PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV TRANSMISSION

Kenneth Mayer, MD
Douglas Krakower, MD
LEARNING OBJECTIVES

By the end of today’s session, learners will be able to:

1. Explain the rationale for PrEP as an HIV prevention strategy for gay and bisexual men
2. Summarize current research on PrEP
3. Discuss strategies for dealing with issues related to PrEP and patient care
POTENTIAL COMPETING INTERESTS

- Dr. Mayer: unrestricted research and educational grants from:
  - Gilead Sciences
  - Bristol-Myers Squibb
  - Merck
- Dr. Krakower: investigator-initiated research regarding HIV prevention
  - National Institutes of Health
    - NIMH K23 MH098795
  - Gilead Sciences
  - Bristol-Myers Squibb
  - AMA Foundation
- No other competing interests
MEN WHO HAVE SEX WITH MEN ARE AT GREATLY INCREASED RISK FOR HIV ACQUISITION

- Male-to-Male Sexual Contact (MSM): 64%
- Injection Drug Use (IDU): 6%
- MSM/IDU: 3%
- Heterosexual Contact: 17%
- Other: 10%

BLACK AND LATINO PERSONS ARE AT INCREASED RISK

% of US Population  % of HIV Incidence

- White
- Black/African American
- Hispanic/Latino
- Asian
- American Indian/Alaskan Native
- Native Hawaiian/Other Pacific Islander
- Multiple Races

US Census and CDC Data, 2010
Pre- vs Post-Exposure Prophylaxis

Postexposure prophylaxis—initiated soon after an exposure—reduces the chance of HIV infection.

HIV

Postexposure prophylaxis

0 hr 36 hrs 72 hrs 1 mos 3 mos 5 mos

HIV infection
Pre-exposure prophylaxis might protect against a period of ongoing risk by having a continuing level of medication available.
PREP: CAN A PILL PREVENT HIV?

- Is it effective?
- Is it safe?
- How often do you really need to take it for it to work?
- Will it lead to increases in risky behaviors?
- What if my partner is HIV+ but undetectable?
PREP WORKS, BUT ADHERENCE IS CRITICAL

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy overall</th>
<th>Drug detected overall</th>
<th>Estimated Risk reduction with drug detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>42%</td>
<td>~50%</td>
<td>92%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>67-75%</td>
<td>82%</td>
<td>86% (TDF) 90% (FTC/TDF)</td>
</tr>
<tr>
<td>TDF-2</td>
<td>62%</td>
<td>80%</td>
<td>78%</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>No efficacy</td>
<td>26%</td>
<td>“adherence too low to assess efficacy”</td>
</tr>
<tr>
<td>VOICE</td>
<td>No efficacy</td>
<td>29%</td>
<td>“ ”</td>
</tr>
<tr>
<td>Thai IDU</td>
<td>49%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
THE EFFICACY OF PREP IS STRONGLY ASSOCIATED WITH DEGREE OF MEDICATION ADHERENCE

iPrEx: Prophylactic effect correlated with detectable drug levels

Partners PrEP: detected drug in 31% of infected, 82% of uninfected

TDF2: 50% vs. 80%

FEM-PrEP: 15% vs. 24

PREP CONCERNS

- Risk Compensation: not seen in trials
- Renal insufficiency: rare, reversible
  - Patients had to have normal function for trials
- Bone demineralization: statistically significant, not clinically significant at 18 months, needs f/u
- Transmission of resistance
  - Rare, almost all in patients with acute HIV
  - Tenofovir resistance very rare
- But it is early, and ongoing monitoring needed
TDF-FTC IS FDA APPROVED FOR USE AS PREP TO PREVENT SEXUAL TRANSMISSION OF HIV

FDA NEWS RELEASE
For Immediate Release: July 16, 2012
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves first drug for reducing the risk of sexually acquired HIV infection
Evidence-based approach enhances existing prevention strategies

Today, the U.S. Food and Drug Administration approved Truvada (emtricitabine/tenofovir disoproxil fumarate), the first drug approved to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners. Truvada, taken daily, is to be used for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually-acquired HIV infection in adults at high risk.

The FDA previously approved Truvada to be used in combination with other antiretroviral agents for the treatment of HIV-infected adults and children 12 years or older.

As part of PrEP, HIV-uninfected individuals who are at high risk will take Truvada daily to lower their chances of becoming infected with HIV should they be exposed to the virus. A PrEP indication means Truvada is approved for use as part of a comprehensive HIV prevention strategy that includes other prevention methods, such as safe sex practices, risk reduction counseling, and regular HIV testing.

