Let's Talk PrEP: The rise of interventions for HIV prevention

Sean Kelly, MD
Assistant Professor, Vanderbilt Division of Infectious Diseases
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Disclosures

- None declared
Agenda

- What is PrEP?
- How effective is it?
- Why do we need it?
- Who benefits from PrEP?
- What are drawbacks?
- Who can prescribe?
- How to prescribe?
- The future of PrEP
But first, a case

62-year-old man presents to discuss primary prevention to reduce his risk of MI and stroke. He has a 30-pack-year smoking history (quit 2 years ago), is moderately overweight, and has well-controlled hypertension on HCTZ. What do you do?
Case 1

A: Encourage weight loss only
B: Recommend daily aspirin 81mg
C: Congratulate him on his smoking cessation
D: Refer him to a cardiologist

(you can only do only do one thing)
22-year-old man presents to discuss primary prevention to reduce his risk of HIV infection. He has a 20 lifetime sexual partners (uses condoms), practices anal receptive sex, and has a history of treated chlamydia. What do you do?
Case 2.0

A: Encourage abstinence only
B: Recommend daily Truvada PrEP
C: Congratulate him on his condom use
D: Refer him to an Infectious Disease specialist
What is PrEP?
PrEP is primary prevention

It is intended to PREVENT the onset of a disease in those who are AT RISK

It is a concept, fulfilled by medication that has been FDA-approved for this purpose
But what is PrEP, really?

- Right now, PrEP is Truvada®
  - Fixed dose combination of tenofovir disoproxil fumarate (TDF) 300mg/emtracitabine (FTC) 200mg
  - Developed by Gilead
  - FDA-approved for use as PrEP on June 6, 2012
- Generic TDF/FTC approved 6/2017

Also approved in Australia, Canada, France, Norway, Belgium, Netherlands, Peru, Israel, Kenya, Botswana, Zimbabwe and South Africa

Coming soon in: Brazil, Nigeria, Zambia, Malawi, Uganda, India, Thailand, United Kingdom, Italy
This is different from PEP

- **PrEP = Pre-Exposure Prophylaxis**
  - HIV exposure has not yet occurred
- **PEP = Post-Exposure Prophylaxis**
  - HIV exposure HAS occurred
  - Goal is to reduce incidence of established infection
  - THREE drugs required: Truvada® (TDF/FTC) + dolutegravir
How well does PrEP work?
iPrEX

44% HIV risk reduction, but 92% risk reduction when taken consistently among MSM and transgender women
62.2% HIV risk reduction among heterosexual men and women
75% HIV risk reduction among heterosexual sero-discordant couples, 90% among those with detectable drug levels
48.9% risk reduction, but 74% HIV risk reduction when taken consistently, among IDUs (TDF only)
86% HIV risk reduction in MSM using on-demand PrEP
IPERGAY

- Study was discontinued early, all offered on-demand PrEP in open-label phase and more enrolled.
- Mean pill use: 18 pills/month
- 97% reduction in relative risk of HIV in this extended arm versus the discontinued placebo arm
Dosing matters

Using drug concentrations in iPrEX and STRAND, pharmacokinetic models predict 76% risk reduction with 2 doses/week, 96% with 4 doses/week, and 99% with 7 doses/week.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Dosing</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEX</td>
<td>MSM</td>
<td>Daily</td>
<td>44% (92% with ideal adherence)</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexual men and women</td>
<td>Daily</td>
<td>62.2%</td>
</tr>
<tr>
<td>Partners</td>
<td>Sero-discordant heterosexual couples</td>
<td>Daily</td>
<td>75% (90% with ideal adherence)</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study Group</td>
<td>Intravenous drug users</td>
<td>Daily</td>
<td>48.9% (74% with ideal adherence)</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>MSM</td>
<td>On-demand</td>
<td>86%</td>
</tr>
</tbody>
</table>
Why PrEP matters
Joint United Nations Program on HIV/AIDS (UNAIDS) goal to have 90% of those living with HIV to know their status, 90% of those to be on ART, and 90% of those on ART to be virologically suppressed by 2020.
As of 2015, 60% of those living with HIV know their status, 46% of those are on ART, and 38% of those on ART are virally suppressed.

