Pre-Exposure Prophylaxis: Indications for Future Treatment

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Disclosures

• Co-Investigator for studies sponsored by Gilead and GSK Pharmaceuticals
Case

• 46 y/o MSM, from NYC, long-term, open stable relationship with a male
• Multiple sexual partners
• Treated for syphilis in the past, RPR nonreactive. HIV testing is negative
• Healthy, on NSAIDS for back pain
• Uncircumcised

HIV Prevention strategies:

– Condoms
– Potential benefits of circumcision.

• He asks you about PrEP
NEJM RESPONSES

• Would you recommend initiating preexposure prophylaxis for this 46-year-old New York man who has sex with men?

Poll closed August 9, 2012 (1115 total Responses)

NO 48%

YES 51%

Learning Objectives

• Explain the best practice use of pre-exposure prophylaxis for those at risk of acquiring HIV infection
• List the types of antiretrovirals being evaluated as topical microbicides for prevention of HIV and summarize the results of the studies to date
• Describe the CDC Interim Guidance on HIV infection PrEP for high risk sexually active heterosexuals and MSMs
The Need for HIV Prevention

• MSM represent 4% of the population, in 2010 accounted for 78% of new infections among males and 63% of all new infections, 52% of all people living with HIV infection in 2009
• Canada: Portion of MSM making up estimated number of incident infections increased between 2005-2008
• Increased incidence in Young MSMs (13-24yrs)

CDC, British Columbia CDC 2010

The Need for HIV prevention

• Blacks/African Americans represent 12% of the population, accounted for 44% of new infections in 2010 and for 44% of people living with HIV infection in 2009
• Women accounted for 20% of estimated new HIV infections in 2010, and 24% of those living with HIV infection in 2009
• Women are disproportionally affected by AIDS in Sub-Saharan Africa

CDC, WHO
HIV Prevalence in the U.S. and Africa

In subpopulations in the U.S., HIV prevalence rates mirror those in Africa

Opportunities for Preventing Sexually Transmitted HIV Infection

Unexposed

Exposed (precoital/coital)

Exposed (postcoital)

Infected

Behavioural, structural

Male circumcision, Vaccine, Condoms

Topical microbicides, oral PrEP, Vaccine, Condoms

Vaccine, PEP

Treatment of HIV, reduced infectivity

- Male circumcision
- Oral pre exposure prophylaxis (daily PrEP)
- Topical PrEP (daily gels or intra-vaginal rings (microbicides)
- Preventive Vaccines

- Oral pre exposure prophylaxis (intermittent PrEP)
- Coitally dependent topical PrEP (microbicides)

- Oral post exposure prophylaxis (PEP)

- Anti-retroviral therapy
- Immediate treatment of positive partners in discordant couples
- Treatment for prevention in all who test positive for HIV (T4P)

HPTN 052: Treatment as Prevention in HIV+ Persons

1,763 discordant couples (97% heterosexual) in Africa, Asia, Americas. Those HIV+ had CD4 range of 350-550

HIV+ partner randomized to start HIV treatment immediately or deferred until CD4 <250
DSMB Interim analysis:
90% on ART had HIV RNA <400
40 incident cases of HIV
29 linked genetically to partner

96% reduction in transmission!

Cohen IAS 2011 #MOAX0102 and NEJM 2011;365:493

HPTN 052: Key questions

• Can these results be applied to:
  – High risk heterosexual couples with higher and lower CD4 counts than HPTN 052
  – MSMs and IDUs
  – Acute/Early HIV infection
• Does antiretroviral therapy (ARV) reduce infectivity through anal sex by the same magnitude as for vaginal sex?

http://www.oppositesattract.net.au/
High Level HIV RNA Shedding Occurs Despite Undetectable Plasma HIV RNA

- Prospective study of HIV-infected men initiating HAART and undetectable plasma HIV RNA by week 16 (n=25)
- HIV RNA shedding in semen
  - Isolated (any level): 48%
  - High level (>5000 copies/mL): 16%
- Semen isolated was infectious
- No drug resistant mutations


