HIV Prevention in Primary Care Practice: Focus on PrEP and PEP

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ADVANCING LGBTQ HEALTH

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Continuing Medical Education Disclosure

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HIV Overview: 2017

1.1 million people in the U.S. are living with HIV.

1 in 7 people with HIV are unaware of their infection.

8 of the 10 states with the highest rates of new HIV diagnoses are in the South.

From 2005-2014, new HIV diagnoses in the U.S. decreased by 19%, but increased among men who have sex with men (MSM).

Less than 50% of people in the U.S. have ever been tested for HIV.

The CDC recommends everyone ages 13-64 get tested for HIV at least once.

Testing

Early diagnosis

Engagement in care
Clinical Practices to Improve HIV Prevention
Basic Steps to Improve HIV Prevention in Clinical Settings

- Universal HIV Screening
  - HIV Positive
    - HIV care / antiretroviral therapy / Counseling / Adherence
  - HIV Negative
    - Safer sex
    - Address STIs
    - PEP or PrEP
    - Counseling / Adherence

Reduce HIV Incidence

(USPSTF, 2013 and CDC, 2010)
PEP and PrEP

- Antiretroviral (ART) therapy not only helps people living with HIV. It also plays a role in preventing transmission of the virus.

- **Post-exposure prophylaxis (PEP):** PEP involves taking a short course of ART drugs, usually for a month, after a high-risk exposure. To be most effective, PEP should be started immediately after possible exposure, waiting no more than 72 hours.

- **nPEP** refers to when PEP is prescribed after high risk sexual exposure rather than occupational exposure.

- No randomized, placebo-controlled clinical trial of nPEP has been conducted. However, data relevant to nPEP guidelines are available from animal transmission models, perinatal clinical trials, observational studies of health care workers receiving prophylaxis after occupational exposures, and observational and case studies of nPEP use.

- Newer data continue to support the assertion that nPEP initiated soon after exposure and continued for 28 days with sufficient medication adherence can reduce the risk for acquiring HIV infection after nonoccupational exposures.
nPEP

- Health care providers should evaluate persons rapidly for nPEP when care is sought \( \leq 72 \) hours after a potential non-occupational exposure that presents a substantial risk for HIV acquisition.
- All persons considered for nPEP should have determination of their HIV infection status by HIV testing, preferably by using rapid combined Ag/Ab, or antibody blood tests.
- If rapid HIV blood test results are unavailable, and nPEP is otherwise indicated, it should be initiated without delay and can be discontinued if the patient is later determined to have HIV infection already or the source is determined.
- All persons offered nPEP should be prescribed a 28-day course of a 3-drug antiretroviral regimen.
  - The preferred regimen for otherwise healthy adults and adolescents:
  - tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with emtricitabine (200 mg) once daily plus raltegravir (RAL) 400 mg twice daily or dolutegravir (DTG) 50 mg daily.
nPEP

- All persons evaluated for possible nPEP should be provided any indicated prevention, treatment, or supportive care for other exposure-associated health risks and conditions (e.g., bacterial sexually transmitted infections, traumatic injuries, hepatitis B virus and hepatitis C virus infection, or pregnancy).

- All persons who report behaviors or situations that place them at risk for frequently recurring HIV exposures (e.g., injection drug use, or sex without condoms) or who report receipt of ≥1 course of nPEP in the past year should be provided risk-reduction counseling and intervention services, including consideration of pre-exposure prophylaxis PrEP.
PrEP

- PrEP is an HIV prevention tool in which an HIV-negative person takes antiretroviral medication to reduce the risk of contracting HIV. Currently, the available form of PrEP entails taking the pill Truvada, which is made of two drugs—tenofovir and emtricitabine. When these meds build up in the human body, they can stop HIV from replicating and establishing an infection.

