HIV Preexposure Prophylaxis (PrEP) 2019

Roy M. Gulick, MD, MPH
Chief, Division of Infectious Diseases
Rochelle Belfer Professor in Medicine
Weill Cornell Medicine
New York City, New York

Learning Objectives

After attending this presentation, learners will be able to:

- Discuss the current data to support the use of HIV PrEP
- Discuss investigational agents for HIV PrEP

New HIV Infections: Global

UNAIDS: http://aidsinfo.unaids.org/2019
New HIV Diagnoses, NYC, 2017

Source: NYC DOHMH, Bureau of HIV Surveillance Data

Governor Cuomo’s Plan to End AIDS in New York -- 2014

1. Diagnose HIV and link to care
2. Link, retain and treat to achieve virologic suppression
3. Provide PrEP for high-risk people to keep them HIV negative


Federal Plan to End AIDS by 2030

GOAL:
- Our goals are ambitious and the pathway is clear - employ strategic practices in the cities focused on the right people to:
  - Diagnose all people with HIV in early stages.
  - Treat the infection rapidly and effectively to achieve sustained virologic suppression.
  - Provide people at risk for HIV infection with preventive options to reduce risk of infection.
  - End new infections.

February 2019
https://www.hiv.gov/
Oral PrEP Studies (1)

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study population</th>
<th>Design</th>
<th>Results: ↓HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPREX</td>
<td>2499 gay men</td>
<td>TDF/FTC vs. placebo</td>
<td>TDF/FTC: 45% (92% if tenofovir detected)</td>
</tr>
<tr>
<td>Partners PREP</td>
<td>4758 discordant Kenya and Uganda couples</td>
<td>TDF vs. TDF/FTC vs. placebo</td>
<td>TDF: 67% TDF/FTC: 75% (86-90% if tenofovir detected)</td>
</tr>
<tr>
<td>CDC – TDF-2</td>
<td>1200 Botswana adults (45% women)</td>
<td>TDF/FTC vs. placebo</td>
<td>TDF/FTC: 65% (84% if tenofovir detected)</td>
</tr>
</tbody>
</table>

PrEP Approvals

- In July 2012, U.S. FDA approves TDF/FTC for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk.

- Additional approvals followed including: Australia, Canada, France, India, Israel, Kenya, Peru, South Africa

Oral PrEP Studies (2)

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study population</th>
<th>Design</th>
<th>Results: Reduction in HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEM-PREP</td>
<td>2120 women in Kenya, South Africa, Tanzania</td>
<td>TDF/FTC vs. placebo</td>
<td>TDF/FTC: 0% (adherence &lt;40%)</td>
</tr>
<tr>
<td>VOICE</td>
<td>5029 women in South Africa, Uganda, Zimbabwe</td>
<td>1% TDF gel vs. placebo gel, oral TDF vs. TDF/FTC vs. placebo</td>
<td>0% -- no study drugs effective (adherence &lt; 30%)</td>
</tr>
</tbody>
</table>
Oral PrEP Studies (3)

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study population</th>
<th>Design</th>
<th>Results: Reduction in HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPERGAY</td>
<td>414 MSM in France and Canada</td>
<td>TDF/FTC vs. placebo (event-driven)</td>
<td>TDF/FTC: 86%</td>
</tr>
<tr>
<td>PROUD</td>
<td>545 men in England</td>
<td>TDF/FTC vs. placebo</td>
<td>TDF/FTC: 86%</td>
</tr>
</tbody>
</table>

Oral TDF/FTC PrEP Trials: Effectiveness Improves With Adherence

Oral PrEP Studies (4)

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study population</th>
<th>Design</th>
<th>Results: Reduction in HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thai IDU</td>
<td>2413 Thai injection drug users</td>
<td>TDF vs. placebo</td>
<td>TDF: 49% (70% if TFV detected)</td>
</tr>
</tbody>
</table>
WHO Evaluation of PrEP Data 2015