Non-Occupational Post-Exposure Prophylaxis for MSM: Efficacy Concerns

- Public health impact of NPEP is considered limited and only cost-effective in very specific situations
- Animal data show no protection against rectal SHIV challenge if started too late (+24 hrs) but some protection if started timely (+2hrs)
- Observational studies in MSM show no clear effect on transmission
- Men fail to timely recognize high risk exposure, even in the presence of direct access to ARVs
- Concern about negative behavioral side-effects
  - In some studies NPEP recipients were at higher subsequent risk for HIV seroconversion due to continued exposure or re-exposure
  - No increases in high risk behavior after NPEP were observed
    - but no decreases were observed either

Non-occupational post exposure prophylaxis (nPEP)

- PEP led to PrEP
  - If you need to take so soon after, why not take it before?
- Series of animal studies looking at the timing of drug intake versus exposure, 2 hrs before, 24 hrs after etc, etc.
- Particularly relevant are the rectal challenge models
- The results of these experiments are driving the PrEP research agenda for MSM & Heterosexuals

Efficacy of daily and pre- and post-exposure oral FTC/TFV in preventing SHIV infection following rectal challenge in macaques

Garcia-Lerma et al, PLOS, 2008
Antiretroviral Pre-Exposure prophylaxis: PrEP

- The daily or intermittent administration of antiretrovirals (ARVs) to HIV seronegative individuals with high risk of exposure to HIV


ARVs for PrEP

- Does the agent work?
- Can the agent be given at the right time to work?
- Will at risk individuals use the agent properly and reliably?
- Will cost and toxicity out weigh the benefit(s)?

- THE RIGHT DRUGS MUST BE USED AT THE RIGHT TIME FOR THE RIGHT DURATION
Ideal drug or regimen for PrEP

- Good tolerability and safety
- Low pill burden
- High potency
- Once daily dosing
- Long half life
- High barrier to resistance and lack of cross-resistance with other drugs


How does PrEP work?

- “Window of opportunity” for PrEP
  - Brief period of time after exposure where HIV has not yet spread throughout the body
  - PrEP may be able to stop HIV from causing infection
- Ideal Microbicide
  - Contraceptive, noncontraceptive
  - Reduce risk of other STIs
  - Used without a partner’s cooperation
  - Used vaginally or rectally
  - Inexpensive and available
  - Can be used by HIV+ (product not based on ARVs)

Potential Types of PrEP

- How are ARVs used?:
  - Oral pill
  - Topical: rectal or vaginal gel before/after sex
  - Injection
  - Intravaginal ring (monthly)
- How often are ARVs used?:
  - Daily, intermittently, coitally
- How many are used?: single or combination
- What ARVs are used?: Over 25 available

Pre-exposure prophylaxis strategies

- Tenofovir (TDF)
- Tenofovir/emtricitabine TDF/FTC
- Topical PrEP: 1% tenofovir gel
- Injectable PrEP: subcutaneous or intramuscular (Phase 1 trials)
- Intermittent PrEP trials

- iPrEx
- Partners PrEP
- TDF2
- CAPRISA 004
- ASPIRE and IPM trials
What’s being researched?

- Large studies
  - Tenofovir
  - Tenofovir + emtricitabine
  - Tenofovir vaginal gel used before or after sex or daily
- Small studies
  - Gels used rectally
  - Pills used intermittently or before/after sex
  - Slow release intravaginal rings
  - Long acting injections (TMC 278LA)
  - Other ARVs: miravirco, raltegravir, rilpivirine


PrEP Trials

- Proof of efficacy study of topical tenofovir gel in women
  - CAPRISA 004
- First oral PrEP study of TDF/FTC for MSM
  - iPrEx
- Proof of efficacy studies in young, HP adults in Africa
  - Partners PrEP
  - TDF2 (CDC4940)
- Early termination due to futility of PrEP in women
  - FEM-PrEP (oral TDF-FTC or placebo)
  - VOICE ( Oral TDF, TDF-FTC, TDF gel, or placebo)
CAPRISA 004: 1% TFV Vaginal Gel for Prevention of HIV in Heterosexual Women

**Double-blind study**
- South Africa sites (Kwa-Zulu, Natal)
- Sexually active HIV-uninfected women not using barrier contraception
- Screened (n=2160)

