>
<tr>
<td></td>
<td>• Percent reporting sex without condom remained stable</td>
</tr>
<tr>
<td>Bangkok Tenofovir</td>
<td>• Reports of injecting drugs, sharing needles, and sex with more than 1 partner in preceding 3 months declined</td>
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Grants et al. NEJM 2010; 363:2587-2599
Baeten et al NEJM 2012;367:399-410;CROI 2014: Abstract 43
Thigpen, et al. NEJM 2012;367:423-34

Marrazzo et al. CROI 2013: Abstract 26LB
Implementation Insights from PrEP Trials

- **TDF-based PrEP can be highly effective in reducing HIV acquisition risk- up to 92% in these studies - if medication adherence is high**

- **Risk of viral resistance highest if beginning PrEP with unrecognized HIV infection**
  - Need to test for HIV infection, ideally both acute and established, before and during use

- **Risk of acquiring HIV is not completely eliminated:**
  - Combine PrEP with other prevention methods for optimal results
    - Consistent and correct condom use
    - Substance use treatment programs, use of injection equipment that has not been used by other persons
    - Antiretroviral treatment for HIV-infected partner in HIV-discordant couples
Implementation Insight from PrEP Trials

- Safety monitoring will be important in real-world setting
- Health care providers who are not HIV specialists need comprehensive education about PrEP
  - How to talk with patients about benefits and risks of PrEP
  - How to initiate and monitor PrEP to minimize toxicity and maximize effectiveness
  - How to discuss and support adherence
  - How to support other risk reduction strategies
  - How to manage HIV infection if it occurs
Program and Policy Challenges for Delivery of PrEP

Dawn K. Smith, MD, MS, MPH
Biomedical Interventions Activity Lead
Prevention with Negatives Team
Epidemiology Branch, Division of HIV/AIDS Prevention
NCHHSTP
FDA Approval and Plans for Mitigating Health Risks for PrEP Use

July 2012 approval of Truvada®

- Indication for PrEP with sexually-active adults
- Risk Evaluation and Mitigation Strategy (REMS)
  - No restriction to specific providers or dispensing sites
  - Required medication guide and provider training
  - Required educational materials for HIV-negative persons
  - Annual assessment of effectiveness of REMS

Elements to Assure Safe and Effective Use

- Added language to package insert
  - Required HIV testing (boxed warning)
  - Indications/contraindications for prescribing PrEP
  - Strict adherence to daily dosing
  - Use in combination with other prevention methods

Implementation in Context of Rapidly Evolving Evidence Base

- Need to understand how to support PrEP when delivered as clinical HIV prevention in communities
  - Solicited lessons learned from implementation and evaluation science
  - Learn what providers and potential users know about PrEP
    - Focus group with young adults in Atlanta
    - Questions added to an existing clinician survey (DocStyles)

Smith DK et al., AIDS Education and Prevention, 2012
“Roadmap” for PrEP Implementation in the US

Needs
- Documented efficacy and safety
- Consensus on PH use
- Provider support
- User acceptability
- Advocates for access
- Policy /Regulatory support
- Evaluation framework

Activities
- Trials
- Consultations
- Targeted Evaluations

Outputs
- Guidelines
- Policy development
- Training materials
- Educational materials
- Tool Creation
- Media campaigns

Immediate Outcomes (outreach and access)
- Providers trained
- Risk ppn recruited
- Funding available
- Counseling available

Intermediate Outcomes (coverage and compliance)
- Adherence high
- Little risk compensation

Objective
- PrEP provided to risk ppn
- Reduced HIV incidence

Sphere of Control

Sphere of Influence

Identify needed improvements

Smith DK et al., Am J Public Health 2013
External Stakeholder and Expert Engagement

Guidelines Work Groups
- Clinical Care
- Clinic-based Counseling
- PrEP integration with other prevention services
- IDU
- MSM
- Heterosexual men
- Women
- Adolescents

Technical Expert Meetings
- Public Health Ethics
- Monitoring and Evaluation
- Financing/Reimbursement
- HIV discordant couples and conception/pregnancy
- Network Science
- Public Health Law
- Insurers
Supporting Introduction and Scale Up for Public Health Impact

- Adapting interim guidance as the evidence evolved
  - Men who have sex with men, 2011
  - Heterosexually active adults, 2012-2013
  - Injection drug users, 2013

- Public Health Service Clinical Practice Guidelines for PrEP Use in the US (May 14, 2014)
  - These Clinical Practice Guidelines replace the previous interim guidance documents

MMWR. 2011;60(3):65-68.
Public Health Service
Clinical Practice Guidelines: Key Messages

- **Daily, oral PrEP with Truvada®**
  - Is recommended as one prevention option for persons at substantial risk of HIV infection including:
    - Sexually-active MSM
    - Heterosexually active men and women
    - Injection drug users
  - Should be discussed with HIV discordant couples for use during conception and pregnancy
  - Use should be weighed carefully for adolescent minors

- **Support medication adherence and risk reduction practices**

# Indications for PrEP Use by Subpopulation

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<td>• Recent bacterial STI</td>
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<td>• Sharing injection equipment</td>
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<td>• Recent drug treatment (but currently injecting)</td>
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<td>• History of inconsistent or no condom use</td>
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For **Injection Drug Users**: In a high-prevalence area or network.