- Efficacy: Effective across groups, genders
- Adherence: Heterogeneous
- Side effects: no more common than placebo (subclinical renal/bone issues)
- Drug resistance: low (0.1%) risk
- Risk compensation: did not increase
- Cost: could be cost-effective/cost-saving
- Logistics: significant concerns

PrEP Safety: Meta Analysis
13 randomized trials of PrEP vs. placebo (or no treatment) (N=15,678)

Pilkington J Virus Erad 2018;4:215-224

Genotypic Drug Resistance (DR) to TDF or FTC in PrEP Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Incident DR Infections PrEP</th>
<th>PrEP arm N</th>
<th>Incident DR Infections Placebo</th>
<th>Placebo arm N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok TDF</td>
<td>0</td>
<td>1204</td>
<td>0</td>
<td>1299</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>0</td>
<td>1034</td>
<td>0</td>
<td>1032</td>
</tr>
<tr>
<td>iPrEx</td>
<td>0</td>
<td>1251</td>
<td>0</td>
<td>1248</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>0</td>
<td>1155</td>
<td>0</td>
<td>1578</td>
</tr>
<tr>
<td>TDF2</td>
<td>0</td>
<td>633</td>
<td>0</td>
<td>656</td>
</tr>
<tr>
<td>VOICE</td>
<td>1</td>
<td>1778</td>
<td>0</td>
<td>999</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5</td>
<td>9222</td>
<td>1</td>
<td>9672</td>
</tr>
</tbody>
</table>

Overall risk of FTC or TFV resistance is 5/9222 (0.05%)
**Case Reports:**

**HIV Infection with High Adherence to PrEP (N=6)**

| Case Reference | Years | Methods of confirming HIV infection | Clinically significant STI, other sexually transmitted infections | CD4+ T-cell count | HIV RNA 
|----------------|-------|------------------------------------|-------------------------------------------------|----------------|-------------

**PrEP and STIs**

**Systematic Review and Meta-Analysis**

8 studies with 4,388 participants


"Recommended for substantial risk of HIV Infection"

- Rule out acute HIV infection
- Assess baseline renal function
- Prescribe 3 months of TDF/FTC
- Follow-up visits every 3 months for:
  - HIV testing
  - Adherence and risk reduction counseling
  - Side effect assessment
  - Sexually transmitted infection symptom assessment and routine testing (chlamydia, gonorrhea, syphilis); treat if necessary
- Assess renal function every 6 months

U.S. Preventive Services Task Force (USPSTF)

Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at high risk of HIV acquisition</td>
<td>The USPSTF recommends that clinicians offer PrEP with effective ART to persons who are at high risk of HIV acquisition.</td>
<td>A</td>
</tr>
</tbody>
</table>

Federal Rule: Private insurance and Medicare must offer A or B services without a co-pay.

ARS Question 1:

Have you prescribed oral daily TDF/FTC for PrEP?

A. Yes
B. No
C. I’m not a prescriber
In 2017 → 120,000 PrEP users
In 2019 → 270,000 PrEP users
PrEP Initiations by Country 2018

Source: AVAC Global PrEP Initiation Tracker 2018

>300,000 PrEP starts globally
>200,000 in the US

Intermittent PrEP (I-PrEP)

IPREX Follow-Up: Modeling Pharmacokinetics in Men Who Have Sex With Men (MSM)

Using data from a separate PK study:

- 7 doses/week: 99% risk reduction
- 4 doses/week: 97% risk reduction
- 2 doses/week: 76% risk reduction


ARS Question 2:

Have you recommended “on-demand” TDF/FTC for PrEP?