**Randomization 1:1**
- Tenofovir Gel (n=445)
- Placebo (n=444)

**Similar baseline demographic characteristics, sexual history/behavior, and contraception use**

**Administration of placebo/tenofovir DF gel**
- Insert 1 dose within 12 hours before sex
- Insert 1 dose ASAP, within 12 hours after sex
- No more than 2 doses within 24 hours

**Study continued until 92 HIV infections observed**


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**HIV Incidence in CAPRISA 004**

<table>
<thead>
<tr>
<th>Mos of Follow-up</th>
<th>Placebo</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>12</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>18</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>24</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>30</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>36</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>42</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>48</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>54</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>60</td>
<td>0.20</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Cumulative HIV endpoints**
- Placebo: 37, 65, 88, 97, 98
- TDF: 432, 833, 1143, 1305, 1341

**HIV incidence rates (TDF vs placebo)**
- 6.0 vs 11.2
- 5.2 vs 10.5
- 5.3 vs 10.2
- 5.6 vs 10.2
- 5.6 vs 9.1

**Effectiveness, % (P value)**
- Placebo: 47 (%.064)
- TDF: 50 (%.007)
- Placebo: 47 (%.004)
- TDF: 40 (%.013)
- Placebo: 39 (%.017)

**No K65R resistance mutations among seroconverters**

iPrEx: Eligibility

- Male sex at birth (N = 2499)
- 18 yrs of age or older
- HIV-seronegative status
- Evidence of risk for acquisition of HIV infection

### iPrEx: Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 2499)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Younger than 25 yrs</td>
<td>50</td>
</tr>
<tr>
<td>25-39 yrs</td>
<td>40</td>
</tr>
<tr>
<td>40 yrs or older</td>
<td>10</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>17</td>
</tr>
<tr>
<td>Black</td>
<td>9</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
</tr>
<tr>
<td>Mixed/other</td>
<td>69</td>
</tr>
<tr>
<td>Latino</td>
<td>72</td>
</tr>
<tr>
<td>Completed some college</td>
<td>43</td>
</tr>
</tbody>
</table>


### iPrEx: Baseline Risk Characteristics

<table>
<thead>
<tr>
<th>Risk Characteristic</th>
<th>Overall (N = 2499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of sex partners in past 12 wks</td>
<td>18</td>
</tr>
<tr>
<td>Unprotected anal sex with partner with positive/unknown HIV status in past 6 mos, %</td>
<td>80</td>
</tr>
<tr>
<td>Transactional sex in past 6 mos, %</td>
<td>41</td>
</tr>
<tr>
<td>HIV-positive sexual partner in past 6 mos, %</td>
<td>2</td>
</tr>
<tr>
<td>Self-reported STD in past 6 mos, %</td>
<td>25</td>
</tr>
<tr>
<td>Syphilis seropositivity, %</td>
<td>13</td>
</tr>
<tr>
<td>HSV-2 seropositivity, %</td>
<td>36</td>
</tr>
</tbody>
</table>

iPrEx Study: Comprehensive Package of Prevention Services

- All subjects received HIV testing, risk-reduction counseling, condoms, and diagnosis and treatment of symptomatic STIs
- At 24-week intervals, subjects screened for
  - Asymptomatic urethritis, syphilis, antibodies to HSV-2, genital warts/ulcers
  - Treatment was provided when indicated
- Sexual partners
  - Offered treatment of STIs
- As needed, linkage to local prevention and treatment services
- Counseled on the use of conventional methods to protect from HIV
- HBV vaccination offered to susceptible subjects


Partners PrEP: TDF vs TDF/FTC vs Placebo in HIV-Serodiscordant Couples

HIV-negative partners in HIV-serodiscordant heterosexual couples
(N = 4747)

Oral Tenofovir QD
(n = 1584)

Oral Tenofovir/Emtricitabine QD
(n = 1579)

Oral Placebo*
(n = 1584)

Follow-up: 36 mos

*Bilateral arm terminated early on July 10, 2011, by data and safety monitoring board.
TDF2: PrEP With TDF/FTC in HIV-Negative Heterosexuals in Botswana

HIV-uninfected adults, heterosexually active, aged 18-39 yrs
(N = 1219)*

≥ 12-mo follow-up

Oral Tenofovir/Emtricitabine
(n = 601)

Oral Placebo
(n = 599)

* n = 19 patients excluded for failure to start study medication or HIV infection.