- PrEP was approved in 2012 by the U.S. Food and Drug Administration (FDA) with the requirement that it be used every day, even during periods of minimal or low-risk sexual activity. Future studies are exploring intermittent dosing strategies (for example, using PrEP only during high-risk periods). Researchers are also looking into injectable, long-lasting forms of PrEP as well as different medications that could be used as PrEP.
PrEP

- The Centers for Disease Control and Prevention (CDC) recommends PrEP for those at high risk of HIV, including:
  - Those in a relationship with an HIV-positive partner.
  - Men who don’t use condoms when having sex with men.
  - Men who have been diagnosed with a sexually transmitted infection (STI) in the past six months and who are not in a mutually monogamous relationship with an HIV-negative partner.
  - Heterosexuals who don’t always use condoms for sex with partners who are themselves at high risk for HIV.
  - Anyone who, in the past six months, has shared equipment when injecting illicit drugs or who has been in an injection drug treatment program.
Reaching The Tipping Point

A tipping point is the moment when the momentum for change becomes unstoppable.....
Who Meets the CDC Guidelines?

1,232,000 People Estimated Eligible for PrEP in the US

- 1 in 4 MSM
- 1 in 5 IDU
- 1 in 200 Heterosexual

PrEP scale up has been slow in the United States

- **2010** – Publication of first 2 studies supporting PrEP
- **2012** – PrEP approved by the FDA
- **2014** – 3,253 people have started PrEP
- **2015** – ~22,000 people on PrEP
- **2017-?**

Providers Report Barriers to Uptake

- Difficult to determine eligibility
- Adherence concerns
- Risk compensation concerns, e.g. more unprotected sex
- Possible side effects
- Uncertain about insurance coverage
- Implementation concerns – how to fit PrEP into clinical practice

Adapted from slide by Sarah Calabrese. (Adams et al. 2015; Blumenthal et al., 2015; Karris et al., 2014; Krakower et al., 2014; Mullins et al., 2015; Sharma et al., 2014)
Basic Steps to Improve HIV Prevention in Clinical Settings

Universal HIV Screening

HIV Positive
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Reduce HIV Incidence

HIV Negative
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(USPSTF, 2013 and CDC, 2010)
PrEP: The Basics

- PrEP refers to the use of antiretroviral medication by HIV-uninfected people for the purpose of preventing HIV infection.
- Once daily, oral tenofovir-emtricitabine is the only medication currently FDA-approved for PrEP.
- CDC and WHO both recommend PrEP for individuals with a high risk of HIV infection.
Antiretrovirals play a central role in HIV treatment and prevention.

**HIV-positive persons**
- Individual health benefit (START, TEMPRANO)
- Prevention of transmission to others (HPTN 052)

**HIV-negative persons**
- PrEP for those at highest risk
Pre-exposure prophylaxis (PrEP)

- Oral or topical antiretrovirals taken in a continuous or episodic manner
- Once-daily oral tenofovir-emtricitabine approved for PrEP by the FDA
- Does not require the knowledge or cooperation of one’s partners
RCTs have demonstrated the efficacy of oral PrEP in several groups.

**Men who have sex with men** (iPrEX, N Engl J Med 2010)
- **Population:** 2,499 MSM and transgender women in 6 countries
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** Reduced HIV acquisition by 44%

- **Population:** 4,747 serodiscordant couples in Kenya and Uganda
- **Intervention:** Oral tenofovir-emtricitabine or tenofovir alone
- **Results:** Reduced HIV acquisition by 67-75%

- **Population:** 1,219 heterosexual men and women in Botswana
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** Reduced HIV acquisition by 62%
2 RCTs in African women have not shown a benefit to oral PrEP.

- **Population:** 2,120 women in sub-Saharan Africa
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** No HIV risk reduction with PrEP

**VOICE (N Engl J Med 2015)**
- **Population:** 5,029 women in sub-Saharan Africa
- **Intervention:** Oral tenofovir-emtricitabine, oral/vaginal tenofovir
- **Results:** No HIV risk reduction with PrEP

In VOICE and FEM PrEP, fewer than 50% of participants ever took the study drug.
Imperfect adherence may be less forgiving for women.

Time to maximal tissue tenofovir levels with daily use

- Cervicovaginal tissue
- Rectal tissue

Does PrEP work in transgender women?

- No benefit in 339 transgender women in a post-hoc analysis of iPrEX
- 18% of transgender women had protective drug levels, compared to 36% of MSM.
- No transgender women who contracted HIV had detectable drug levels at the time of diagnosis.
- 0 infections occurred in transgender women taking 4 or more doses of PrEP per week.
- **Bottom line:** PrEP can work, but adherence is crucial.

PrEP Is Effective: Adherence Is Critical

Pearson correlation: 0.86 (P=0.003).

