ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals
PrEP

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• 1. Explain the rationale behind PrEP
• 2. Review PrEP guidelines and studies, along with their implications for practice
• 3. Discuss challenges and controversies in PrEP therapy
Faculty and Planning Committee Disclosures
Please consult your program book.

No financial disclosures

**Off-Label Disclosure**
The following off-label/investigational uses will be discussed in this presentation:

- PrEP therapies currently in development
How many individuals have you prescribed PrEP for?

1. 0 I am not a prescriber
2. 0 I am a prescriber
3. 1-5
4. 6-20
5. >20
Overview

PrEP questions:

- Who needs PrEP?
- Is PrEP effective?
- Is PrEP safe?
- Does PrEP lead to increased risk behaviors/STI’s?
- What is in the PrEP pipeline?
Definitions

**HIV PEP (Post Exposure Prophylaxis)**

The use of antiviral medication, initiated **AFTER** exposure, to prevent HIV infection - short term

Tenofovir/Emtricitabine (Truvada) plus raltegravir (Isentress) or dolutegravir (Tivicay)

- **HIV PrEP (Pre-exposure prophylaxis)**

  Use of antiviral medication in an HIV negative person, initiated **BEFORE** exposure, to prevent HIV infection

  Tenofovir/emtricitabine (TDF/FTC) = Truvada
Jamal

24 yo AA gay male; initially seen 5 months ago when he presented for PEP after an encounter of condomless anal sex with partner of unknown HIV status after a night of heavy drinking

Comes in today presenting again for PEP, due to another condomless encounter he had last night with someone of unknown HIV status. Has been mostly consistent with condoms but sometimes “I just get caught up in the moment”
What do you recommend regarding PrEP?

1. I would recommend he start PrEP today

2. I would recommend PEP, but I would not recommend PrEP at this point as he is not high risk.

3. I would recommend PEP and then immediate transition to PrEP if he agrees to PrEP.

4. I would recommend PEP and then refer him for counseling to reduce his risk prior to considering PrEP.
Estimated annual HIV infections in the U.S. declined **18%**

Between 2008 - 2014 infections fell from 45,700 to 37,600

- **56%** decline among people who inject drugs
- **36%** decline among heterosexuals
- **26%** decline among gay and bisexual men aged 35-44 years
- **18%** decline among gay and bisexual men aged 13-24 years

Gay and bisexual men remain most affected

- **37,600** New HIV Infections in 2014
  - Heterosexuals: 8,600 infections (23%)
  - People who inject drugs: 1,700 infections (5%)
  - Gay and bisexual men who inject drugs: 1,100 infections (3%)
  - Gay and bisexual men: 26,200 infections (70%)
CDC: HIV Incidence down 18% from 2008 to 2014, BUT

New HIV infections remained stable or decreased in many MSM, but rose in MSM aged 25-34.

Further breakdown of this category: the rise is occurring in 24-27 yo
CDC Feb 2018

Rates have not decreased in Black MSM, and have risen in Latino MSM

66% of new infections in heterosexuals are AA

February 14, 2017.
HIV Diagnoses Among the Most-Affected Subpopulations, 2015—United States

- Black MSM: 10,315
- White MSM: 7,570
- Hispanic/Latino MSM: 7,013
- Black Women, Heterosexual Contact: 4,142
- Black Men, Heterosexual Contact: 1,926
- Hispanic/Latina Women, Heterosexual Contact: 1,010
- White Women, Heterosexual Women: 968

Shifting Prevention Strategies

1980’s - 2008: Education/behavior change/condoms/clean needles

Now: Education/behavior change/condoms/clean needles, but also:

1. TasP (Treatment as Prevention)
2. HIV Testing and linkage to care
3. PEP
4. PrEP
FDA Approval

• In July 16, 2012, FDA approved the use of tenofovir (300mg) + emtricitabine (200 mg) (TDF/FTC or Truvada®) for HIV PrEP in adults who are at high risk for becoming HIV-infected

