Preventing HIV with PrEP: A Clinical Update

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Continuing Medical Education Disclosure

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- **Disclosure**: No relevant financial relationships. Presentation does not include discussion of off-label products.

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Objectives

1. Describe clinical approaches to common dilemmas in PrEP management.
2. Apply findings from research to clinical cases.
3. Understand the status of new innovations in PrEP.
A quick review of PrEP basics

- Indicated for persons with a high HIV risk
- Daily tenofovir-emtricitabine is FDA-approved

**Baseline testing**
- HIV antibody
- HBsAg
- Creatinine (to calculate creatinine clearance)
- Pregnancy test

**Monitoring:**
- **3 months:** HIV antibody, pregnancy test, creatinine
- **6 months:** STI screening
My talking points with a new patient

- PrEP efficacy and importance of adherence
- Periodic HIV testing and creatinine checks are mandatory.
- 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 sexually transmitted infections.
Case 1

- A 27 year-old woman presents for a well visit.
- She is sexually active with one male partner who has HIV and intermittently takes ART.
- They do not consistently use condoms.
- She is interested in PrEP.
- A medical student working with you says, “I heard PrEP doesn’t work in women.”
Polling Question: Which statement about women and PrEP is true?

a) PrEP with oral tenofovir-emtricitabine does not protect against HIV in women.

b) Oral contraceptives reduce the effectiveness of PrEP.

c) A dapivirine-impregnated vaginal ring reduces the risk of HIV infection.

d) The pharmacokinetics of tenofovir are the same in rectal and cervicovaginal tissue.
Studies of oral PrEP in women have shown disparate results.

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

- **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
Differences in study outcomes likely relate to adherence.


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But biological differences may also play a role.

Time to maximal tissue tenofovir levels with daily use

Cervicovaginal tissue

Rectal tissue

A vaginal dapivirine ring reduced HIV acquisition in African women.

- **Study**: MTN-020 ASPIRE
- **Population**: 2629 African women
- **Intervention**: Dapivirine-impregnated vaginal ring or placebo ring
- **Results**: 27% HIV risk reduction (56% in women older than 21 years)

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
- He asks if he could take PrEP in an “event-driven” manner (i.e., only in conjunction with sex) to reduce costs and the risk of side effects.
Polling Question:
Would you recommend...

a) Event-driven PrEP?
b) Daily PrEP?
c) Something else?
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.

PrEP dosing varied in IPERGAY.

Case 3

- 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. She also asks if PrEP has been studied in transgender women.
Polling Question: 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.
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.

Case 4

- A 34 year-old man is referred for PrEP.
- He is sexually active with 1 primary and 2 occasional male partners.
- He was treated for secondary syphilis 3 months ago.
- Past medical history includes IgA nephropathy.
- An HIV antibody/antigen test is negative. Serum creatinine is 1.72 (eGFR ~ 40).
Polling Question: What would you recommend for PrEP for this patient?

a) Tenofovir-emtricitabine (TDF-FTC)
b) Tenofovir alafenamide-emtricitabine (TAF-FTC)
c) Maraviroc
d) No PrEP
There is insufficient evidence to recommend TAF for PrEP.

<table>
<thead>
<tr>
<th>Animal Data</th>
<th>Human data</th>
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<tr>
<td>▪ 12 macaques exposed rectally to SHIV</td>
<td>▪ 8 healthy women administered a single dose of TAF</td>
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<td>▪ 6 animals given PrEP with TAF-FTC were protected.</td>
<td>▪ Drug levels measured in blood and tissue from the cervix, vagina, and rectum</td>
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<td>▪ 6 control animals became infected.</td>
<td>▪ Tenofovir concentrations were undetectable in 83% of tissue samples.</td>
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There is insufficient evidence to recommend maraviroc for PrEP.

- **Study:** Phase II study of maraviroc for PrEP
- **Population:** 406 high-risk MSM
- **Intervention:**
  - Maraviroc
  - Maraviroc + emtricitabine
  - Maraviroc + tenofovir
  - Tenofovir + emtricitabine
- **Results:**
  - Maraviroc was safe and well-tolerated.
  - 5 HIV infections occurred, all in maraviroc arms; 4 associated with low or undetectable drug levels.

Topical and injectable formulations are in development.

Rectal microbicides

Injections of long-acting PrEP (cabotegravir?)
Case 5

- 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.
Polling Question: Would you recommend PrEP for this patient?

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.
- Some patients desire an HIV prevention method they themselves control.
- 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)\(^{(1)}\)
  - **IAS 2015**: 0 transmissions after the HIV-infected partner was stably suppressed on ART.

- **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)\(^{(2)}\)

Case 6

- A 21 year-old man presents in follow-up after treatment for rectal gonorrhea.
- He is sexually active with 5 male partners per month; he rarely uses condoms.
- You recommend PrEP and discuss the risks and benefits of this intervention.
- He is concerned about decreased bone mineral density, as his grandfather just fractured his hip.
Polling Question: Which statement is true?

a) Loss of bone mineral density from PrEP reverses with discontinuation of the drug.

b) Bisphosphonates prevent the loss of bone mineral density from PrEP.

c) PrEP increases the risk of fracture by 1-2%, but the absolute risk is very low.

d) PrEP is contraindicated in patients with a family history of osteoporosis.
Bone mineral density rebounds after stopping PrEP.

- **Study:** Sub-study of iPrEx
- **Population:** 498 MSM and transgender women
- **Methods:** DXA every 24 weeks, measurement of tenofovir drug levels
- **Results:** Bone mineral density recovered in the hip and spine within 6-18 months

Case 7

- A 36 year-old woman and her 39 year-old husband present to discuss conception.
- He’s HIV infected and virologically suppressed on ART; she’s HIV-negative.
- They want to conceive a child and cannot afford sperm washing.
- They ask if you would recommend PrEP for her and condomless sex in this situation.
Polling Question:
Would you recommend PrEP and condomless sex in this setting?

a) Yes
b) No
PrEP may be part of a safe conception strategy.

- No increased birth defects with tenofovir-emtricitabine among women in the Antiretroviral Pregnancy Registry
- No difference in birth outcomes among women receiving PrEP versus placebo in the Partner PrEP study
- However, modeling suggests PrEP adds little, assuming ART and other factors are optimized.

Case 8

- A 56 year-old man presents in follow-up, 14 months after starting PrEP.
- He reports perfect medication adherence.
- He is concerned about a news report he read which described the development of drug-resistant HIV in a man who was highly adherent to PrEP.
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

- Daily tenofovir-emtricitabine substantially reduces the risk of HIV infection in individuals at high risk.
- No other medications are FDA approved for PrEP at this time, but several in development.
- Bone mineral density appears to recover after stopping PrEP.
- There is no evidence yet of adverse pregnancy outcomes among women who conceive on tenofovir-emtricitabine.

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Thank you

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