Moving beyond condoms to prevent HIV transmission

Are you Prepared for HIV PrEP?

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UNC Chapel Hill
The Issues

• New HIV infections in the US continue
• Vast majority of infections are sexually acquired
• Condoms work but are not loved by all
• TDF/FTC PrEP has been demonstrated to be effective
• TDF/FTC PrEP is a reality
• How do we get PrEP to those who want it and can benefit from it
A Snapshot of HIV/AIDS in the United States

- Number of people living with HIV: 1.2 million
- Number of new infections: ~50,000 per year
- Percent of people who are infected and unaware: 14%

HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.
AIDSVu (www.aidsvu.org). Emory University, Rollins School of Public Health. Accessed 2/26/15;
Current Prevention Methods Are Insufficient


IDU = injection drug user.
How are people getting HIV in the US?

CDC 2013 Surveillance data

Males
N = 38,479

- 81% Male-to-male sexual contact
- 10% Injection drug use (IDU)
- 5% Male-to-male sexual contact and IDU
- 3% <1%

Females
N = 9,479

- 86% Heterosexual contact
- 13%
- 1%
- Other
- Other

a: Male-to-male sexual contact
b: Injection drug use (IDU)

Male-to-male sexual contact and IDU
Current HIV Prevention Methods Are Insufficient


MSM = men who have sex with men.

Multiple, proven prevention strategies
Evidence-Based HIV Prevention Strategies

- Condom access and distribution
- Health education and risk reduction counseling
- Needle and syringe exchange
- STI screening and testing
- HIV testing
- ART for prevention
- Post-exposure prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)
What is PrEP?

Pre-exposure prophylaxis
Use of anti-HIV medications **before** an exposure, to reduce the risk of becoming infected

**Tenofovir** is the most studied agent for PrEP
- Pharmacokinetics allow infrequent dosing
- Few drug-drug interactions
- Safe and well tolerated
- Resistance less likely
Fixed-dose TDF/FTC is the recommended PrEP regimen* for MSM, heterosexually active men and women, and IDU who meet prescribing criteria:

- FDA approved indication

- Dosed as a single pill (300/200 mg) once daily

*MSM, heterosexually active men and women, and IDU who meet PrEP prescribing criteria.

Concept rooted in 4 lines of evidence

Prophylactic use of anti-infectives
Concept rooted in 4 lines of evidence

Prevention of mother-to-child transmission
Concept rooted in 4 lines of evidence

Studies in animal models (macaques)
Concept rooted in 4 lines of evidence

Post-exposure prophylaxis (PEP)
iPrEx Study: MSM and Transgender Women

Multinational study
HIV-negative men or transgender women who have sex with men
Screened (n=4905)

Randomization 1:1

Double-Blind

Emtricitabine/tenofovir DF (n=1251)
Similar baseline demographic characteristics (except mean age), sexual risk factors, STIs, and HBV status
Follow-Up 3324 person-years (median 1.2 years)

Placebo (n=1248)

Study Outcomes
- HIV seroconversion
- Adverse events
- Metabolic effects
- HBV exacerbations
- Risk behavior and STIs (including HSV)
- Adherence

iPrEx Study Results: MSM and Transgender Women

- Multinational, randomized controlled trial (n=4905 MSM and transgendered women)
- HIV incidence
  - Placebo: 3.9/100 person years
  - PrEP provided 44% additional reduction in HIV incidence
- Risk reduction with PrEP
  - 96% if drug concentrations indicated use of 4 tablets/week
  - 99% if drug concentrations indicated use of 7 tablets/week

iPrEx Study: Unprotected Receptive Anal Intercourse

Overall Patient Population

Patients (%) vs Weeks

- Emtricitabine/tenofovir DF
- Placebo

Patients Who Believed They Were Receiving FTC/TDF

Patients (%) vs Weeks

- Emtricitabine/tenofovir DF
- Placebo

P = 0.30
P = 0.44

Five major studies demonstrated PrEP’s preventive efficacy across risk groups

<table>
<thead>
<tr>
<th>Study</th>
<th>ARV Used</th>
<th>Frequency</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>Tenofovir vaginal gel</td>
<td>Before &amp; after sex</td>
<td>Heterosexual women</td>
</tr>
<tr>
<td>iPrEx</td>
<td>Truvada oral</td>
<td>Daily</td>
<td>MSM &amp; transwomen</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Tenofovir &amp; Truvada oral</td>
<td>Daily</td>
<td>Heterosexual discordant couples</td>
</tr>
<tr>
<td>TDF2</td>
<td>Tenofovir &amp; Truvada oral</td>
<td>Daily</td>
<td>Heterosexual men &amp; women</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>Tenofovir oral</td>
<td>Daily</td>
<td>Injection drug users</td>
</tr>
</tbody>
</table>
Two major studies demonstrated a lack of efficacy among heterosexual women.

