HIV Pre-Exposure Prophylaxis

Vidhu Kariyawasam, MD
Assistant Professor of Medicine/Infectious Disease
North Florida AIDS Education and Training Center
University of Florida

Faculty Disclosure
I do not have financial or other relationships with the manufacture(s) of any commercial services discussed in this educational activity.

Objectives
- Identify patients at risk for HIV acquisition who may benefit from pre-exposure prophylaxis (PrEP)
- Describe steps for prescribing PrEP
- Discuss steps to counsel and provide PrEP to patients at high risk for HIV
- Discuss indications to stop PrEP
Pre-exposure Prophylaxis (PrEP) is an HIV prevention method in which people who do not have HIV infection take a pill daily to reduce their risk of becoming infected.

Why PrEP?

50,000 estimated new HIV infections each year in the US. No Vaccine or Cure available.

Endings the HIV Epidemic: A Plan for America

GOAL:

- Diagnose all people with HIV as early as possible.
- Treat the infection rapidly and effectively to achieve sustained viral suppression.
- Prevent new HIV infections by using proven interventions, including pre-exposure prophylaxis (PrEP) and other harm-reduction programs.
- Respond quickly to potential HIV outbreaks in gay men, women, and people who need them.


No Vaccine or Cure available.
The Centers for Disease Control and Prevention (CDC) recommends all sexually active adult and adolescent patients receive information about PrEP.

"Any licensed prescriber can prescribe PrEP. Specialization in infectious diseases or HIV medicine is not required. In fact, primary care providers who routinely see people at risk for HIV acquisition should consider offering PrEP to all eligible patients."
Potential Benefits of PrEP

- Prevent HIV transmission
- Bring more attention to sexual health – proactive / taking control
- Can help resolve “discordance dilemma”
- Decreased anxiety, increased communication,
- Increased disclosure
- Increased trust
- Increased self-efficacy
- Increased sexual pleasure
- Increased intimacy

PrEP Use in the U.S.

<table>
<thead>
<tr>
<th>Transmission risk group</th>
<th>% with PrEP indication</th>
<th>Estimated no. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men, aged 16-59 yrs</td>
<td>24.7</td>
<td>492,000 (212,000-772,000)</td>
</tr>
<tr>
<td>Adults who inject drugs, aged ≥18 yrs</td>
<td>18.3</td>
<td>119,000 (48,000-189,000)</td>
</tr>
<tr>
<td>Heterosexual active adults, aged 16-59 yrs</td>
<td>0.4</td>
<td>624,000 (364,000-846,000)</td>
</tr>
<tr>
<td>Men</td>
<td>0.2</td>
<td>157,000 (62,000-252,000)</td>
</tr>
<tr>
<td>Women</td>
<td>0.6</td>
<td>468,000 (274,000-662,000)</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>1,272,000 (661,000-1,893,000)</td>
</tr>
</tbody>
</table>

CDC estimates 100,000 used PrEP in 2017

HIV prevention pill is not reaching most who could potentially benefit – especially African Americans and Latinos

- 44% of people who could potentially benefit from PrEP are African Americans – approximately 100,000 people
- But only 1% of those (~1,000) were prescribed PrEP

- 25% of people who could potentially benefit from PrEP are Latinos – nearly 300,000 people
- But only 3% of those (~9,000) were prescribed PrEP
FDA approved Oral Medications for PrEP - One pill once a day

- Emtricitabine (F) 200 mg combined with tenofovir disoproxil fumarate (TDF) 300 mg (F/TDF)
- Emtricitabine (F) 200 mg combined with tenofovir alafenamide (TAF) 25 mg (F/TAF)

All preparations are approved to prevent HIV in adults and adolescents who weigh at least 77 pounds.

FDA approved Intramuscular Preparation for PrEP

- 600 mg of cabotegravir injected into gluteal muscle every 2 months

All preparations are approved to prevent HIV in adults and adolescents who weigh at least 77 pounds.