• Dosage: One tablet once daily taken orally with or without food
PrEP guidelines
# Table 1: Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th></th>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Persons Who Inject Drugs</th>
</tr>
</thead>
</table>
| **Detecting substantial risk of acquiring HIV infection** | HIV-positive sexual partner  
Recent bacterial STI
High number of sex partners
History of inconsistent or no condom use
Commercial sex work | HIV-positive sexual partner  
Recent bacterial STI
High number of sex partners
History of inconsistent or no condom use
Commercial sex work | HIV-positive injecting partner
Sharing injection equipment |
| **Clinically eligible** | Documented negative HIV test result before prescribing PrEP
No signs/symptoms of acute HIV infection
Normal renal function; no contraindicated medications
Documented hepatitis B virus infection and vaccination status | | |
| **Prescription** | Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply | | |
| **Other services** | Follow-up visits at least every 3 months to provide the following:
HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment
At 3 months and every 6 months thereafter, assess renal function
Every 3-6 months, test for bacterial STIs | Do oral/rectal STI testing
For women, assess pregnancy intent
Pregnancy test every 3 months | Access to clean needles/syringes and drug treatment services |

STI: sexually transmitted infection

1. Gonorrhea, chlamydia, syphilis for MSM including those who inject drugs
2. Gonorrhea, syphilis for heterosexual women and men including those who inject drugs

Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2017 Update Clinical Practice Guideline
Provider-Patient Barriers

- Surveyed users of gay pick up website (n=1394)
- 42% are not comfortable discussing sex with PCP
- >80% have not discussed PrEP with PCP
- 75% don’t think their provider would prescribe PrEP
- **48% had condomless anal sex with 3 or more partners in 3 months**

Communication about risk behaviors and about PrEP in primary care is KEY

Krakow, et.al IAS 2015, Vancouver. Abstract TUPEC506
Is PrEP Effective?
iPREX Trial

- Phase 3, double-blind, randomized, placebo-controlled, 11 sites in 6 countries, n=2499

- Adult HIV(-) MSM or transgender women in the US, Peru, Ecuador, Brazil, Thailand, South Africa, 18 yo or older, at high risk of HIV acquisition

- Two study arms:
  - TDF/FTC (300mg/200mg) orally once daily
  - Placebo

- Primary Outcome: Prevention of HIV
- Outcome: 44% reduction in HIV acquisition (p <0.002)

## iPREX: HIV by Group and Drug Detection

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug Detection</th>
<th>HIV Infections</th>
<th>Incidence Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>No</td>
<td>64</td>
<td>3.86</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>No</td>
<td>33</td>
<td>4.04</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>Yes</td>
<td>3</td>
<td>0.35</td>
</tr>
</tbody>
</table>

### Relative Rate Reduction by use of FTC/TDF

91%

PrEP Works if You Take It — Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

Percentage of participants' samples that had detectable drug levels

Effectiveness (%)
How much adherence is enough?
iPrEx Open-Label Extension (OLE):
HIV Incidence and Risk Reduction by Detectable Drug

No new HIV infections in those who took 4 or more tabs per week

Grant RM, et al. 20th IAC. Melbourne, 2014. Abstract TUAC0105LB.
Drug concentration varies in different mucosal tissues

PrEP does not reach the same levels in vagina and cervix

Estimated that women need to take 6-7 doses/wk for efficacy

Role of the vaginal microbiome

- Healthy vaginal microbiome (lactobacillus predominant) is important to HIV prevention
- Vaginal dysbiosis - key factor in vaginal inflammation, epithelial barrier integrity and HIV acquisition
- Dysbiotic bacteria can metabolize TDF and dapivirine
  - CAPRISA 004 Tenofovir gel
    - Overall: 39% efficacy
    - Lactobacillus dominant: 61% efficacy
    - Dysbiotic: 18% efficacy
- Effect of dysbiosis on oral drug metabolism?

Nicole Klatt, plenary CROI 2018
Adherence may need to be significantly higher in IDU

- The Bangkok Tenofovir Study
  - DOT participants
  - 70% decrease in HIV
  - Higher adherence levels to get same protection as rectal exposure

Time to protection

- Time to maximum intracellular concentrations (healthy volunteers):
  - Rectal tissue: ~7 days
  - Blood: ~20 days
  - Cervico-vaginal tissue: ~20 days
  - Penile tissue: ???
  - Neo-vagina: ???