HAART alone is not the only key

FIVE PREVENTION PILLARS

1. Young women and adolescent girls and their male partners
2. Key populations
3. Condoms
4. Voluntary medical male circumcision
5. Pre-exposure prophylaxis

United Nations General Assembly prevention targets

- Ensure that 90% of people at risk of HIV infection access comprehensive prevention services, including harm reduction, by 2020.
- Reduce below 100,000 per year the number of adolescent girls and young women aged 15–24 years newly infected with HIV globally by 2020.
- Ensure that 90% of people at risk of HIV infection access comprehensive prevention services, including harm reduction by 2020.
- Make 20 billion condoms annually available in low- and middle-income countries by 2020.
- Reach 25 million additional young men in high HIV incidence areas with voluntary medical male circumcision by 2020.
- Reach 3 million people at higher risk of HIV infection with pre-exposure prophylaxis by 2020.

How are we doing?

- Late 2016: out of 1.2 million individuals at high risk for HIV in USA
- 136,000 are receiving TDF/FTC
- Up from 80,000 the previous year


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

- Gay and bisexual men: 26,200 infections (70%)
- People who inject drugs: 1,700 infections (5%)
- Gay and bisexual men who inject drugs: 1,100 infections (3%)
- Heterosexuals: 8,600 infections (23%)

Diagnoses of HIV Infection among Men Who Have Sex with Men, by Region of Residence and Race/Ethnicity 2014 - United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include men with HIV infection attributed to male-to-male sexual contact and injection drug use. * Hispanics/Latinos can be of any race.
Diagnoses of HIV Infection among Men Who Have Sex with Men, by Age Group, 2010–2014—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include men with HIV infection attributed to male-to-male sexual contact and injection drug use.
HIV Risk by State

Estimated Lifetime Risk of HIV
HIV Risk by Race/Ethnicity and MSM

- White women: 1 in 880
- White men: 1 in 132
- Hispanic women: 1 in 227
- Hispanic men: 1 in 48
- Black women: 1 in 48
- Black men: 1 in 20
- White MSM: 1 in 11
- Hispanic MSM: 1 in 4
- Black MSM: 1 in 2

Who benefits from PrEP?
CDC Recommendations (for MSM)

- 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

CDC Recommendations (for heterosexual men and women)

- Adult person
- Without acute or established HIV infection
- Any sex with opposite sex partners in past 6 months
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual)
- Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner

CDC Recommendations (for IDU)

- Adult person
- Without acute or established HIV infection
- Any injection of drugs not prescribed by a clinician in past 6 months
- AND at least one of the following
  - Any sharing of injection or drug preparation equipment in past 6 months
  - Been in a methadone, buprenorphine, or suboxone treatment program in past 6 months
  - Risk of sexual acquisition

Who benefits from PrEP?

- Sero-discordant sexual activity (couples)
- Multiple sex partners (especially sex partners with unknown HIV status or at risk for HIV) with inconsistent or no condom use
- History of sexually transmitted infections
- Exchange of sex for money or commodities
- Injection drug use
Who doesn’t benefit?

- HIV infection
- Those at risk for adverse effects due to pre-existing comorbid conditions (chronic kidney disease)
- Unwilling to take daily medication
- Not engaging in activity with increased HIV risk
Special considerations

- **Pregnant or breastfeeding women**
  - Pregnancy Category B (No known risk)
  - Minimally secreted in breastmilk, not contraindicated in breastfeeding

- **Chronic HBV**
  - TDF and FTC are active against HBV
  - If TDF/FTC no longer used for PrEP, consider continuing with chronic HBV as the indication

- **Chronic Renal Failure (eGFR <60ml/min)**
  - Don’t use TDF/FTC; safety has not been adequately determined

- **Adolescent Minors**
  - Careful consideration, no subjects <18 years were included in trials
Adolescent Trials Network for HIV/AIDS Interventions (ATN) study