Summary of PrEP Efficacy Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>mITT* % Reduction in HIV Incidence (95% CI)</th>
<th>Combined Self-Report and Pill-Count Medication Adherence (95% CI)</th>
<th>Pill-Count Medication Adherence (95% CI)</th>
<th>TFV Blood Detectionb</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>44% (15-63%)</td>
<td>&gt;50%*; 50% (15-70%)</td>
<td>&gt;90%*; 73% (41-88%)</td>
<td>NR 92% (40-99%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partners PrEP</th>
<th>Overall Men Women</th>
<th>Heterosexual discordant couples</th>
<th>75% (55-87%) 84% (54-95%) 66% (28-84%)</th>
<th>NR 100% (87-100%) 90% (58-98%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterosexual men and women</td>
<td>62% (22-83%) 80% (25-97%) 49% (-21 to 81%, NS)</td>
<td>NR</td>
<td>NR</td>
<td>84% (-62 to 98%, NS)</td>
</tr>
<tr>
<td>FEM-PrEP Heterosexual women</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Excluded only those enrolled patients later found to be infected at randomization and those with no follow-up visit or HIV test.

bThe percentage of reduction in HIV incidence among those with TFV detected in blood, compared with those without detectable TFV.

*The percentage of reduction in HIV incidence, compared with placebo, is presented for 3 groups: those with 50% medication adherence & those with 90% medication adherence.

“PrEP Partners” is a substudy of participants who provided counts via home-based unannounced pill counts with supplementary adherence counseling if the counts were <80%.

CDC. MMWR 2012;61:586-589
Partners PrEP: Both PrEP Strategies Significantly Reduce HIV Acquisition

<table>
<thead>
<tr>
<th>Primary Efficacy Outcome, mITT Analysis</th>
<th>TDF (n = 1584)</th>
<th>TDF/FTC (n = 1579)</th>
<th>Placebo (n = 1584)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV acquisitions, n</td>
<td>17</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>HIV incidence/100 PY</td>
<td>0.65</td>
<td>0.50</td>
<td>1.99</td>
</tr>
<tr>
<td>Efficacy vs placebo, % (95% CI)</td>
<td>67 (44-81)</td>
<td>75 (55-87)</td>
<td>--</td>
</tr>
<tr>
<td>• P value</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>--</td>
</tr>
</tbody>
</table>

- Both PrEP strategies associated with significant reduction in HIV acquisition vs placebo in both men and women
  - TDF efficacy: 71% in women, 63% in men
  - TDF/FTC efficacy: 66% in women, 84% in men


Partners PrEP: Efficacy in Highest Risk Subgroups

- PrEP efficacy was assessed among high-risk subgroups, including high-risk women
  - PrEP was protective against HIV-1 acquisition in all subgroups (efficacy 52-87%) among higher risk subgroups of women with high HIV incidence (>5.0 infections/100 PY), efficacy estimates ranged from 66-84%
- Both FTC/TDF and TDF alone demonstrated consistently high efficacy for HIV-1 protection among higher risk subgroups

Murnane P, et al. CROI 2013; Atlanta, GA. #1000

* For time-dependent variables, N in these subgroups represents participants who were categorized as high-risk during at least one month of follow up. Participants who reported unprotected sex within the prior three months were classified as high-risk.
Relative Efficacy of TasP, PrEP and Other Prevention Strategies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction in HIV Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 052 (ARV treatment as prevention)</td>
<td>96%</td>
</tr>
<tr>
<td>iPrEx (FTC/TDF) in MSM</td>
<td>44%</td>
</tr>
<tr>
<td>Subjects with detectable drug levels</td>
<td>94%</td>
</tr>
<tr>
<td>Partners PrEP (FTC/TDF) in discordant couples</td>
<td>75%</td>
</tr>
<tr>
<td>Subjects with detectable drug levels</td>
<td>90%</td>
</tr>
<tr>
<td>Condoms in heterosexuals</td>
<td>80%</td>
</tr>
<tr>
<td>Condoms in US MSM</td>
<td>70%</td>
</tr>
<tr>
<td>TDF2 (FTC/TDF) in men &amp; women</td>
<td>62%</td>
</tr>
<tr>
<td>Medical male circumcision</td>
<td>54%</td>
</tr>
<tr>
<td>STD treatment</td>
<td>42%</td>
</tr>
<tr>
<td>CAPRISA 004 (1% TFV vaginal gel) in women</td>
<td>39%</td>
</tr>
<tr>
<td>FEM-PrEP (FTC/TDF) in women, VOICE (FTC/TDF, TDF, TFV vaginal gel) in women, HIV vaccine (RV144)</td>
<td>Not Significant</td>
</tr>
</tbody>
</table>