Comprehensive HIV Prevention

PrEP is always part of a comprehensive HIV prevention package
- Condoms
- Counseling
- Frequent STD testing and treatment
- Frequent HIV testing
Taking a Sexual History

- Make it a normal part of each visit
- The Five “P”s
  - Partners
  - Practices
  - Protection from STDs
  - Past history of STDs
  - Prevention of pregnancy


PrEP Steps

1. Identify indications for PrEP
2. Assess risk for HIV acquisition
3. Laboratory evaluation
4. Prescribe PrEP
5. Clinical follow-up and monitoring

Step 1: Who Should be Offered PrEP?

- Sexually active adults and adolescents
- Persons with high-risk HIV exposure

- History of discordant or discordant sex partners
- History of high-risk sex partners
- History of injection drug use
- Sex while under the influence of substances

All AI recommendations

Step 2: Assess risk for HIV acquisition

- Acute or Chronic HIV infection needs to be ruled out prior to initiating PrEP
- Screen for signs of acute HIV or suspect acute HIV infection in persons who have engaged in exposure-prone behaviors in the 4 weeks prior to evaluation for PrEP
- Should have a documented negative HIV test result prior to starting PrEP.
- If anticipating doing long acting IM cabotegravir obtain HIV RNA prior to starting PrEP
- Clinicians should not accept patient-reported test results or documented anonymous test results.
- Rapid tests that use oral fluid should not be used to screen for HIV infection

Main symptoms of Acute HIV infection

- Constitutional: - Fever - Weight loss
- Pharyngitis
- Mouth - Sore Throat
- Encephalopathy - Nausea
- Muscles: - Myalgia
- Lymph nodes - Lymphadenopathy
- Gastro: - Diarrhea - Vomiting

http://upload.wikimedia.org/wikipedia/commons/4/4a/Symptoms_of_acute_HIV_infection.png

HIV Testing in Patients on Oral or Intramuscular PrEP

- Testing may be more unreliable in patients who acquire HIV while on PrEP.
- The antiretrovirals used for PrEP can suppress early viral replication which can affect the timing of antibody development.
- In HPTN 083, detection of HIV in the cabotegravir group with Ag/Ab testing was delayed by a mean of 62 days compared to detection by qualitative HIV-1 RNA assay for infections determined to have been present at baseline; the delay was 98 days for incident infections.
- Among participants in the F/TDF group, detection by Ag/Ab testing was delayed by a mean of 34 days from qualitative HIV-1 RNA detection for baseline infections and 31 days for incident infections.
- Given this the traditional method of using 4th generation test is insufficient to rule out HIV while on PrEP.

Monitoring HIV status while on PrEP

- The diagram illustrates the testing strategies and timelines for monitoring HIV status while on PrEP.
- It shows the timing and types of tests recommended for individuals on PrEP.
- The legend explains the symbols and colors used in the diagram to represent different test results and intervals.

HIV testing for PrEP - Summary

- For patients who are starting or restarting Oral PrEP after a long stop, test using an HIV antigen/antibody test (laboratory-based is preferred).
- If Patient starting long acting Cabotegravir – HIV RNA in addition to Ag/AB test is preferred
- For patients who are taking or have recently taken PrEP (including patients who have taken oral PrEP in the last 3 months or patients who had a CAB injection in the last 12 months), test using an HIV antibody/antigen assay AND a qualitative or quantitative HIV-1 RNA assay.

FDA Indications for F/TDF vs F/TAF

- **F/TDF**
  - Prevention of HIV infection among all people at risk through sex or injection drug use
  - Renal function: eGFR > 60 mL/min
- **F/TAF**
  - Prevention of HIV infection among people at risk through sex, excluding people at risk through receptive vaginal sex
  - Renal function: eGFR > 30 mL/min

(F/TDF)

- Approved for HIV PrEP in 2012
- One pill by mouth daily with or without food
- **Do not use for PrEP if estimated eGFR < 60 mL/min**
- Potential side effects
  - Headache, abdominal pain and weight loss – usually resolves in 2-4 weeks
  - Decreased bone mineral density (no fracture risk)
  - Renal dysfunction including Fanconi syndrome
  Typically reversible with stopping F/TDF
(F/TAF)

