HIV Pre-Exposure Prophylaxis

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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?

- Estimated 50,000 new HIV infections each year in the US
- No cure
- No effective vaccine yet
- In multiple studies, there is a significantly decreased risk of HIV acquisition in those who took PrEP consistently

<table>
<thead>
<tr>
<th>Transmission Route</th>
<th>Effectiveness Estimate</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual</td>
<td>~50%</td>
<td>Very high levels of adherence to PrEP ensure maximum effectiveness.</td>
</tr>
<tr>
<td>Injected drug user</td>
<td>74% - 84%</td>
<td>These estimates are based on tenofovir alone and not necessarily when taken daily. The effectiveness may be greater for the tenofovir pill and if used daily.</td>
</tr>
</tbody>
</table>
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.*

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### 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

**Ware NC, et al., JAIDS, April 2012.**
PrEP Use in U.S.

<table>
<thead>
<tr>
<th>Transmission risk group</th>
<th>% with PrEP indication</th>
<th>95% CI</th>
<th>Estimated no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men, aged 18-59 yrs</td>
<td>24.7</td>
<td>492,000</td>
<td>(212,000–722,000)</td>
</tr>
<tr>
<td>Adults who inject drugs, aged ≥18 yrs</td>
<td>18.5</td>
<td>115,000</td>
<td>(45,000–185,000)</td>
</tr>
<tr>
<td>Heterosexual active adults, aged 18-59 yrs</td>
<td>0.4</td>
<td>624,000</td>
<td>(404,000–848,000)</td>
</tr>
<tr>
<td>Men</td>
<td>0.2</td>
<td>137,000</td>
<td>(62,000–252,000)</td>
</tr>
<tr>
<td>Women</td>
<td>0.6</td>
<td>468,000</td>
<td>(274,000–662,000)</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>1,323,000</td>
<td>(661,000–2,003,000)</td>
</tr>
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</table>


**FDA-Approved Medications for PrEP**

- **Oral medications for PrEP** – one pill once a day
  - Emtricitabine (F) 200 mg combined with tenofovir disoproxil fumarate (TDF) 300 mg (F/TDF – brand name Truvada)
  - Emtricitabine (F) 200 mg combined with tenofovir alafenamide (TAF) 25 mg (F/TAF – brand name Descovy)

- **Intramuscular Preparation**
  - 600 mg of cabotegravir (Apretude) injected into gluteal muscle every 2 months – approved December 2021

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. Prescribing PrEP
5. Clinical follow-up and monitoring
Step 1: Who Should be Offered PrEP?

- Sexually-Active Adults and Adolescents
  - Anorectal or vaginal sex in past 6 months AND any of the following:
    - HIV-positive sexual partner (especially if partner has unknown or detectable viral load)
    - Recent HIV test results
    - History of inconsistent or no condom use with sexual partners

- Person Who Inject Drugs
  - History of injection drug use

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
- 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 because they are less sensitive for the detection of acute or recent infection than blood tests

Main symptoms of Acute HIV infection

- Fever
- Muscle aches
- Headache
- Fatigue
- Rash
- Nausea
- Vomiting
- Swollen lymph nodes
- Fatigue
- Weakness

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 063, 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

HIV testing for PrEP- Summary

- For patients who are starting or restarting PrEP after a long stop, test using an HIV antigen/antibody test (laboratory-based 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 (Truvada)
  - Prevention of HIV infection among all people at risk through sex or injection drug use
  - Renal function: eGFR > 60 mL/min
- F/TAF (Descovy)
  - Prevention of HIV infection among people at risk through sex, excluding people at risk through receptive vaginal sex
  - Renal function: eGFR > 30 mL/min
Truvada (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

Descovy (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

Which medication should you prescribe for daily PrEP

![Comparison chart of Truvada (TDF) and Descovy (TAF)]
Eligibility for Oral PrEP

1. Negative HIV test within 1 week before prescribing PrEP
2. No signs/symptoms of acute HIV infection
3. Normal renal function
4. No contraindicated medications