Condom Efficacy By Consistency of Use Among Men Who Have Sex with Men (MSM) in the US

Analyzed efficacy of condoms in reducing HIV transmission in HIV-uninfected MSM who had anal sex with at least 1 HIV-infected partner from 2 US studies (N=3490): VaxGen 004 and Project Explore

<table>
<thead>
<tr>
<th>Reported sexual behavior and condom use in 6-month interval</th>
<th>Efficacy</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive or Insertive Anal Intercourse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always use vs. Never use</td>
<td>69.7</td>
<td>57.1-78.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sometime vs. Never use</td>
<td>4.4</td>
<td>-29.4-29.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

• Comparing “Always using condoms” to “Never using condoms”, the estimated efficacy (70%) among MSM reporting anal sex with an HIV-positive partner is less than the overall efficacy estimated for heterosexuals (80%); however, analyses to determine if these estimates are statistically different are not yet completed

Condoms offer substantial but partial protection against HIV infection

1. Smith DK, et al. CROI 2013; Atlanta, GA. Oral #32
FEM-PrEP study

- Phase III study of oral TDF-FTC vs Placebo
  - 3900 high risk African women
  - April 2011 ended early due to lack of efficacy
  - 35 vs 33 in the placebo and TDF-FTC arms
  - TDF blood levels too low (<40%) to assess efficacy
  - 4 vs 1 patient with M184V/I in the TDF-FTC placebo arms


PrEP: The VOICE Trial
Final Results
N=5029 HIV- Women: Primary Efficacy Results (mITT)

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>Oral Placebo</th>
<th>FTC/TDF</th>
<th>Oral Placebo</th>
<th>TFV Gel</th>
<th>Gel Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>823</td>
<td>837</td>
<td>1285</td>
<td>1306</td>
<td>1026</td>
<td>1030</td>
</tr>
<tr>
<td>No. of HIV Infections</td>
<td>52</td>
<td>35</td>
<td>61</td>
<td>60</td>
<td>61</td>
<td>70</td>
</tr>
<tr>
<td>HIV incidence per 100 p-y</td>
<td>6.3 (4.7, 8.3)</td>
<td>4.2 (2.9, 5.8)</td>
<td>4.7 (3.6, 6.1)</td>
<td>4.6 (3.5, 5.9)</td>
<td>5.9 (4.5, 7.6)</td>
<td>6.8 (5.3, 8.6)</td>
</tr>
<tr>
<td>% samples with TFV detected</td>
<td>30%</td>
<td>29%</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% women with no TFV detected ever</td>
<td>58%</td>
<td>50%</td>
<td>55%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Saahin J. et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 25LB.
VOICE Study

Vaginal and Oral Interventions to Control the Epidemic

- 334 seroconversions occurred over 5,511 PY
  - 22 were present at enrollment
  - HIV incidence rate = 5.7/100 PY
- None of the study arms significantly reduced risk of HIV acquisition

<table>
<thead>
<tr>
<th>HIV Infections</th>
<th>FTC/TDF</th>
<th>TDF</th>
<th>TFV Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Protection vs. Matched Placebo, HR (95% CI)</td>
<td>1.04 (0.7, 1.5)</td>
<td>1.49 (0.97, 2.3)</td>
<td>0.85 (0.6, 1.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>&gt;0.2</td>
<td>0.07</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

- No safety concerns were identified
- In a case-control subset (n=773), 25-30% of samples has detectable TFV (≥ 0.3ng/mL) despite high self-reported adherence
  - 50-58% of women never had drug detected

Marrazzo JM, et al. CROI 2013; Atlanta, GA. Oral #26LB

Safety

- iPrEx: No difference in adverse events, BMD changes were small, no difference in fracture rates between groups
- Partners PrEP: no difference in adverse events, mild GI toxicity
- TDF2: No difference in adverse events, Higher rate of GI side effects in the TDF/FTC group, decrease in BMD but no increase in fractures
iPrEx Study: Renal Safety

- Elevation in serum creatinine ≥1.1xULN
  - FTC/TDF (2%) vs placebo (1%) (P=0.08)
  - Normalized after treatment discontinuation
    - 4 of 5 participants who restarted FTC/TDF did not experience a new elevation
- Similar safety findings in other PrEP trials
  - Partners PrEP study
  - TDF2 study
  - FEM-PrEP


What do we know about PrEP?