- Approved for HIV PrEP for prevention of sexual transmission, excluding individuals at risk from receptive vaginal sex on October 3, 2019
- One pill by mouth daily with or without food
- Do not use if estimated eGFR < 30 mL/min
- Potential side effects
  - Headache, diarrhea and abdominal pain – usually resolves in 2-4 weeks
  - Decreased bone mineral density (no fracture risk)
  - Renal dysfunction including Fanconi syndrome

- Typically reversible with stopping F/TAF

---

Which medication should you prescribe for daily PrEP

---

Eligibility for Oral PrEP

- HIV test within 1 week before prescribing PrEP
- No signs or symptoms of acute HIV infection
- Normal renal function
- No contraindicated medications
Baseline Lab Evaluation for Oral PrEP

- HIV test: HIV ag/ab +/- HIV RNA
- STI screen
- Serologic testing for hepatitis B & C
- Creatinine clearance
- Lipid panel if TAF/FTC to be used

Hepatitis B and Oral PrEP

- Check hepatitis B serology before initiating oral PrEP
- Severe acute exacerbations of hepatitis B can occur in patients infected with hepatitis B who discontinue current PrEP medications
- Vaccinate if nonimmune

Clinically significant Oral PrEP Medication Drug Interaction

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>TDF</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir, sofosbuvir; ribavirin</td>
<td>Serum concentrations of TDF may be increased. Monitor for toxicity</td>
<td>No significant effect</td>
</tr>
<tr>
<td>St John's Wort</td>
<td>No significant effect</td>
<td>Do not co-administer with TAF. Decrease in TAF concentration possible</td>
</tr>
<tr>
<td>Rifabutin, rifapentine</td>
<td>No significant effect</td>
<td>Do not co-administer with TAF unless benefits outweigh risks</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No significant effect</td>
<td>Do not co-administer with TAF</td>
</tr>
</tbody>
</table>

Prescribing and Monitoring

- TDF/FTC or TAF/FTC with or without food
- No more than 90 day supply
- How long does it take for protection from HIV after starting oral PrEP?

Adherence Is Critical


<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Every 3 months</th>
<th>At least every 6 months</th>
<th>Every 12 months</th>
<th>When stopping</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Ab/Ag and HIV RNA</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CrCL</td>
<td></td>
<td></td>
<td>If age &lt;50 or CrCL &lt; 90 at PrEP initiation</td>
<td>X</td>
</tr>
<tr>
<td>If age &gt;50 or CrCL &gt; 90 at PrEP initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>MSM/TGW</td>
<td>X</td>
<td>MSM/TGW</td>
<td>X</td>
</tr>
<tr>
<td>Gonorrhea/Chlamydia</td>
<td>MSM/TGW</td>
<td>X</td>
<td>MSM/TGW</td>
<td></td>
</tr>
<tr>
<td>Lipid Panel/weight (FTAF)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
**Long Acting Intra-Muscular PrEP**

- 600 mg of cabotegravir injected into gluteal muscle every 2 months
- Can delay identification of baseline HIV – so ideally should do HIV RNA + HIV Ag/AB prior to starting long acting cabotegravir
- Cannot be self administered at home.
- This may be especially appropriate for patients with significant renal disease, those who have had difficulty with adherent use of daily oral PrEP, but can be compliant with clinic visits

**Efficacy/Safety of LA Injectable CAB vs Daily Oral FTC/TDF**

- HPTN 083 and 084: International, randomized, double-blind phase IIb/III (083) and phase III (084) trials

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Wk 5</th>
<th>Step 2</th>
<th>Wk 9</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB 100 mg PO QD + Placebo PO QD</td>
<td>CAB LA 400 mg IM Q2M* + Placebo FTC QD for 1 yr</td>
<td>FTC/TDF PO QD + Placebo PO QD</td>
<td>FTC/TDF PO QD + Placebo IM Q12M for 3 yr</td>
<td></td>
</tr>
</tbody>
</table>

*HPTN 083: Men age 18-50 y, age at high risk of HIV infection ≥6 months (N = 4130)†

*HPTN 084: Sexually active, (N = 3274)†

*Any mirror image arm/strand and intravenous, V5 partner, lab STDs, rectal anal or oral sex, or anogenital syphilis or other sexu.

*Part 2: Doo twice a week or every 2-3 mo hereafter.