Infection with Multidrug Resistant HIV Despite Adherence to PrEP - 2 case reports

- Case report 1: 43 yo MSM, adherence verified by mass spectography and dried blood spot.
  

- Case report 2: MSM 20’s, hair samples showed adherence.
  
  mutations: K65R, M184V, K103S, E138Q, Y188L

**PrEP adherence, but exposed to virus from partners with extensive mutations**

Knox, D. et.al. CROI 2016, Boston, MA. #169aLB
HIV Acquisition despite adherence: case report

- 50 yo MSM, reported excellent adherence on PrEP (Adequate TDF levels at 6 and 8 mos)
- 8 months after starting PrEP
  
  Fever and dysuria
  
  HIV Ab+, HIV Ag and HIV RNA neg, HIV DNA neg
  
  PrEP stopped, HIV RNA developed 3 weeks later

- **No mutations on sequencing**

- During PrEP use
  
  38-70 anal sex partners per month, 2 episodes anal GC, 1 episode anal CT
  
  Drug use during sex (cocaine, amphetamine, GHB/GBL, mephedrone, ketamine)

Hoornenborg E, et al. CROI 2017. Seattle, WA. Poster #953
PrEP effectiveness takeaways:

Perfect adherence to PrEP is an excellent but not perfect predictor of PrEP success

Site of exposure dictates degree of adherence required/degree of forgiveness of missed doses

Tenofovir resistance in HIV+ is rare, but when present, can overcome HIV protection from PrEP with TDF/FTC
Is PrEP safe?
iPREX Results: Safety

TDF/FTC was well tolerated

- GI-Nausea (2% vs <1%) and weight loss >5% (2% vs 1%)
- No differences in severe (grade 3) or life-threatening (grade 4) laboratory abnormalities

Renal safety

- No cases of RTA
- 10 subjects (7 tdf/ftc, 3 placebo) discontinued for creatinine elevation, all normalized
  - 9 reinitiated treatment

Bone safety (BMD substudy)

- Small net decrease in spine and total hip BMD (<1%) vs placebo at 24 weeks, stable at 96 weeks
- BMD recovered after discontinuation of drug. No difference in fracture rates.

iPrEx OLE: Probability of eGFR Decreasing to <70 mL/min Within a Year

Jamal

24 yo AA gay male; initially seen 5 months ago when he presented for PEP after an encounter of condomless anal sex with a partner of unknown HIV status after a night of heavy drinking

Comes in today presenting again for PEP, due to another condomless encounter he had last night with someone of unknown HIV status. He states he has been mostly consistent with condoms but sometimes “I just get caught up in the moment”
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James is a 42 yo gay man who comes in asking for PrEP.

He is tired of feeling anxious that he will get infected every time he has sex.

He states that he is tired of using condoms, and wants to experience the intimacy that comes from not using them.
Would you prescribe PrEP for James?

1. Yes, I would prescribe PrEP.
2. No, I would not prescribe PrEP since he does not meet the guidelines for high risk.
3. I don’t know what I would do.
James

- Condom fatigue
- Intimacy
- Anxiety about becoming infected
- Control for receptive partners
• PrEP is a “demand-driven” intervention, meaning that “the indication for PrEP is that someone asks for it.” This implies that people are good at determining their own risk and that overly tight criteria for offering PrEP are unnecessary because people will self-regulate in terms of use and uptake.

• Robert Grant of UCSF
James, 6 months later

James states that he is doing well with PrEP, has a system so is not missing doses. He has no symptoms today and is feeling well.

On routine screening he is found to have anal chlamydia.
Does PrEP increase risk behavior/increase STIs?
iPrEx Study: Risk compensation

Condomless Receptive Anal Intercourse

Overall Patient Population

Patients (%)

Weeks

Emtricitabine/tenofovir DF
Placebo

Patients Who Believed They Were Receiving FTC/TDF

Patients (%)