"Today's approval marks an important milestone in our fight against HIV," said FDA Commissioner Margaret A. Hamburg, M.D. "Every year, about 50,000 U.S. adults and adolescents are diagnosed with HIV infection, despite the availability of prevention methods and strategies to educate, test, and care for people living with the disease. New treatments as well as prevention methods are needed to fight the HIV epidemic in this country."

As a part of this action, the FDA is strengthening Truvada's Boxed Warning to alert health care professionals and uninfected individuals that Truvada for PrEP must only be used by individuals who are confirmed to be HIV-negative prior to prescribing the drug and at least every three months during use. The drug is contraindicated for PrEP in individuals with unknown or positive HIV status. The FDA strongly recommend against sexual use.
CDC GUIDANCE ON PRESCRIBING PREP

- Determine Eligibility (negative HIV test, at high-risk for HIV acquisition, screen/treat for STDs, screen/vaccinate for Hep B; pregnancy test)
- Prescribe tenofovir-emtricitabine 1 tablet by mouth daily
- Provide condoms and risk-reduction counseling
- Monitor closely (at 1 month, then q 2-3 months: HIV testing, follow BUN/Cr, repeated risk assessment and counseling)
- Also see NYS DOH guidelines (hivguidelines.org)
BUT, PILL TAKING AND SAFER SEX WILL ONLY WORK IF BEHAVIORAL HEALTH ISSUES ARE ADDRESSED

Depression, anxiety, mental health problems, substance use

Disease prevention
Pleasure reduction
Social Models
Self efficacy
Safer Sex Adherence

Wulfert, Safren, et al., 1999; Journal of Applied Social Psychology
STRATEGIES TO IMPROVE PREP DELIVERY AND ADHERENCE

New PrEP drugs and dosing strategies

ASPIRE (Dapivirine)

Rectal Microbicides:
MTN-017 (TFV rectal gel)

Injectables:
Rilpivirine-LA GSK744

Novel adherence strategies

The Future

Alternative delivery systems and formulations

Intra-vaginal rings:
ASPIRE (Dapivirine)

Injectables:
Rilpivirine-LA GSK744
WEB/VIDEO RESOURCES

- Ken Like Barbie: The Frontier of HIV Prevention is Changing - A Video Fact Sheet on PrEP
  - [http://myprepexperience.blogspot.com/2013/05/ken-like-barbie-frontier-of-hiv.html](http://myprepexperience.blogspot.com/2013/05/ken-like-barbie-frontier-of-hiv.html)

- Insurance tracking
  - [http://myprepexperience.blogspot.com/p/truvada-track.html](http://myprepexperience.blogspot.com/p/truvada-track.html)

- Project inform: videos, booklets
  - [http://www.projectinform.org/prep/](http://www.projectinform.org/prep/)

- Fenway
  - [http://thefenwayinstitute.org/prepinfo/](http://thefenwayinstitute.org/prepinfo/)
COMBINATION ANTIRETROVIRAL PREVENTION

Interventions to Increase Testing

- Test
  - HIV Negative
    - Risk Assessment
    - PrEP, Adherence Counseling
    - Address concomitant concerns: depression, substance use, relationship dynamics
  - HIV Positive
    - Linkage To Care
    - Positive Prevention
    - Decrease in HIV Transmission

- Enroll in Care
  - ART Initiation
  - Treat
  - Adherence to ART
  - Maintain Viral Suppression
YOUR PREP EXPERIENCES

Check all that apply.

I have...

a) Discussed PrEP with a patient, where I brought it up
b) Discussed PrEP with a patient, where the patient brought it up
c) Recommended that a patient take PrEP
d) Had a patient request a prescription for PrEP
e) Prescribed PrEP to 1 patient
f) Prescribed PrEP to 2 or more patients
g) None of the above
CASE #1: MSM PATIENT WHO REQUESTS STI TESTING

- 31M who presents to primary care clinic with request for STI testing
- 5 male sexual contacts in past 6 months
- Oral sex with all partners; all partners of unknown HIV status; condomless receptive anal sex with 3 partners, last 6 weeks ago
- Persistent worry about most recent sexual encounter; had sex hours after meeting on mobile app
- Normal exam, HIV Ab and STI screens negative
CDC GUIDANCE ON PRESCRIBING PREP

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- Provide condoms and risk-reduction counseling
- Monitor closely (at 1 month, then q 2-3 months: HIV testing, follow BUN/Cr, repeated risk assessment and counseling)
- Also see NYS DOH guidelines (hivguidelines.org)
RISK ASSESSMENT TO INFORM WHO IS MOST LIKELY TO BENEFIT FROM PREP

- Have you ever had a sexually transmitted infection?
- Do you know the HIV status of your partners?
- Have you had anal sex? Was it receptive (another person’s penis in your anus), insertive (your penis in another person’s anus), or both?
- Have you exchanged sex for money, goods, or services?
- Have you had sex with strangers?
A TOOL FOR RISK-STRATIFYING MSM: CDC RISK INDEX ("HIRI-MSM")

"In the past (year) have you had sex?"