Baseline Lab Evaluation for Oral PrEP

- HIV test
- STI screen
  - Gonorrhea & chlamydia at all mucosal sites of exposure
  - Syphilis testing
- Serologic testing for Hepatitis B & C
- Creatinine clearance
- Lipid panel if TAF/FTC (Descovy) 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, velpatasvir, voxilaprevir</td>
<td>Serum concentrations of TDF may be increased. Monitor for toxicities</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>Rifampin</td>
<td>No significant effect</td>
<td>Do not co-administer with TAF unless benefits outweigh risks</td>
</tr>
<tr>
<td>Rifabutin, Rifapentine</td>
<td>No significant effect</td>
<td>Do not co-administer with TAF</td>
</tr>
</tbody>
</table>

Step 4: Prescribing PrEP

- Prescribe PrEP if Indicated
  - Daily TDF/FTC (Truvada®)
  - Daily TAF/FTC (Descovy®) only for male or transwomen
  - ≤ 90 day supply

Prescribing and Monitoring

- Truvada or Descovy with or without food
  - No more than 90 day supply
- How long does it take for protection from HIV after starting oral PrEP?
  - TDF/FTC (Truvada) estimates –
    - 20 days for cervicovaginal tissue
    - 7 days for blood mononuclear cells and rectal tissue
  - Data for TAF/FTC (Descovy) not available

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>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CrCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>MSM/IDU</td>
<td>X</td>
<td>MSM/IDU</td>
<td></td>
</tr>
<tr>
<td>Gonorrhea/Chlamydia</td>
<td>MSM/IDU</td>
<td>X</td>
<td>MSM/IDU</td>
<td></td>
</tr>
<tr>
<td>Lipid Panel/weight (F/TAF)</td>
<td></td>
<td></td>
<td></td>
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Long Acting Intra-Muscular PrEP

- 600 mg of cabotegravir injected into gluteal muscle every 2 months is recommended for PrEP in adults at risk of acquiring HIV.
- 30 mg daily oral cabotegravir is optional for a 4-week lead-in prior to injections. (Do not prescribe ongoing daily oral CAB other than for 4 week lead in)
- Cannot be self-administered at home – so patient will need bi-monthly clinic visits for administration – has to be given in the gluteal muscle
- 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

HPTN 083 and 084: HIV Incidence:
- LA CAB met criteria for superiority vs FTC/TDF in both 083 and 084

CAB PrEP Initiation Visit
- Negative HIV Ag/Ab 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</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin, rifapentin</td>
<td>Do not co-administer with CAB</td>
</tr>
<tr>
<td></td>
<td>Rifampicin and rifapentine increase metabolism of CAB and may result in significantly reduced exposure to protective levels of CAB.</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Co-administer with caution</td>
</tr>
<tr>
<td></td>
<td>Rifabutin moderately increases metabolism of CAB and may result in somewhat reduced exposure to protective levels of CAB.</td>
</tr>
<tr>
<td>Carbamazepine, oxcarbazepine, phenytoin, phenobarbital</td>
<td>Do not co-administer with CAB</td>
</tr>
<tr>
<td></td>
<td>Concern that these anticonvulsants may result in significantly reduced exposure to protective levels of CAB but strength of evidence is weak.</td>
</tr>
</tbody>
</table>

### CAB Administration

- **Dosing:** 3 ml suspension of CAB 600 mg IM in gluteal muscle
  - 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 following CAB injections.
  - 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 when assessing for acquisition off HIV while on PrEP – you may get discordant results:
  - Either a positive HIV ag/ab with a negative HIV RNA or a negative HIV ag/ab with a positive HIV RNA
- 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 CAB concentrations; not observed in 3 tail-phase infections or 1 tail "escape" case