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<tr>
<td>FEM-PrEP</td>
<td>Truvada oral</td>
<td>Daily</td>
<td>Heterosexual women</td>
</tr>
<tr>
<td>VOICE (MTN-003)</td>
<td>Tenofovir gel, tenofovir oral,</td>
<td>Daily</td>
<td>Heterosexual women</td>
</tr>
<tr>
<td></td>
<td>Truvada oral</td>
<td></td>
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## Adherence to PrEP Is Critical

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall Efficacy, %</th>
<th>Blood Samples with TFV Detected, %</th>
<th>Efficacy by Blood Detection of TFV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>44</td>
<td>51</td>
<td>92</td>
</tr>
<tr>
<td>iPrEx OLE</td>
<td>49</td>
<td>71</td>
<td>NR</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>67 (TDF) 75 (TDF/FTC)</td>
<td>81</td>
<td>86 (TDF) 90 (TDF/FTC)</td>
</tr>
<tr>
<td>TDF2</td>
<td>62</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>Bangkok TFV</td>
<td>49</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>No efficacy</td>
<td>&lt; 30</td>
<td>NR</td>
</tr>
<tr>
<td>VOICE</td>
<td>No efficacy</td>
<td>&lt; 30</td>
<td>NR</td>
</tr>
</tbody>
</table>

Adherence is critical

Protective efficacy (%)

All participants: 44
High adherers: 92

62-73 → ~95

iPrEx OLE confirmed prior estimates

Key points

Daily dosing affords greatest protection

Occasional missed dose probably OK

Nonadherence creates opportunities for infection
# Two Recent PrEP Studies: A Comparison of IPERGAY and PROUD

<table>
<thead>
<tr>
<th>PROUD Study (UK)</th>
<th>IPERGAY Study (Fr &amp; Canada)</th>
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<tbody>
<tr>
<td>• High-risk MSM and transgender women (N = 545)</td>
<td>• High-risk MSM and transgender women (N = 400)</td>
</tr>
<tr>
<td>• Randomized; deferred arm</td>
<td>• Randomized; placebo arm</td>
</tr>
<tr>
<td>‣ Immediate vs deferred PrEP*</td>
<td>• Flexible dosing schedule*</td>
</tr>
<tr>
<td>‣ Daily dosing schedule</td>
<td>‣ “On demand”</td>
</tr>
<tr>
<td>‣ Whether or not they were sexually active</td>
<td>‣ 2 tabs taken 2-24 hrs before sex</td>
</tr>
<tr>
<td>‣ All participants received full preventive services</td>
<td>‣ 1 tab day after sex and another 1 tab day after that</td>
</tr>
<tr>
<td>‣ 86% reduced risk of HIV</td>
<td>• All participants received full preventive services</td>
</tr>
<tr>
<td></td>
<td>• 86% reduced risk of HIV</td>
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*adherence assessed by face-to-face interviews, pill counts, TDF/FTC plasma and hair concentrations
†PrEP given 1 year after enrolling.
PROUD Study: Results

- Significantly fewer new HIV infections with immediate versus deferred PrEP (3 versus 19 cases)
  - 86% reduction ($P=0.0002$)
  - Number needed to treat to prevent 1 infection: 13
- PEP used by 31% in deferred arm
- Preliminary analysis found that risk behaviors were similar between the 2 arms

PEP: post-exposure prophylaxis.

IPERGAY Trial: Results

• Significantly fewer new HIV infections with intermittent PrEP versus placebo (2 versus 14 cases)
  – 86% reduction after a mean follow-up of 13 months ($P=0.002$)

• Safety of on-demand PrEP was similar to placebo except for GI adverse events

• Adherence to PrEP was good, supporting the acceptability of on-demand PrEP

Risk Behavior during IPERGAY

No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting

Jonathan E. Velie, Julia L. Marcus, Tony Phamvasavasy, Sara Birchinger, Doug Pongpipat, Stephen Fulmer,* and C. Bradley Marck

Departments of Adult and Family Medicine, Kaiser Permanente San Francisco Medical Center, and Division of Research, Kaiser Permanente Northern California, California

(Sec the Editorial Commentary by Kuester and Grant on pages 1694-5.)

July 2012-February 2015: 1,045 referrals for PrEP, of which 835 (80%) led to an in-person evaluation.

Of the 801 participants with at least 1 intake visit, 657 (82%) opted to start PrEP—including 20 who restarted PrEP after discontinuing it. 144 people (18%) decided not to do so.