HIV acquisition is rare in MSM taking ≥ 4 doses of PrEP per week.

In the real world, PrEP may work at least as well as in RCTs.

**PROUD (Lancet 2015)**
- **Population**: 545 high-risk MSM in the United Kingdom
- **Intervention**: Immediate or deferred oral tenofovir-emtricitabine
- **Results**: Reduced HIV acquisition by 86%

**TDF2 OLE (IAS 2015)**
- **Population**: 229 men and women in Botswana
- **Intervention**: Oral tenofovir-emtricitabine
- **Results**: 0 HIV infections; 5-6 expected

**Kaiser (Clin Infect Dis 2015)**
- **Population**: 657 people in San Francisco, predominantly MSM
- **Intervention**: Oral tenofovir-emtricitabine
- **Results**: 0 HIV infections; ~9% incidence expected
PrEP is safe.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PrEP</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>69%</td>
<td>70%</td>
<td>0.50</td>
</tr>
<tr>
<td>Any serious event</td>
<td>5%</td>
<td>5%</td>
<td>0.57</td>
</tr>
<tr>
<td>Grade 3 or 4 events</td>
<td>12%</td>
<td>13%</td>
<td>0.51</td>
</tr>
<tr>
<td>Discontinuation of study drug</td>
<td>6%</td>
<td>6%</td>
<td>0.49</td>
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As Safe as Aspirin....

https://www.sciencedaily.com/releases/2016/01/160114110954.htm
PrEP is not foolproof, even with optimal adherence.

- 43-year-old man who developed HIV infection after 24 months on PrEP
- Clinical, pharmacy, and pharmacokinetic data indicated adherence to tenofovir-emtricitabine.
- HIV infection featured multi-class resistance (NRTI, NNRTI, INSTI)
- Failure of PrEP was likely due to exposure to a drug-resistant virus.

Take-home points

- Oral tenofovir-emtricitabine substantially reduces the risk of HIV infection if taken regularly.
- Serious adverse events were not more common with PrEP than with placebo in clinical trials.
- Injectable formulations, alternative oral drugs, and vaginal rings for PrEP are under development.
Case Studies in PrEP Management
Case 1

- 24 year-old man referred from STI clinic
- 5 male sexual partners per month; engages in oral and anal sex; condom use inconsistent
- No chronic medical problems
- No prior sexually-transmitted infections
- Physical examination unremarkable
- HIV and STI testing one month ago was negative
- Is he a candidate for PrEP?
Is he a candidate for PrEP?

- Yes; according to the CDC, MSM who fulfill the following criteria are candidates:
  - Adult man
  - Without acute or established HIV infection
  - Any male sex partners in past 6 months
  - Not in a monogamous partnership with a recently tested, HIV-negative man
  
  **AND at least one of the following**
  
  - Any anal sex without condoms (receptive or insertive) in past 6 months
  - Any STI diagnosed or reported in past 6 months
  - Is in an ongoing sexual relationship with an HIV-positive male partner

Who is “high risk?”

**MSM**
- Condomless anal sex
- Recent sexually-transmitted infection
- HIV-infected partner

**Heterosexual adults**
- Condomless sex with a partner who injects drugs
- A bisexual man
- HIV-infected partner

**Injection drug users**
- Use of shared injection equipment

Core for HIV Prevention: Implementing Quality Systems

- History of sexual health and risks
  - Are you sexually active?
  - Who do you have sex with?
  - How many people in the past six months?
  - Do you engage in anal receptive or penetrative sex?
  - Have you had an STI in the past year?

- Those at high risk, should have HIV and STI screening 3-4 times per year.
Which tests must be sent before starting PrEP?

A. HIV antibody, hepatitis B surface antibody, urinalysis
B. HIV antibody, hepatitis B surface Ag and Ab, serum creatinine
C. HIV RNA, hepatitis B surface antibody, urinalysis
D. HIV RNA, hepatitis B surface antigen, serum creatinine
PrEP prescribing guidelines

1. **Determine eligibility**: Document negative HIV test and high risk of infection, confirm creatinine clearance > 60 mL/min

2. **Assess for conditions of concern**: HBsAg/HBsAb for everyone, pregnancy test for fertile women

3. **Prescribe**: Tenofovir-emtricitabine, 1 tablet by mouth daily (< 90-day supply)

4. **Monitor**: Creatinine, HIV status, pregnancy status every 3 months; STI screening every 6 months; counsel regarding risk reduction

What would you tell him about side effects?