**Efficacy/Safety of LA Injectable CAB vs Daily Oral FTC/TDF**

<table>
<thead>
<tr>
<th></th>
<th>HPTN 083</th>
<th>HPTN 084</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Efficacy Endpoints</strong></td>
<td>CAB (n = 3164)</td>
<td>FTC/TDF (n = 3147)</td>
</tr>
<tr>
<td>HIV infections, n</td>
<td>31†</td>
<td>31</td>
</tr>
<tr>
<td>PFPY</td>
<td>3205</td>
<td>3187</td>
</tr>
<tr>
<td>HIV incidence per 100 PY</td>
<td>0.41</td>
<td>1.12</td>
</tr>
</tbody>
</table>

HR for CAB vs FTC/TDF (95% CI): 0.34 (0.18-0.64); 0.06 (0.03-0.19)

*Includes 1 case adjudicated post for sex (1 in each arm). Revised HR based on sex adjustment, CAB: 0.37 (95% CI: 0.19-0.72), FTC/TDF: 0.06 (95% CI: 0.03-0.10).
CAB PrEP Initiation Visit

- Negative HIV Ag/Ab test + HIV RNA test + no concern for acute HIV
- STI screen
  - Gonorrhea & chlamydia at all mucosal sites of exposure
  - Syphilis testing
- Testing NOT needed for CAB PrEP patients:
  - creatinine, CrCl, hepatitis B serology, lipid panels, liver function tests
- Oral lead in not required—may be optionally used for patients who are especially worried about side effects to relieve anxiety about using the long-acting CAB injection.

Cabotegravir (CAB) PrEP Drug Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interaction</th>
</tr>
</thead>
</table>
| Rifampicin, rifapentin | Do not co-administer with CAB
| Rifabutin           | Co-administer with caution
| Carbamazepine, oxcarbazepine, phenytoin, phenobarbital | Do not co-administer with CAB

CAB Administration

- Dosing: 3 ml suspension of CAB 600 mg IM in gluteal muscle
  - Second dose 4 weeks after first dose (month 1 follow-up visit)
  - Every 8 weeks thereafter

- Managing Injection Site reactions
  - In the clinical trials, injection site reactions (pain, tenderness, induration) were frequent
  - These reactions were generally mild or moderate, lasted only a few days, and occurred most frequently after the first 2-3 injections
  - Patients should be informed that these reactions are common and transient
  - Take an over-the-counter pain medication soon after the injection
  - Apply a warm compress or heating pad to the injection site for 15-20 minutes after the injection

Timing of CAB PrEP-Associated Laboratory Tests

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Every 2 months</th>
<th>Every 4 months</th>
<th>Every 6 months</th>
<th>When stopping</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Ab/Ag and HIV RNA</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Syphilis</td>
<td>MSM/TGW</td>
<td>X</td>
<td></td>
<td>MSM/TGW</td>
</tr>
<tr>
<td>Gonorrhea/Chlamydia</td>
<td>MSM/TGW</td>
<td>X</td>
<td></td>
<td>MSM/TGW</td>
</tr>
</tbody>
</table>


Implementation Considerations to Facilitate Uptake/Use of Long-Acting Injectable HIV Prevention

- Shot clinics (in and out) in clinical programs
- Pharmacies administer shots
- Constant supply of oral formulations at home for “bridges” when shot dose missed
- Incentives
- Mobile vans
- Good staff communication, teamwork
- Effective appointment reminder systems, designated staff for appointment tracking

What if the HIV test is positive?

- Do confirmatory test if rapid test positive
- Convert the PrEP regimen to an HIV treatment regimen recommended by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents
- Order an HIV-1 RNA PCR, HIV-1 Genotype, CD4 count and other baseline labs
- Reinforce need for adherence to medications
- Discuss the importance of condom use to protect sex partners and provide condoms
- Offer HIV testing for sex and drug injection partners, nPEP and assistance with disclosure
- Ask if they have a family member they would like to be contacted for support and provide support and counselling
Managing PrEP Patients with Ambiguous HIV test Results

- Given that you are doing both a HIV ag/ab test and a HIV RNA test for patients while on PrEP – you may get discordant results:
- In this situation you should assess adherence and draw a new blood specimen after a few days for repeat laboratory HIV including Ag/Ab and HIV RNA.
- You can consult the National Clinician Consultation line for further guidance about continuing/discontinuing PrEP.