- 78 HIV-negative MSM, ages 15-17, who reported HIV risk behavior during the previous 6 months received daily PrEP.
- Follow-up monthly for 12 weeks, then quarterly for the remainder of the 48-week study.
- Adherence was high during monthly follow-up, then dropped dramatically (by more than half).
- 32 discontinued before the end of the study.
- HIV acquisition rate: 6.4%
HIV risk is behavioral

The only way to know is to ask
Taking a sexual history promotes comprehensive STI risk reduction counseling

Condom use
Knowing HIV status
Knowing partner’s HIV status
PrEP
Sexual history and comprehension of PrEP

- Counseling on PrEP after a sexual history discussion significantly increases comprehension of HIV-prevention strategies.
- Engagement in a sexual history discussion may heighten the self-relevance of information, increasing memory and cognitive processing during PrEP education.
A preventative measure against the consequences of sexual activity

... *condones* sexual activity

... *promotes* sexual activity

... *causes* sexual activity
Stigma

- PrEP is a “party drug”
- PrEP promotes “bareback sex”
- PrEP users will stop using condoms
- PrEP users will acquire more STIs
But actually…

Active commitment to health

- Pre-Contemplation
- Contemplation
- Action
- Planning
But actually…

Active commitment to health
Confidence in sexual health

Pre-Contemplation
Contemplation
Planning
Action
But actually…

- Pre-Contemplation
- Contemplation
- Planning
- Action
- Stronger relationships
- Confidence in sexual health
- Active commitment to health
- But actually…
But actually…

- Pre-Contemplation
- Contemplation
- Planning
- Action
- Fewer sexual partners
- Stronger relationships
- Confidence in sexual health
- Active commitment to health
But actually…

- Pre-Contemplation
- Contemplation
- Planning
- Action
- Active commitment to health
- Confidence in sexual health
- Stronger relationships
- Fewer sexual partners
- Further risk reduction
No evidence of sexual risk compensation in the iPrEx trial of daily oral PrEP

For patients believing they were on PrEP, the number of receptive anal intercourse partners decreased.

For patients believing they were on PrEP, condom use increased.

Syphilis incidence also decreased in both study arms.

Real questions, real barriers

- Cost
- Judgment from providers
- Judgment from partners
- Partner could find out about sex outside of the relationship
- Partner would misinterpret taking PrEP as having HIV

The drawbacks of PrEP
Cost

- $13,000 for one year in USA
- Covered by most private insurance companies
  - Variable co-pays, deductibles, etc.
- Medicaid coverage varies by state
- Co-pay and cost assistance available
  - Up to $3,600/year in co-pay assistance
  - Medication assistance if <500% federal poverty level
**Adverse Events**

### Table 2. Adverse Events.  

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>FTC-TDF (N = 1251)</th>
<th>Placebo (N = 1248)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event</strong></td>
<td>867 (60)</td>
<td>2630</td>
<td>2611</td>
</tr>
<tr>
<td><strong>Any serious adverse event</strong></td>
<td>60 (5)</td>
<td>76</td>
<td>67 (5)</td>
</tr>
<tr>
<td><strong>Any grade 3 or 4 event</strong></td>
<td>151 (12)</td>
<td>248</td>
<td>164 (13)</td>
</tr>
<tr>
<td><strong>Grade 3 event</strong></td>
<td>110 (9)</td>
<td>197</td>
<td>117 (9)</td>
</tr>
<tr>
<td><strong>Grade 4 event</strong></td>
<td>41 (3)</td>
<td>51</td>
<td>47 (4)</td>
</tr>
<tr>
<td><strong>Elevated creatinine level</strong></td>
<td>25 (2)</td>
<td>28</td>
<td>14 (1)</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>55 (4)</td>
<td>55</td>
<td>41 (3)</td>
</tr>
</tbody>
</table>

### Nausea

<table>
<thead>
<tr>
<th></th>
<th>FTC-TDF (N = 1251)</th>
<th>Placebo (N = 1248)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>20 (2)</td>
<td>22</td>
<td>9 (&lt;1)</td>
</tr>
</tbody>
</table>

### Unintentional weight loss (≥5%)

<table>
<thead>
<tr>
<th></th>
<th>FTC-TDF (N = 1251)</th>
<th>Placebo (N = 1248)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unintentional weight loss (≥5%)</td>
<td>27 (2)</td>
<td>34</td>
<td>14 (1)</td>
</tr>
</tbody>
</table>

- Death: 1 (<1)%
- Discontinuation of study drug:
  - Permanently: 25 (2)
  - Temporarily: 79 (6)

A listing of all laboratory abnormalities and clinical adverse events of grade 2 or higher that were reported in 25 or more subjects (13%) is provided in Tables S9 and S10 in the Supplementary Appendix. FTC-TDF denotes emtricitabine and tenofovir disoproxil fumarate.