- Nausea may occur with initiation of tenofovir-emtricitabine; it typically resolves with time.
- Kidney injury occurs rarely (2% in iPrex).
  - Periodic monitoring is obligatory.
  - Abnormalities usually resolve with drug discontinuation.
- A small decrease in bone mineral density may occur; the clinical significance of this is unknown.
- Antiretroviral resistance is unlikely but possible.
How would you counsel about…

- The length of time on PrEP before he is maximally protected?
  - 7 days, when maximal levels are achieved in rectal tissue. Longer in vaginal tissue.

- If stopping PrEP, how long he should take it beyond his last high-risk sexual encounter?
  - 4 weeks, by analogy to PEP?
My talking points with a new patient

- PrEP efficacy and importance of adherence
- Periodic HIV testing and creatinine checks are mandatory.
- The risk of HIV drug resistance if he/she becomes infected with HIV while on PrEP
- Side effects: GI, renal, bone
- What we think about time to maximal protection, time to continue after last high-risk encounter
- PrEP does not protect against other STIs, except perhaps HSV (Celum, Ann Intern Med, 2014).
Case 2

- 38 year-old man referred after diagnosis of rectal HSV; eager to start PrEP
- 1-2 new sexual encounters per month, mostly with male partners
- Physical examination unremarkable
- HIV antigen/antibody negative, HBsAg negative, creatinine 0.89 (eGFR > 60)
- Unprotected receptive anal sex 1 day ago
How would you manage his recent, high risk exposure in the context of PrEP?

A. Send an HIV viral load and start PrEP if it’s negative

B. Wait 4 weeks, then recheck an HIV antibody/antigen test and start PrEP if negative

C. Start PrEP now

D. Start post-exposure prophylaxis with tenofovir-emtricitabine + dolutegravir, then continue PrEP alone after 28 days
Case 2, follow-up

- He starts 3-drug PEP, then continues PrEP alone after 28 days.
- At a 3-month follow-up, his HIV test is negative, and his creatinine is stable.
- His sexual behavior is unchanged.
- He has heard that “on-demand” PrEP (that taken only in the context of sex) can also reduce HIV transmission and wants to stop daily use.
Would you…

A. Endorse “on-demand” (episodic) PrEP?
B. Recommend that he continue daily PrEP?
IPERGAY supports “on-demand” PrEP in MSM with frequent sex

- **Population**: 400 MSM reporting unprotected sex with 2 or more partners in the past 6 months
- **Intervention**: Event-driven PrEP versus placebo
- **Results**: 86% reduction in HIV incidence
- **IPERGAY regimen**: 4 pills, 3 doses over 3 days

HIV acquisition is rare in MSM taking ≥ 4 doses of PrEP per week.

Case 3

- A 27 year-old gay man in generally good health presents to establish care.
- He has had a cold with fever, sore throat, and swollen glands for 2 days; taking frequent ibuprofen.
- Unprotected anal sex with 1 primary and 2 occasional male sex partners; most recently 10 days ago.
- HIV antibody and HBsAg negative; creatinine normal.
- Interested in PrEP.
Would you…

A. Start PrEP
B. Send an HIV viral load and base the PrEP decision on the result
C. Wait until his cold has improved and he’s stopped ibuprofen; then start PrEP
D. Start PEP, then transition to PrEP after 28 days
Remember features of acute HIV

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>FREQUENCY (%)</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>77</td>
</tr>
<tr>
<td>Myalgia</td>
<td>52</td>
</tr>
<tr>
<td>Rash</td>
<td>51</td>
</tr>
<tr>
<td>Headache</td>
<td>47</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>43</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>41</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
</tr>
</tbody>
</table>

Case 3, follow-up

- HIV RNA 2.5 million; antibody seroconversion within one week

- Acute HIV and PrEP:
  - Patients may be symptomatic from acute HIV but have negative serologic testing (i.e., in the “window period”).
  - In clinical trials of PrEP, drug resistance has been seen in those who were in the window period at enrollment.
  - Use of the 4th-generation antibody/antigen test decreases but does not eliminate the window period.
  - Send an HIV RNA if in doubt.
Resistance is rare but occurs in those who are in the window period upon PrEP initiation.