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**Rates of Females Living with an HIV or AIDS Diagnosis, by ZIP Code, Atlanta, 2010**
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</tr>
<tr>
<td>• High number of sex partners</td>
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<td>• Recent drug treatment (but currently injecting)</td>
</tr>
<tr>
<td>• History of inconsistent or no condom use</td>
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<td>• In high-prevalence area or network</td>
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## Assessing for Contraindications and Prescribing PrEP

### Clinically eligible

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<tr>
<td>• Documented negative HIV test result before prescribing PrEP</td>
<td>• No signs/symptoms of acute HIV infection</td>
<td>• Normal renal function; no contraindicated medications</td>
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<td>• Normal renal function; no contraindicated medications</td>
<td>• Documented hepatitis B virus infection and vaccination status</td>
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### Prescription

- Daily, continuing, oral doses of TDF/FTC (Truvada®), ≤90-day supply

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Excluding Acute or Established HIV Infection

HIV immunoassay blood test (rapid test if available)

- Signs/symptoms of acute HIV infection

  - Option 1: Retest antibody in one month. Defer PrEP decision
  - Option 2: Send blood for HIV antibody/antigen assay*
  - Option 3: Send blood for HIV-1 viral load (VL) assay

* Use only HIV antigen/antibody tests that are approved by FDA for diagnostic purposes

## Follow-up Visits While Prescribing PrEP

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Clinical Providers Supplement to Guidelines: Educational and Training Materials

- **Patient factsheets**
  - PrEP
  - Truvada®
  - Acute HIV infection

- **Provider materials**
  - Patient/Provider checklist
  - Information on PrEP during conception, pregnancy, and breastfeeding
  - HIV incidence risk index for MSM
  - Potential PrEP practice quality measures
  - Supplemental counseling information

www.cdc.gov/hiv/pdf/guidelines/PrEPProviderSupplement2014.pdf
Tools for Implementation of PrEP in Clinical Practice

- Materials for persons considering PrEP
- Guide for billing codes
- Risk screening tools
  - Published for MSM
  - Under development for HIV-discordant couples, injection drug users

Choose an ARCH tool

MSM
Men who have sex with men.

Start

MSM: men who have sex with men
ARCH: Assessing the risk for contracting HIV
Policy Development to Mitigate PrEP Costs

- **Average retail pharmacy price for a one month supply of Truvada® is $1400**
  - Negotiated drug price reductions
  - Most private employer, school-based and public insurers (e.g. Medicaid) provide coverage for PrEP medications and care

- **PrEP drug and co-pay assistance programs available**
  - Free medication for those with low income and no insurance coverage
    - Gilead Sciences
      - Free condoms and HIV testing can be provided
      - Free hepatitis B screening, and HIV resistance testing for those who seroconvert while on PrEP
    - Washington State

Cost-effectiveness of PrEP

- 4 cost-effectiveness studies in MSM in the US
- Delivery of PrEP is most cost-effective when:
  - Targeted to populations with high HIV incidence
  - High coverage is achieved in targeted populations
  - Medication adherence is high
  - Cost of medication and clinical services are minimized

Analysis of a commercial pharmacy database
- Includes 55% of U.S. prescriptions

PrEP prescribers in ~700 US cities, 49 states
- 31% family practice and internal medicine
- 17% non-physician prescribers (NP and PA)
- 14% emergency medicine
- 12% infectious disease

Prescriptions rose 8.5-fold
- 150 in 2011 to 1274 in 2012
- 48% of prescribing for women
- 14% for persons under age 25 years
An Early Study to Evaluate PrEP Uptake and Adherence

- MSM recruited in STD clinics; 60% of eligible patients enrolled
- Medication adherence assessed at 4 weeks by blood drug level
  - Daily adherence suboptimal; ≥4 doses/week adherence higher
- Other modeled data* suggest high efficacy may be achieved at ≥4 doses/wk

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Cohen S et al., Poster 954, CROI 2014
*Anderson PL et al., Science Translational Medicine, 2012

DC: Washington, DC
SF: San Francisco
Study of PrEP as Implemented in Community Health Centers

- **Health Services Observational Cohort (SHIPP Study)**
  - Collects de-identified data from medical records
  - Evaluate prescribing practices, patient outcomes, and service costs for all clinic patients receiving PrEP

- **Medication Adherence Substudy (SHIPP Study)**
  - Offers participation with informed consent
  - Collects dried blood spots to measure drug levels
  - Provides adherence aids to those with suboptimal adherence

- **Community Surveys (Context Matters Study)**
  - Clinician attitudes about PrEP and its provision in each clinic
  - Knowledge and attitudes about PrEP among lay persons and key stakeholders in communities served by each clinic

Observational Cohort NCT02074891 at www.clinicaltrials.gov
Role of PrEP in HIV Prevention

The United States will become a place where new HIV infections are rare…

-National HIV/AIDS Strategy Vision Statement
# Clinician Resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>URL</th>
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<tbody>
<tr>
<td>REMS clinician materials</td>
<td><a href="www.truvadapreprems.com/truvadaprep-resources">www.truvadapreprems.com/truvadaprep-resources</a></td>
</tr>
<tr>
<td>Co-Pay Assistance Program</td>
<td><a href="www.gileadcopay.com/">www.gileadcopay.com/</a></td>
</tr>
<tr>
<td>Free condoms for patients</td>
<td><a href="https://start.truvada.com/individual/truvadaprep-patient-resources">https://start.truvada.com/individual/truvadaprep-patient-resources</a></td>
</tr>
<tr>
<td>Free HIV testing for patients</td>
<td><a href="https://start.truvada.com/hcp#">https://start.truvada.com/hcp#</a></td>
</tr>
<tr>
<td>Online HIV Data maps:</td>
<td></td>
</tr>
<tr>
<td>CDC NCHHSTP Atlas</td>
<td><a href="www.cdc.gov/nchhstp/atlas">www.cdc.gov/nchhstp/atlas</a></td>
</tr>
<tr>
<td>AIDSVu</td>
<td><a href="aidsvu.org/">aidsvu.org/</a></td>
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