A. Yes
B. No
C. I’m not a prescriber
Event-Driven PrEP: Status

PrEP 2-1-1:

- FDA label of TDF/FTC specifies once-daily
- Recommended by IAS-USA, BHIVA, EACS (2018) and WHO (2019)

Prevenir INTERIM REPORT

- Open-label, prospective, cohort study in Paris
- Cohort population: HIV high-risk adults, inconsistent condom use, GFR ≥50, HBsAg negative if using on-demand (N=3057)
- Rx: Choose TDF/FTC daily or on-demand dosing (and can switch); f/u every 3 months
- Goal: Show 15% ↓ in new HIV infections in Paris
- Results (HIV modified ITT analysis):
  - 2 seroconversions, both off PrEP
  - 3 PrEP discontinuations due to GI sx

Rates of Detectable TFV/TFV-metabolite detection in Female Mucosal Tissues – Single Dose Study

Cottrell J Antimicrob Chemother 2017;72:1731-1740
ARS Question 3:
Have you prescribed oral daily TAF/FTC for PrEP?

A. Yes  
B. No  
C. I’m (still) not a prescriber

Newer PrEP Agents

<table>
<thead>
<tr>
<th>study drug</th>
<th>mechanism</th>
<th>dosing route</th>
<th>dosing</th>
<th>PrEP stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF</td>
<td>NRTI</td>
<td>oral</td>
<td>daily</td>
<td>phase 3 completed</td>
</tr>
<tr>
<td>cabotegravir</td>
<td>integrase inhibitor</td>
<td>injectable, subcutaneous</td>
<td>once every other month</td>
<td>phase 3 studies</td>
</tr>
<tr>
<td>monoclonal antibodies</td>
<td>CD4 or gp120 attachment inhibitors</td>
<td>Injectable subcutaneous</td>
<td>pilot studies; phase 2b/3 AMP studies</td>
<td></td>
</tr>
</tbody>
</table>

Rates of Detectable TFV/TFV-metabolite detection in Female Mucosal Tissues – Single Dose Study

<table>
<thead>
<tr>
<th>TAF 25mg</th>
<th>TDF 300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal Tissue 100%</td>
<td>Rectal Tissue 37%</td>
</tr>
</tbody>
</table>
DISCOVER: TDF vs. TAF for PrEP

- Double-blind, non-inferiority PrEP study
- Study population: MSM and TGW (N=5387)
  - median 34 yo, 84% W, 24% L, 16% non-white, 74 TGW
- Study rx: daily oral TDF vs. TAF
- Results:
  - 22 incident infections
    - 5 at first visit
    - 15 with ↓ drug levels
    - 2 with adeq. drug levels
  - >57% with STI
  - Improved bone, renal markers with TAF
- Conclusion: TAF non-inferior to TDF for PrEP

DISCOVER: TAF/FTC vs. TDF/FTC

- Subanalyses:
  - No difference in:
    - number of condomless RAI partners
    - rectal GC/chlamydia
    - self-reported adherence, pill counts
    - TFV-DP levels by dried blood spots
  - HIV cases << controls
- Published data: TAF achieves EC90 within 4 hrs, TDF takes 3 days
- Conclusions: TAF “potentially more efficacious”
- FDA Advisory Committee (8/7/19):
  - TAF/FTC PrEP approval vote: men: 16-2 for ♂; women: 10-8 against

HPTN 083: PrEP with TDF/FTC oral vs. cabotegravir (CAB) intramuscular

- Study population: Adult MSM and transgender women at high-risk for HIV acquisition (N=4500)
- Study regimen: TDF/FTC daily oral vs. CAB every 2 month injections
  - double-blind, double-dummy design
- Design: non-inferiority, efficacy study
- 4358 (97%) enrolled globally (as of 9/10/19)
Islatravir (ISL, formerly MK-8591) Implant

Impact: Big Cities

San Francisco: 50+% ↓ in new HIV infections in the past decade
SFDPH Annual Report 2017

Sydney: 32% ↓ (25% ↓ in 2 years)
Grulich Lancet HIV 2018;5:e629-e637

London: 42% ↓
Nwokolo Lancet HIV 2017;4:e482-e483

New York: 37% ↓ 2011 → 2017
NYC HIV Surveillance Report 2017

PreP Aware Week

Let's make everyone aware that PrEP can prevent HIV.
www.prepforsex.org

New York State AIDS Institute
Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
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- AIDS Clinical Trials Group (ACTG)
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