No new HIV diagnoses occurred among PrEP users during 388 person-years of follow-up.

After 6 months, 30% of diagnosed with any STI, 18% rectal STI, 17% chlamydia, 15% gonorrhea, and 3.3% syphilis; After 12 months, the corresponding percentages were 50%, 33%, 33%, 28%, and 5.5%, respectively.

Among the 143 PrEP users after 6 months on PrEP, 56% said condom use unchanged, 41% reported a decrease, and 3% reported an increase; 74% said their number of sexual partners stayed the same, 15% reported a decrease, and 11% reported an increase.
FDA Approves First Medication to Reduce HIV Risk

People diagnosed with HIV—the human immunodeficiency virus that without treatment develops into AIDS—take antiretroviral medications to control the infection that attacks their immune system.

Now, for the first time, adults who do not have HIV but are at risk of becoming infected can take a medication to reduce the risk of sexual transmission of the virus.

The Food and Drug Administration (FDA) has approved the new use of Truvada—to be taken once daily and used in combination with safer sex practices—to reduce the risk of sexually acquired HIV-1 infection in adults who do not have HIV but are at high risk of becoming infected. (HIV-1 is the most common form of HIV.)

In two large clinical trials, daily use of Truvada was shown to significantly reduce the risk of HIV infection—by 42 percent in a study sponsored by the National Institutes of Health (NIH) of about 2,500 HIV-negative gay and bisexual men and transgender women, and by 77 percent in a study sponsored by the University of Washington of about 4,500 heterosexual couples in which one partner was HIV-positive and the other was not.

Elisha Benchkarev, M.D., director of the Division of Antiretroviral Products in FDA, explains that Truvada works to prevent HIV from establishing itself and multiplying in the body. The notion that Truvada is not a new product, Truvada was first approved in 2004 for use in combination with other medications to treat HIV-infected adults and children over 12 years old.

In the 80s and early 90s, HIV was viewed as a life-threatening disease in some parts of the world. It is still a medical advance, along with the availability of close to 30 approved individual HIV drugs, have enabled us to treat it as a chronic disease most of the time,” Benchkarev says.

“But it is still better to prevent HIV than to treat a life-long, infectious disease,” she adds.

Benchkarev stresses that Truvada is meant to be used as part of a comprehensive HIV prevention plan that includes consistent and correct condom use, risk reduction counseling, regular HIV testing, and treatment of any other sexually transmitted infections. Truvada is not a substitute for safer sex practices, she says.

Person Must Be HIV Negative

Truvada, produced by Gilead Sciences Inc., is a combination of two antiretroviral medications used to treat HIV—an integrase-disrupting and nucleoside reverse transcriptase inhibitor. When Truvada is used as a treatment for HIV rather than as a preventive, the patient also takes a daily dose of a non-HIV medication. When the other approved HIV drugs are added, it depends on the needs of the patient.

Before this medicine is prescribed, Benchkarev says there are several factors...
CDC PrEP Guidance: For Whom Is PrEP Recommended?

Daily oral PrEP is recommended for adults at substantial risk of acquiring HIV infection:

- Sexually active MSM
- Heterosexually active men and women
- Injection drug users

<table>
<thead>
<tr>
<th>Detecting substantial risk of acquiring HIV infection</th>
<th>MSM</th>
<th>Heterosexual Women and Men</th>
<th>IDUs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV-positive sexual partner</td>
<td>• HIV-positive sexual partner</td>
<td>• HIV-positive injecting partner</td>
<td></td>
</tr>
<tr>
<td>• Recent bacterial STI</td>
<td>• Recent bacterial STI</td>
<td>• Sharing injection equipment</td>
<td></td>
</tr>
<tr>
<td>• High number of sex partners</td>
<td>• High number of sex partners</td>
<td>• Recent drug treatment</td>
<td></td>
</tr>
<tr>
<td>• History of inconsistent or no condom use</td>
<td>• History of inconsistent or no condom use</td>
<td>(but currently injecting)</td>
<td></td>
</tr>
<tr>
<td>• Commercial sex work</td>
<td>• Commercial sex work</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• In high-prevalence area or network</td>
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Step 1: Assess need

Open a dialogue about sexual health

• Get to know your patient and her/his risk(s)
• Ask lots of embarrassing questions!
• Educate about signs & symptoms of STIs
• Don’t forget about drug use around sex
• Don’t forget about shared drug paraphernalia
Step 1: Assess need

Tips for talking about sex with patients

• Avoid preface statements before inquiring
• Make sure definition of “sexually active” is clear
• It’s OK to use colloquial terminology
• My standard brief history:
  • “Do you have sex with men, women, or both?”
  • For MSM: “Do you top, bottom, or both?”
  • “Are you in a relationship with anyone?”
  • “Do you have sex with anyone (else)?”
  • “How often do you use condoms for…?”
Step 2: Determine clinical eligibility

HIV status
- Ag/Ab (4th gen)
- Rapid (blood)
- ELISA / EIA

Must be HIV(–)
→ Maybe RNA, too?