- In combination with a comprehensive package of prevention services...
  1. Daily FTC/TDF reduced the risk of infection when used by
     - MSM and trans women
     - Heterosexual men and women
  2. Daily TDF reduced the risk of infection when used by heterosexual men and women
  3. A vaginal tenofovir gel used before and after sex reduced the risk of infection when used by women.
- It needs to be used consistently for it to work.
- The risk of side effects, toxicity, and drug resistance are low.
What don’t we know about PrEP?

- Safety/effectiveness of...
  - A pill taken occasionally
  - A gel used in the rectum
  - Long-lasting options (intravaginal ring or injection)
  - Other antiretrovirals

- Safety/effectiveness of tenofovir, FTC/TDF and tenofovir gel...
  - In populations not included in trials
  - Over a longer period of time
  - In the “real world”

Impact outside of a clinical trial

1. Uptake
   - How many people are using it?
     - Awareness – Do people know it’s available?
     - Acceptability – Do people want to use it?
     - Access – Can people access it if they want to?
   - Who is using it?

2. Adherence
   - Are people using it consistently and correctly?

3. Risk behavior
   - Are people increasing their risk behavior?
### Ongoing PrEP Efficacy Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Anticipated Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC Bangkok TDF Study¹</td>
<td>IDU (Men and Women)</td>
<td>2,413</td>
<td>2012</td>
</tr>
<tr>
<td>PROUD³</td>
<td>MSM</td>
<td>500</td>
<td>n/a</td>
</tr>
<tr>
<td>ANRS IPERGAY⁴</td>
<td>MSM</td>
<td>1900</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>9,842</td>
</tr>
</tbody>
</table>

*Per DSMB recommendations, the oral TDF and matched placebo arms have been discontinued, as well as the TFV and placebo gel arms

3. Data on file. PROUD study protocol. Medical Research Council Clinical Trials Unit

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### CDC PrEP Guidelines

- Why were these guidelines released before regulatory approval?

- “Concerns exist that without early guidance, various unsafe and potentially less effective PrEP-related practices could develop”
  
  - Such as...
    - Use of other antiretrovirals
    - Use of other dosing schedules
    - Not screening for HIV status before initiating PrEP
    - Providing in absence of other HIV prevention services
How to Implement PrEP

• Provider willingness
• Barriers to prescribing:
  – Integrating published data into real world practice
  – Assessing risk for HIV at baseline and ongoing
  – Communicating efficacy to patients
  – Implementing monitoring systems into practice
  – Cost effectiveness

Aids Patient Care STDs 2012; 26: 395-405

Key Components of PrEP

• 1. Target populations at high risk for HIV acquisition
  – MSMs
  – Requires assessment of high risk
• 2. Deliver PrEP as part of a comprehensive set of prevention services (“bundle”)
  – Risk reduction
  – Access to condoms
  – Identification and treatment of STIs
  – Medication adherence counseling
Factors to Help Identify Individuals at High Risk

- Has a partner known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and one or more of the following:
  - Inconsistent or no condom use
  - Diagnosis of sexually transmitted infections
  - Exchange of sex for commodities (such as money, food, shelter, or drugs)
  - Use of illicit drugs or alcohol dependence
  - Incarceration
  - Partner(s) of unknown HIV-1 status with any of the factors listed above

Key Components of PrEP

- 3. Monitor at regular intervals:
  - HIV testing
  - Pregnancy
  - Side effects
  - Adherence
  - Risk behaviors
Before PrEP: All patients

- Document HIV negative
- Test for acute infection (symptoms, recent HIV risk contact with known HIV +)
- Confirm ongoing high risk exposure
- Ensure HIV+ partners are linked to care
- Screening:
  - Chronic Hepatitis B
  - Renal function (CrCl)
  - Active STIs