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>RESISTANCE AMONG THOSE INFECTED AT ENROLLMENT</th>
<th>RESISTANCE AMONG THOSE INFECTED LATER IN THE STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrex</td>
<td>1 of 8 in the placebo arm 2 of 2 in the PrEP arm</td>
<td>0 of 64 in the placebo arm 0 of 36 in the PrEP arm</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>0 of 6 in the placebo arm 2 of 8 in the PrEP arms</td>
<td>0 of 52 in the placebo arm 0 of 30 in the PrEP arms</td>
</tr>
<tr>
<td>TDF2</td>
<td>0 of 2 in the placebo arm 1 of 1 in the PrEP arm</td>
<td>1 of 24 in the placebo arm 0 of 9 in the PrEP arm</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1 of 16 in placebo arms 5 of 11 in PrEP arms</td>
<td>1 of 140 in placebo arms 0 of 75 in PrEP arms</td>
</tr>
</tbody>
</table>

Of 7 subjects who had drug resistance, 5 were unknowingly infected with HIV when they started PrEP.
Case 4

- 48 year-old man referred for PrEP
- Obesity, hypertension, sleep apnea
- Monogamous with one male partner who is HIV infected but virologically suppressed
- HIV antibody/antigen and HBsAg negative; creatinine 1.09 (eGFR > 60)
- He asks if PrEP for him is worthwhile since his partner is undetectable.
Would you recommend PrEP?

A. Yes
B. No
The utility of PrEP on top of HIV treatment is unknown.

**No**
- HIV treatment prevents transmission; the additional benefit of PrEP may not outweigh its risks, however small.

**Yes**
- Viral rebound may occur because of poor ART adherence or other reasons.
- People may not be monogamous.
- CDC guidelines support PrEP in this context.
ART substantially reduces HIV transmission.

- **HPTN 052 study**: HIV treatment reduced HIV transmission by 96% in serodiscordant couples (incidence with ART 0.1 [0-0.4] per 100 person-years)\(^{(1)}\)

- **Opposites Attract study**: 0 HIV transmissions in 152 serodiscordant MSM couples despite ~6,000 episodes of condomless anal sex (incidence 0 [0-4] per 100 couple-years)\(^{(2)}\)

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A middle path: PrEP as a bridge to ART

- **Study**: Partners PrEP Demo Project
- **Population**: 1,013 heterosexual serodiscordant couples
- **Intervention**: PrEP until seropositive partner on ART for 6 months
- **Results**: 96% risk reduction compared to a historical control (incidence = 0.2 [0-1.3] per 100 person-years)

Case 5

- A 42-year-old transgender woman presents with rectal pain and discharge.
- She reports having multiple male sexual partners with whom she engages in receptive anal sex, often without condoms.
- Rectal NAAT testing is positive for gonorrhea; she receives ceftriaxone and azithromycin, and her symptoms resolve.
- At follow-up, you suggest she consider PrEP for HIV prevention.
- She has been using an estradiol patch for 5 years and is concerned that PrEP may interact with her hormonal therapy.
Which is true about PrEP and hormonal therapy?

A. Estradiol lowers the concentrations of tenofovir-emtricitabine, so the dose of PrEP should be doubled.

B. PrEP lowers the concentrations of estrogen in the body, so her estradiol dose may need to be increased.

C. Use of PrEP along with hormonal therapies is contraindicated.

D. There are no known drug interactions between tenofovir-emtricitabine and cross-sex hormonal treatment.
Take-home points

- Daily tenofovir-emtricitabine substantially reduces the risk of HIV infection in individuals at high risk.
- Serious side effects are rare; renal function must be monitored periodically while on PrEP.
- Before starting PrEP, test for acute HIV if there are any suggestive clinical signs or symptoms.
- There is no evidence of adverse pregnancy outcomes among women who conceive on tenofovir-emtricitabine.
Comprehensive PrEP Program Elements

- Comprehensive PrEP Services
  - PrEP medication access
  - Primary care visits
  - Linkage to social support services
  - Mental illness & substance use/abuse services
  - Adherence counseling and support
  - Health insurance enrollment and plan navigation
  - HIV, HCV and STI screening
  - HIV risk reduction counseling
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