"With men, women, or both?"

Score < 9: standard prevention
Score ≥ 10: consider PrEP

Score†
OTHER RISK CALCULATORS FOR MSM

Figure 2. Estimating a patient’s 4-year risk of HIV acquisition according to the simple model.

| Does your patient/client have gonorrhea, chlamydia, or syphilis, or does he have a history of these infections? | If yes, add 4 points If no, add 0 points |
| Has your patient/client used methamphetamine or inhaled nitrites (poppers) in the prior 6 months? | If yes, add 11 points If no, add 0 points |
| Does your patient/client report unprotected anal intercourse with a partner of positive or unknown HIV status in the prior year? | If yes, add 1 point If no, add 0 points |
| Does your patient/client report 10 or more male sexual partners in the prior year? | If yes, add 3 points If no, add 0 points |

Sum total number of points

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Estimated percentage of men with this score who will acquire HIV over 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>1-3</td>
<td>5%-9%</td>
</tr>
<tr>
<td>4-11</td>
<td>10%-14%</td>
</tr>
<tr>
<td>12+</td>
<td>&gt;14%</td>
</tr>
</tbody>
</table>

How to use the chart
1. Calculate your patient’s/client’s risk score.
2. Match the risk score with the point range provided on the table to estimate 4-year HIV risk.
3. Follow up with testing recommendations, referrals to services, and prevention intervention according to risk.
ASSESS ADHERENCE IN A NEUTRAL MANNER

- **Rationale**
  - Reduce “Self-presentation” bias (i.e., desire to look good to provider)
  - Reduce “Gaming” bias (i.e., desire to avoid lecture on adherence)

- **Approach**
  - Framing
    - “I would like to take a few minutes to check in with you about how it has been going with the PrEP medication. Is that OK?”
  - Normalization
    - “Many people find it difficult to take PrEP medications every day”
  - Neutrality
    - “Please know that I am not here to judge you; I want you to feel comfortable reporting anything”
  - Avoid praising or disappointing statements
“NEXT STEP” ADHERENCE COUNSELING

- Review experience with prior strategies
  - “Last time you were here you agreed to try ___. How did that go?…”
- Explore individual barriers/facilitators to adherence
  - “What are the things or times when a tablet a day feels a little more difficult—not such a great fit?”
- Identify adherence-related needs
  - “What would help to support your feeling that this is a good fit for you right now?”
- Strategize with patient on next steps to approach needs
  - “What are some ideas for how you could approach that?”
- Agree on next steps
  - “Of the things we have talked about, which might you be willing to try between now and the next time we meet?”
- Summarize, close
PARTIAL ADHERENCE MAY STILL OFFER SOME PROTECTION AGAINST INFECTION

![Graph showing TFV-DP (fmol/10^6 Cells) distribution.](image)

**STRAND**

- **2/Wk**: n = 21, BLQ: 0%, Median: 11, IQR: 6–13
- **4/Wk**: n = 21, BLQ: 0%, Median: 32, IQR: 25–39
- **7/Wk**: n = 22, BLQ: 0%, Median: 42, IQR: 31–47

**iPrEx**

- **Cases**: n = 42, BLQ: 93%, Median: 11, IQR: 4–15
- **Controls**: n = 144, BLQ: 64%, Median: 16, IQR: 9–27
IPREX PARTICIPANTS DID NOT INCREASE SEXUAL RISK BEHAVIORS

Marcus PLoS One 2013
CDC’s Evidence-Based Behavioral Interventions for Risk Reduction
DON’T FORGET THE TRIPLE DIP

Syphilis serology
Pharyngeal GC
Urine GC/CT
Rectal GC/CT

Slide from: California STD/HIV Prevention Training Center
CASE #2: HETEROSEXUAL SERODISCORDANT COUPLE

- 34F who is HIV-uninfected and in long-term relationship with male partner who was recently dx with HIV
- His HIV VL 28,500
- Sexually active; oral, vaginal sex 1-2 times/week; rarely use condoms
- Exam normal, STI screens negative
WHAT WOULD YOU DO?