<table>
<thead>
<tr>
<th>HIV Infection Testing</th>
<th>Number of Infections</th>
<th>Resistance Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Group A)</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>With recent CAB exposure (or after long delay in scheduled dosing, Group B)</td>
<td>5</td>
<td>M184I n = 3; Y181C, L100I n = 1</td>
</tr>
<tr>
<td>During oral load (before CAB injections, Group C)</td>
<td>2</td>
<td>M184V n = 1; L80V, L90M, G140K, K263R n = 1</td>
</tr>
<tr>
<td>With appropriately timed CAB LA doses and expected plasma CAB levels (Group D)</td>
<td>4</td>
<td>K103N, R222K n = 1; C268R, G138R, V116L n = 2</td>
</tr>
</tbody>
</table>

**Landovitz. NEJM. 2021;385:595**

### HPTN 084: Incident HIV Infections With Cabotegravir

**Infection at baseline**

<table>
<thead>
<tr>
<th>Infection at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection in the absence of CAB LA injection</td>
</tr>
</tbody>
</table>

**Matsukawa. IAS 2021. Abstr PECLB25.**

<table>
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<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline CAB Dosed</strong></td>
<td><strong>CAB LA alone (N)</strong></td>
<td><strong>CAB LA + 12-week overlay</strong></td>
<td><strong>CAB LA + 12-week overlay (TDF/FTC)</strong></td>
<td><strong>CAB LA + 12-week overlay (TDF/FTC)</strong></td>
<td><strong>CAB LA + 12-week overlay (TDF/FTC)</strong></td>
<td><strong>CAB LA + 12-week overlay (TDF/FTC)</strong></td>
</tr>
<tr>
<td><strong>First positive visit</strong></td>
<td><strong>First positive visit</strong></td>
<td><strong>First positive visit</strong></td>
<td><strong>First positive visit</strong></td>
<td><strong>First positive visit</strong></td>
<td><strong>First positive visit</strong></td>
<td><strong>First positive visit</strong></td>
</tr>
</tbody>
</table>

**Nucleic acid INSTI mutations in CAB arm**

HIV detection via routine diagnostic assay
- Designed in patients receiving CAB LA + HIV-1
- RNA testing as primary HIV screen will be evaluated in open label extension
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 May Be Periodic

PrEP in Pregnancy

- F/TDF as PrEP is considered generally safe for pregnant and breastfeeding women
- F/TDF has been widely used for treatment of HIV and continued during pregnancy
- The data on pregnancy outcomes in the Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to these medications
- Both the FDA documentation and the perinatal antiretroviral treatment guidelines permit off-label use in pregnancy.
- Providers should discuss available information about potential risks and benefits of beginning or continuing PrEP during pregnancy so that an informed decision can be made.
"On-Demand" PrEP

- IPERGAY trial found that taking PrEP on a 2-1-1 schedule reduced risk of HIV infection by 86% in MSM - only F/TDF

![PrEP Schedule]

Same Day PrEP Prescribing

- For all patients, safely initiating PrEP requires determination of HIV status and assessment of renal function if they are on oral PrEP
- Some patients may have time or work constraints that impose a significant burden to return to the clinic a week or two after evaluation for a prescription visit.
- Other patients report risk behaviors that put them at substantial risk of acquiring HIV infection in the time between visits for evaluation and PrEP prescription

To use a same-day PrEP initiation protocol, the clinic must be able to:

- Conduct point-of-care HIV testing, ideally with an ag/ab fingerstick or other blood test.
- Draw blood for laboratory creatinine and HIV testing when same day HIV and creatinine test results are not available
- Provide assistance for eligible patients to enroll in health insurance, or medication assistance programs
- Provide rapid follow-up contact for patients whose laboratory test results indicate HIV infection or renal dysfunction • Provide scheduled follow-up care appointments
- Have clinicians available to dispense or prescribe oral PrEP medication, to administer a gluteal intramuscular injection of CAB,
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
- PrEP: Pre-Exposure Prophylaxis
  - National Clinician Consultation
  - http://ncc.ucsf.edu/clinician-consultation/prep-pro-exposure-prophylaxis
THANK YOU!