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Before PrEP: Women

- Determine pregnancy status /plans
- Disclose safety to infants not fully known but no harm reported
- Do not prescribe to breast feeding women

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Beginning PrEP

• Prescribe FTC/TDF with no more than 90 days supply
• Inform women of unknown risk in pregnancy
• Inform patients with Chronic Hepatitis B of concurrent Hepatitis B treatment
• Provide risk reduction and access to condoms
• PrEP medication adherence counselling

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Follow up During PrEP

• Serial HIV testing every 3 months
• F/U pregnancy tests in women
• Reinforce PrEP medication adherence each visit
• Assess high risk behaviors and STIs every 2-3 months
• Screen for bacterial STIs every 6 months even if asymptomatic
• Check Cr every 3 months and then every 6 months

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Discontinuing PrEP

• Check HIV status
• If HIV+, check resistance testing, link to care
• If HIV-, ongoing risk reduction services
• If Chronic Hepatitis B establish need for ongoing treatment
• If pregnant: Inform provider of FTC/TDF use in pregnancy for potential adverse effects

Financial implications for PrEP

• Costs:
  – Drug: $1425/month = $17,000 yearly
  – Lab monitoring: $374-$504 yearly
  – Professional Fees: $310 yearly
• Poorly defined coverage by private and public insurances

Horberg. AMJ Prev Med 44 (1) : S125
Medication Assistance

- Gilead will provide FTC/TDF for PrEP at no cost for individuals who qualify for the assistance program

<table>
<thead>
<tr>
<th>Program Element</th>
<th>FTC/TDF PrEP Medication Assistance Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Criteria</td>
<td>US resident, uninsured or no drug coverage, HIV-negative, low income (200% FPL)</td>
</tr>
<tr>
<td>Drug Fulfillment</td>
<td>Product dispensed by Covance Specialty Pharmacy, labeled for individual patient use and shipped to prescriber (30 day supply); no card or voucher option</td>
</tr>
<tr>
<td>Recertification Period</td>
<td>6 months, with 90 day status check</td>
</tr>
</tbody>
</table>

What is a REMS?

- Risk Evaluation and Mitigation Strategy
- FDA program to manage a known or potential risk associated with a drug
  - Designed to ensure the benefits of a drug outweigh its risks
- Goals of REMS for FTC/TDF for PrEP is to educate prescribers and individuals about
  - The importance of adherence
  - The importance of regular monitoring of HIV-1 serostatus
  - FTC/TDF for PrEP must be part of a comprehensive prevention strategy

Approved by the FDA on July 16, 2012
Additional Non-REMS Measures

- Free HIV & HBV testing for qualified individuals
- Free condoms
- Subsidized HIV-1 viral resistance testing to individuals who seroconvert
- Opt-in reminder service regarding regular testing for HIV and other STDs (to be built)
- Support for community education activities on PrEP
- Support for demonstration projects
- FTC/TDF Medication Assistance Program for PrEP for uninfected individuals who lack insurance coverage

Unknowns

- Populations in which PrEP can be used effectively and safely
  - Long-term toxicity in HIV-negative person unknown
- Adherence
  - Long term
  - Intermittent use
- Resistance
  - Longer time between HIV tests
  - Persistence and spread of resistant virus, if occurs
- Behavior
  - How much will behavior change if PrEP is partially protective?
  - How much will that reduce efficacy?
Summary: Prescribing PrEP

- Daily FTC/TDF shown to have moderate efficacy for HIV-1 prevention among MSM
  - High efficacy among those with high adherence
  - PrEP is a promising HIV prevention strategy for MSM
- Daily TDF and FTC/TDF safe and efficacious among heterosexual couples and young heterosexuals
- Additional data forthcoming on daily tenofovir gel, oral FTC/TDF in women, and TDF in IDUs
- CDC and WHO guidelines forthcoming
- Providers should be prepared to do risk assessment, counseling, and prescribe for high-risk MSM
- Risk assessment and counseling tools to aid providers and prospective users are under development

Concluding Thoughts

“Treatment . . . costs are unsustainable. Greater emphasis must be placed on preventing new infections.”

– Institute of Medicine Report Brief, November 2010

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