† P values were calculated by the log-rank test.

‡ This death was due to a motorcycle accident.
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TDF-FTC (N=613)</th>
<th>Placebo (N=608)</th>
<th>P Value†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of participants (%)</td>
<td>no. of events</td>
<td>no. of participants (%)</td>
<td>no. of events</td>
</tr>
<tr>
<td>Any</td>
<td>557 (91.2)</td>
<td>4357</td>
<td>536 (88.2)</td>
<td>4390</td>
</tr>
<tr>
<td>Any serious</td>
<td>63 (10.3)</td>
<td>68</td>
<td>66 (0.9)</td>
<td>79</td>
</tr>
<tr>
<td>Grade 3 or 4 only</td>
<td>19 (3.1)</td>
<td>21</td>
<td>29 (4.8)</td>
<td>32</td>
</tr>
<tr>
<td>At least possibly related to study drug</td>
<td>20 (3.3)</td>
<td>21</td>
<td>27 (4.4)</td>
<td>29</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>231 (37.8)</td>
<td>385</td>
<td>241 (39.6)</td>
<td>439</td>
</tr>
</tbody>
</table>

### Dizziness

|                  | 92 (15.1) | 109 | 67 (11.0) | 82 | 0.03 |

### Nausea

|                  | 113 (18.5) | 132 | 43 (7.1) | 48 | <0.001 |

### Vomiting

|                  | 69 (11.3) | 87 | 43 (7.1) | 47 | 0.008 |

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**Table 2. Adverse Events, According to Treatment Group.**

**ALT** denotes alanine aminotransferase, and **AST** aspartate aminotransferase.

† All P values were calculated with the use of a time-to-first-event analysis (regression analysis of survival data on the basis of the Cox proportional-hazards model), with the exception of the P values for weight loss of 5% or more and death, which were calculated with the use of Fisher’s exact test.

‡ The causes of death in the TDF-FTC group were motor vehicle accident (one participant) and suicide (one); the causes of death in the placebo group were motor vehicle accident (two), homicide (one), and cerebrovascular accident (one).
Small (2%) but significant decline in estimated creatinine clearance was observed in the TDF/FTC group after taking the drug for, on average, 81 weeks.
Adverse Events

**Table 3. Bone Mineral Density Scores.**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Forearm</th>
<th>Hip</th>
<th>Lumbar Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>T score</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BUT THIS CAN RECOVER!

Bone mineral density recovered after 6 months of stopping TDF/FTC in both young and older adults.

<table>
<thead>
<tr>
<th></th>
<th>18 mo</th>
<th>24 mo</th>
<th>18 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>T score</td>
<td>-0.88</td>
<td>-0.87</td>
<td>-0.21</td>
<td>-0.13</td>
</tr>
<tr>
<td>TDF–FTC</td>
<td>0.18</td>
<td>0.20</td>
<td>0.78</td>
<td>0.76</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.88</td>
<td>-1.09</td>
<td>-0.41</td>
<td>-0.28</td>
</tr>
</tbody>
</table>

* In the TDF–FTC group, 58 participants completed bone mineral density testing at the 6-month visit, 45 at the 12-month visit, 36 at the 18-month visit, and 23 at the 24-month visit. In the placebo group, 66 participants completed bone mineral density testing at the 6-month visit, 44 at the 12-month visit, 33 at the 18-month visit, and 35 at the 24-month visit.
Where to start, learn more

- Review prescribing guidelines
- Start asking your patients
- Confidently recommend
- Use reliable sources:
  - www.cdc.gov/hiv/prep
  - www.truvada.com
Thank you!

Questions?