Check all that apply:

a) Recommend abstinence
b) Explore barriers to condom use
c) Recommend ART for HIV-infected partner as prevention against HIV transmission
d) Recommend PrEP
EARLY ANTIRETROVIRAL THERAPY DECREASES HIV TRANSMISSION

1763 stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm³

Randomization

Early antiretroviral therapy
CD4 350-550

4 infections
1 linked, 3 unlinked

96% relative risk reduction in linked transmissions

Delayed antiretroviral therapy
CD4 ≤ 250

35 infections
27 linked, 8 unlinked

Cohen NEJM 2011
SUPPRESSIVE ART DECREASES HIV TRANSMISSION BETWEEN MEMBERS OF SERODISCORDANT COUPLES

The PARTNER study

- 767 serodiscordant couples, at least some condomless sex, HIV+ partner VL < 200 (other partner not on PrEP/PEP)
- ~40% same-sex couples
- All heterosexual HIV-uninfected partners reported condomless vaginal sex, 72% with ejaculation
- 70% of the HIV-neg MSM partners reported receptive anal sex, 40% with ejaculation
- Undetectable VL: 94% MSM, 85% heterosexuals

**No transmissions within couples**

- Upper bound of 95% confidence interval: 0.4%/yr; 1%/yr for those having anal sex
PARTNERS PREP
PERI-CONCEPTION PREP IS AN OPTION FOR COUPLES WISHING TO CONCEIVE

<table>
<thead>
<tr>
<th>Couple</th>
<th>Method</th>
<th>Estimated risk reduction</th>
<th>Level of evidence&lt;sup&gt;a&lt;/sup&gt;(data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F+M&lt;sup&gt;-&lt;/sup&gt; (goal: female to male transmission)</td>
<td>Nonintercourse insemination&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100%</td>
<td>2A; [23,24]</td>
</tr>
<tr>
<td></td>
<td>Medical male circumcision</td>
<td>66%</td>
<td>1A; [25–28]</td>
</tr>
<tr>
<td>M+F&lt;sup&gt;-&lt;/sup&gt; (goal: male to female transmission)</td>
<td>Sperm washing + IUI or IVF (± ICSI)</td>
<td>~100%</td>
<td>2A; [28–31]</td>
</tr>
<tr>
<td>Either partner infected, pursuing natural conception + adjunct risk reduction strategies (goal: ↓ sexual transmission)</td>
<td>Sex without condoms limited to peak fertility&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Unknown</td>
<td>1A; [23,24,32,33]</td>
</tr>
<tr>
<td></td>
<td>ART for the infected partner</td>
<td>96%</td>
<td>1B; [34**,35,36]</td>
</tr>
<tr>
<td></td>
<td>PrEP (oral, daily FTC/TDF) for the uninfected partner</td>
<td>63–75%</td>
<td>1A&lt;sup&gt;d&lt;/sup&gt;; [37**,39**]</td>
</tr>
<tr>
<td></td>
<td>Treatment of STI’s</td>
<td>≤40%</td>
<td>1B&lt;sup&gt;*&lt;/sup&gt;; [40,41]</td>
</tr>
</tbody>
</table>

ART, antiretroviral treatment; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; PrEP, pre-exposure prophylaxis.

<sup>a</sup>Oxford Centre for Evidence-based Medicine, Levels of Evidence (1A: RCTs with homogeneous support; 1B: individual RCT; 2A: cohort studies with homogeneity; 2C: ecological studies; 5: expert opinion without explicit supporting research) [42].

<sup>b</sup>Man ejaculates into a condom or cup and the contents are introduced via condom reversal or needle-less syringe at home, or through IUI with a healthcare professional – timed to the woman’s peak fertility.

<sup>c</sup>Limiting sex without condoms to times of peak fertility reduces exposure, but does not affect HIV-1 transmission risk per coital act.

<sup>d</sup>Effective for heterosexual men in two of two RCTs and for women in two of four RCTs.

<sup>*</sup>Effective in one of six RCTs.
**DISCONTINUING PREP**

- HIV acquisition
  - HIV genotype testing
  - Link to HIV care
- Patient decision
- Toxicities (e.g., CrCl < 60 mL/min)
- Gray Zones
  - Suboptimal adherence?
  - Using not as directed? (e.g., episodic)
  - Increasing sexual risk? (e.g., ↑STIs)

*Discuss concept of “wash out” period*
THANK YOU!

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