Weeks

Emtricitabine/tenofovir DF
Placebo

P=0.30

P=0.44

PROUD study, IPERGAY study: no risk compensation

STI Data from Community-Based PrEP programs

<table>
<thead>
<tr>
<th></th>
<th>NYC SPARK (n=280)</th>
<th>The Demo Project (n=557)</th>
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<tbody>
<tr>
<td>STIs pre-PrEP</td>
<td>21%</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>STIs on PrEP</td>
<td>13-21% quarterly</td>
<td>18-25% quarterly</td>
</tr>
<tr>
<td>STIs that CDC guidelines* would have missed (asymptomatic at 3M and 9M)</td>
<td>77% at 3M; 68% at 9M</td>
<td>34% GC; 40% CT; 20% syphilis</td>
</tr>
<tr>
<td>Extrapigenital STIs</td>
<td>71-100% quarterly</td>
<td>83% GC; 76% CT</td>
</tr>
</tbody>
</table>

*Current CDC guidelines recommend STI screening q6mo and asking about symptoms quarterly

- Not screening extra-genital sites and only following the CDC’s current STI screening guidelines would miss or delay many STI diagnoses

Screening for STI’s on PrEP

CDC 2014 PrEP guidelines

- Every 3 months: STI symptom assessment
- Every 6 months: test for bacterial STI’s

CDC 2017 PrEP guidelines update:

- Every 3 to 6 months, test for bacterial STI’s

My guideline:

- Test for bacterial STI’s every 3 months, can consider every 6 month screening in individuals at lower STI risk
Increasing PrEP coverage increases screening, which increases diagnosis of asymptomatic STIs

At 40% PrEP coverage and 40% risk compensation, 42% of GC and 40% of CT infections would be avoided in the next 10 years

If STI screening is done quarterly instead of biannually: 50% further reduction in STI rates

Even 80% risk compensation with PrEP use would lead to a decrease in STI rates

Jenness SM, et al. CROI 2017. Seattle, WA. Poster #1034
James, one year later

James comes in for his routine follow up. He states PrEP is going well, and other than “a couple of missed doses” he has been perfect in his adherence to medication.

However, he finds that he is not that sexually active right now, and has heard that the medication can be taken “intermittently”. He wants to know if he can take PrEP only when he plans to have sex, instead of taking it every day if he doesn’t really need it.
**IPERGAY**

**Dosing Schedule: 1 Sexual Event**

- First evidence that an event-driven regimen was effective among high-risk MSM with **frequent** sex (median of 10 sex acts per month and 8 partners every two months).
  - Men were taking PrEP an average of three to four days per week.

- CDC: researchers do not yet know if this regimen will work among MSM who have sex less frequently or among other populations at high risk for HIV infection.

- CDC: urges people at substantial risk for HIV infection and their health care providers to continue to follow current CDC guidelines

Molina J, et al. CROI 2015; Seattle, WA. #23LB
Planning for the Pre-Event Dose: Social Network Survey

59% reported last sex was unplanned or planned only minutes in advance

Milagros

Milagros is a 26 yo transgender female who recently discovered that her boyfriend is HIV+ by finding a pill bottle and looking up the medication on Google.

She is anxious about confronting him, but also worried about getting HIV. She wants to know what she can do to stay safe, since she feels she can not ask him now to start using condoms when they had not been prior.
PrEP/HIV in transgender populations
Which of the following statements is FALSE?

1. Transgender women have higher rates of HIV infection than MSM
2. PrEP was as effective in Trans women as in MSM in the iPrEX study
3. There is less awareness of PrEP in the trans community than in the MSM community
4. Concerns about interactions with hormones lead some transwomen to prioritize hormones over PrEP
HIV/PrEP in trans populations

- Transgender women- ~21.7% HIV prevalence- 34.2 times higher than the general population

- Multilevel HIV vulnerabilities-Stigma, discrimination, violence victimization, limited access to housing, lack of employment opportunities that lead to higher rates of sex work

- PrEP uptake and awareness among TW has been low. Adherence of TW in iPrEX was 18%, and not correlated to risk. Lack of trans-inclusive marketing.