Step 2: Determine clinical eligibility

Viral hepatitis
- HBsAg
- HBsAb
- HCV Ab

Renal function
- Creatinine
- eCrCl

HIV status
- Ag/Ab (4th gen)
- Rapid (blood)
- ELISA / EIA

CAUTION if active HBV!

eCrCl must be ≥ 60 mL/min

Must be HIV(-)
→ Maybe RNA, too?
Step 2: Determine clinical eligibility

Screen for symptoms of acute HIV

- Must be free of these, within prior 4 weeks:
  - Fever (75%)
  - Fatigue (68%)
  - Skin rash (48%)
  - Pharyngitis (40%)
  - Cervical adenopathy (39%)

- Suspect acute HIV? *Send HIV RNA (viral load)*
Step 3: Screen for STIs

If not already done in prior 3-6 months:

- RPR for syphilis
- Gonorrhea and chlamydia
  - NAA testing preferred
  - Extranatal sites too!
Step 3: Screen for STIs
Step 4: Counsel the patient

Establish ground rules

- Ongoing relationship – quarterly visits
- No HIV test? No prescription!

“Startup syndrome”

- Flatulence, nausea / GI upset, headache
- Symptoms resolve within first 30d, for most

Would you sign a Contract?

Step 4: Counsel the patient

Adherence strategies

- Pair pill-taking with daily task (even weekends!)
  - Plugging cell phone in before bedtime
- Set an alarm (clock, watch, or phone)
- Use a pill box
- Keep a dose on / near you
Step 5: Prescribe & follow-up

First Rx: Thirty days, NO refills

Return to clinic in 30 days

☐ Adherence?
☐ Side effects?
☐ Risk behaviors?

2nd Rx: Thirty days, 2 refills
Step 6: Maintenance & reassessment

At least every 3 months
- Assess adherence, side effects, risk behavior
- Repeat HIV testing
- Prescription renewal

At least every 6 months
- Check creatinine and eCrCl
- Screen for STIs, if not already done
- Determine need – “seasons of risk”
Frequently asked questions
Won’t PrEP encourage riskier sex?

Risk compensation

- Repeatedly examined in multiple trials
  - Indices of risk **stable or reduced**
    - Condomless sex
    - Number of partners
    - Bacterial STIs

How long before I’m protected?

Time to Maximum Intracellular Concentration of Tenofovir Diphosphate (TFV-DP)

- Rectal: 7 days
- Blood (PBMC): 20 days
- Cervicovaginal: 20 days

Won’t it be less effective in practice?

Effectiveness is often lower than efficacy

- Condoms (97% → 70-80%)
- Oral contraceptive pills (99% → 90%)

PROUD Study

- 545 MSM, transwomen in English GUM clinics
- Half got PrEP immediately, half waited 1 year
- Stopped early due to strong positive effect
- **Protective effectiveness 86%** (IRR; 95% CI 58, 96)

Can my patient afford PrEP?

Cost to PrEP users

• Out-of-pocket (uninsured) = around $1300/mo.
• Insurance covers (even Medicaid) – **pre-auths**
• Access programs and co-pay assistance
• Potentially free from Gilead if income < $58K

• See NCATEC’s “**For PrEP prescribers**” page


https://twitter.com/peterstaley/status/518554275501178882
Managing Side Effects

- Side effects reported in clinical trials
  - Uncommon and usually resolved within the first month of taking PrEP
    - iPrEx: significant increase in nausea and weight loss
    - Mild decrease in CrCl that was reversible

- Signs/symptoms that require urgent evaluation (renal injury, acute HIV infection)

- Inform about potential for drug-resistant HIV infection if PrEP taken inconsistently and HIV infection occurs

iPrEx = pre-exposure prophylaxis initiative.

North Carolina AIDS Training and Education Center

PrEP Resources

Pre-exposure prophylaxis (PrEP) is a new way of preventing HIV infection. It involves taking antiretroviral drugs to remain HIV-free. It is used to prevent infection in people who are not HIV positive but are at risk of becoming infected with HIV. We have put together these resources to help you to decide whether you are a provider or a consumer.

More info: www.med.unc.edu/ncaidstraining
NCATEC has lots of resources

http://www.med.unc.edu/ncaidstraining/prep