Development of Resistance- Oral PrEP

- Risk is low despite 2 drug therapy with PrEP
  - iPrEx
    - 48 people with HIV – none with significant resistance
  - Partner's PrEP
    - 5 of 63 seroconverters developed resistance
    - M184V

HPTN 083: Incident HIV Infections With Cabotegravir

- INSTI resistance observed upon viremic "escape" at higher CA8 concentrations; not observed in 3 tail-phase infections or 1 tail "escape" case
Discontinuing PrEP

- Positive HIV result / Acute HIV signs or symptoms
- Chronic nonadherence to prescribed dosing regimen or scheduled follow up visits
- Patient choice / changed life situation resulting in lower risk of HIV acquisition
- Document HIV status at time of discontinuation, reason for discontinuation

Advise risk of developing drug resistant HIV during the period of waning drug levels (the "tail period")

CAB levels slowly wane over many months after injections are discontinued. In the HPTN 077 trial, the median time to undetectable CAB plasma levels was 44 weeks for men and 67 weeks for women with a wide range for both sexes.

PrEP in Pregnancy

- F/TDF as PrEP is considered generally safe for pregnant and breastfeeding women
- The data provides no evidence of adverse effects among fetuses exposed to these medications
- Providers should discuss potential risks and benefits of beginning or continuing PrEP during pregnancy

“On-Demand” PrEP

Taking PrEP on a 2-1-1 schedule reduced risk of HIV infection by 86% in MSM—only F/TDF

PrEP in Clinical Practice: What Are the Barriers to PrEP Uptake?

- Users
  - Unaware of HIV risk, PrEP availability, or how to access it
  - No or delayed access to clinical preventive care
  - Lack of knowledge about insurance coverage
  - Adherence challenges
  - Concern about disclosure and stigma

- Providers
  - Unaware of intervention
  - Wary of complexity and time involved
  - Discomfort with assessing risk
  - Uncertain how to bill for intervention
PrEP in Clinical Practice: What Are the Barriers to PrEP Uptake?

- Users
  - Unaware of HIV risk, PrEP availability, or how to access it
  - No or delayed access to clinical preventive care
  - Lack of knowledge about insurance coverage
  - Adherence challenges
  - Concern about disclosure and stigma

- Providers
  - Unaware of intervention
  - Wary of complexity and time involved
  - Discomfort with assessing risk
  - Uncertain how to bill for intervention

Ready, Set, PrEP

- Launched by the US Department of Health and Human Services on 12/3/19
- To qualify, patients must:
  - Test negative for HIV
  - Have a valid prescription from a healthcare provider
  - Not have prescription drug coverage
- Beginning no later than March 30, 2020, patients may obtain PrEP through CVS, Walgreens, Rite Aid or mail order all at no cost
- [https://www.getyourprep.com](https://www.getyourprep.com) or 855-447-8410
- HIV.gov Locator

The PARTNER1 study looked at 888 couples where one was HIV positive and on antiretroviral treatment (ART) and who were already having sex without condoms:
- 548 heterosexual couples
- 340 MSM
- They found that in more than 58,000 acts of condomless sex there were no HIV transmissions from the HIV positive partner among those on treatment with an undetectable viral load
- Couples were followed for a median of 1.3 years
Partner 2 Study:
- Prospective observational study in 14 European countries
- Enrolled 927 homosexual serodiscordant couples between September 2010 and July 2017
- Positive partner was on suppressive ART
- A total of 74568 condomless-sex acts were reported, with 0 cases of within couple HIV transmission

Conclusions/Recommendations
- PrEP Works!
- Easy to prescribe and monitor – with minimal side effects
- Don’t forget other pillars of prevention:
  - HIV Testing that adheres to CDC/USPTF guidelines
  - Treatment as Prevention
  - PEP
  - Raise awareness in the community to increase uptake and reduce stigma

PrEP Resources
http://nccc.ucsf.edu/clinician-consultation/prep-pre-exposure-prophylaxis/