- Concerns about interactions with hormones lead some women to prioritize hormones over PrEP (and ART)

HIV/STI Risk for Trans Men

Even less known about TGM

- Prevalence of HIV 0-3%
- Prevalence of STIs 6-47%
- Sexual partners:
  - Females 30.4%
  - Males only 30.4%
  - Both females and males 34.8%
- Both anal/vaginal sex
- Low rates of condom use (30%)

(Herbst, 2007; Conare, 1997; Kenagy, 2002; Reisner, 2010; Rowniak, 2011; Sevelius 2009; Green, Medicine 94(41) 2015)

Slide courtesy of Dr A Radix
We need to improve outreach, and address social and structural barriers to PrEP

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 American – approximately 500,000 people...
- ...but only 1% of those – 7,000 African Americans were prescribed PrEP*

- 25% of people who could potentially benefit from PrEP are Latino – nearly 300,000 people...
- ...but only 3% of those – 7,600 Latinos were prescribed PrEP*

*Prescription data in this analysis limited to those filled at retail pharmacies or mail order services from September 2015 – August 2016; racial and ethnic information not available for one-third of the prescription data
The PrEP Pipeline

<table>
<thead>
<tr>
<th>Efficacy Trial</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaginal Ring</strong></td>
<td><strong>DMPV (MTN 025)</strong></td>
<td>Open-label trial of the once-monthly slow-release dapivirine vaginal ring; ongoing in 2,500 women in Malawi, South Africa, Uganda, Zimbabwe</td>
<td><strong>DMPV (MTN 025)</strong></td>
<td>Open-label trial of the once-monthly slow-release dapivirine vaginal ring; ongoing in 1,400 women in South Africa and Uganda</td>
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</tr>
<tr>
<td><strong>Antibody</strong></td>
<td><strong>AMP (QVTV 704/ HPTN 065)</strong></td>
<td>Randomized controlled trial of the VIRC01 antibody infused every two months; ongoing in 2,700 MSM and transgender men &amp; women in Brazil, Peru, Switzerland, US</td>
<td><strong>AMP (QVTV 704/ HPTN 065)</strong></td>
<td>Randomized controlled trial of the VIRC01 antibody infused every two months; ongoing in 1,500 women in Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe</td>
<td></td>
</tr>
<tr>
<td><strong>Oral PrEP</strong></td>
<td><strong>DISCOVER</strong></td>
<td>Randomized controlled trial of once-daily TAF/ as PrEP; ongoing in 5,400 MSM and transgender women in Austria, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, UK, US</td>
<td><strong>DISCOVER</strong></td>
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<td></td>
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<tr>
<td><strong>Long-Acting Injectable</strong></td>
<td><strong>HPN 083</strong></td>
<td>Randomized controlled trial of injectable cabotegravir every two months; ongoing in 4,500 MSM and transgender women in Argentina, Brazil, Peru, South Africa, Thailand, US, Vietnam</td>
<td><strong>HPN 084</strong></td>
<td>Randomized controlled trial of injectable cabotegravir every two months; ongoing in 3,200 women in Botswana, Kenya, South Africa, Uganda, Zimbabwe</td>
<td></td>
</tr>
<tr>
<td><strong>Preventive HIV Vaccine</strong></td>
<td><strong>AVAC/Gp120 w/MF59</strong></td>
<td>Randomized controlled trial of AVAC/Gp120 prime-boost with MF59 adjuvant, two doses over 12 months; ongoing in 5,400 men and women in South Africa</td>
<td><strong>AVAC/Gp120 w/MF59</strong></td>
<td>Randomized controlled trial of AVAC/Gp120 prime-boost with MF59 adjuvant, two doses over 12 months; ongoing in 5,400 men and women in South Africa</td>
<td></td>
</tr>
<tr>
<td><strong>Hormonal Contraceptives and HIV</strong></td>
<td><strong>DMPA/Levonorgestrel implant/Copper IUD</strong></td>
<td>Randomized open-label trial comparing HIV incidence and contraceptive benefits; ongoing in 7,000 women in Kenya, South Africa, Swaziland, Zambia</td>
<td><strong>DMPA/Levonorgestrel implant/Copper IUD</strong></td>
<td>Randomized open-label trial comparing HIV incidence and contraceptive benefits; ongoing in 7,000 women in Kenya, South Africa, Swaziland, Zambia</td>
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Summary

- PrEP is now part of a menu of evidence-based interventions to prevent HIV transmission.

- Awareness/interest/demand has risen dramatically in the past couple of years- we need more providers who are comfortable with prescribing PrEP

- We need to do better in reaching out to younger MSM, communities of color, trans men and women
Thank You!