Reproductive Options: A potential role for pre-exposure prophylaxis

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Objectives

• Treatment as Prevention
• HIV Pre-exposure Prophylaxis (PrEP)
  • Safety, monitoring and screening
  • HIV pos man HIV neg woman
• Provider perspectives
• Our local experience

• Disclosure: Investigator initiated funding from Gilead Sciences
Treatment as Prevention

- HIV Prevention Trials Network (HPTN) 052 2011
  - RCT of 1763 HIV mostly heterosexual serodiscordant couples
  - sub-Saharan Africa, Asia and the Americas
  - Early ART at CD4 count 350–550 vs. 200–250
  - 96% decrease in HIV-1 sexual transmission

Prevention of HIV-1 Infection with Early Antiretroviral Therapy
Treatment as Prevention

- Department of Health and Human Services Guidelines (DHHS)
  - As of March 2012, antiretroviral therapy (ART) recommended for all HIV infected individuals.

  - Individual benefit:
    - cardiovascular disease
    - kidney disease
    - liver disease
    - neurologic complications
    - Malignancy

  - Public Health Benefit
    - Prevention of sexual transmission (HPTN 052)
    - Decrease virus in secretions
Why we need more...

- Genetic analysis of transmitted viral strains
  - 11 of 39 uninfected participants who seroconverted on-study acquired HIV from partners outside of their partnership

- Treating infected partners may not provide complete protection for members of discordant couples with other sexual partners.
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Pre-exposure prophylaxis (PrEP)

- Vulnerable people use a part of an HIV drug cocktail on a daily basis to prevent HIV.
- Topical, oral, injectable formulations studied
- Only one FDA approved drug
  - Once daily tablet
  - co-formulated tenofovir disoproxil fumarate 300 mg (TDF) and emtricitabine (FTC) 200 mg
- 44 to 67% effective in clinical trials
  ....If taken perfectly 92% effective
Pre-exposure Prophylaxis Initiative Trial (iPrEx)

- Oral PrEP
- RCT of 2500 gay or bisexual men and transgender women
- once-daily FTC-TDF or placebo
- 44% reduction in HIV incidence in the intervention group

Grant, RM. et al, NEJM 2010

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Oral PrEP
TDF2-CDC

- Randomized Control Trial
- 1200 men and women
  - Botswana
  - Daily oral
  - FTC-TDF vs. placebo

- 63% reduction in the risk of HIV acquisition
Oral PrEP
Partners PrEP

- 4758 HIV sero-discordant heterosexual couples
  - Kenya & Uganda
  - TDF vs. FTC-TDF vs. placebo
  - Pregnancy rate was high (10.3 per 100 person-years) with no difference between groups

- TDF $\rightarrow$ 62% fewer infections
- FTC-TDF $\rightarrow$ 73% fewer infections
## iPrex 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></td>
<td>no. of patients (%)</td>
<td>no. of events</td>
<td>no. of patients (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>867 (69)</td>
<td>2630</td>
<td>877 (70)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>60 (5)</td>
<td>76</td>
<td>67 (5)</td>
</tr>
<tr>
<td>Any grade 3 or 4 event</td>
<td>151 (12)</td>
<td>248</td>
<td>164 (13)</td>
</tr>
<tr>
<td>Grade 3 event</td>
<td>110 (9)</td>
<td>197</td>
<td>117 (9)</td>
</tr>
<tr>
<td>Grade 4 event</td>
<td>41 (3)</td>
<td>51</td>
<td>47 (4)</td>
</tr>
<tr>
<td>Elevated creatinine level</td>
<td>25 (2)</td>
<td>28</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>56 (4)</td>
<td>66</td>
<td>41 (3)</td>
</tr>
<tr>
<td>Depression</td>
<td>43 (3)</td>
<td>46</td>
<td>62 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (2)</td>
<td>22</td>
<td>9 (&lt;1)</td>
</tr>
<tr>
<td>Unintentional weight loss (≥5%)</td>
<td>27 (2)</td>
<td>34</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46 (4)</td>
<td>49</td>
<td>56 (4)</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>15 (1)</td>
<td>16</td>
<td>11 (&lt;1)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1)‡</td>
<td>1</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Discontinuation of study drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanently</td>
<td>25 (2)</td>
<td>26</td>
<td>27 (2)</td>
</tr>
<tr>
<td>Permanently or temporarily</td>
<td>79 (6)</td>
<td>99</td>
<td>72 (6)</td>
</tr>
</tbody>
</table>

*Statistical significance determined using Fisher’s exact test.*

‡ Few events; P value did not converge for these categories.
PrEP Implementation
Before initiating PrEP

- Determine eligibility
- Document negative HIV antibody test
- Test for acute HIV infection
  - symptomatic
  - reports unprotected sex with an HIV-positive person in the preceding month
- Pregnant/breastfeeding
  - safety not fully assessed; no harm reported.
**Table 1: Summary of Guidance for PrEP Use**

<table>
<thead>
<tr>
<th>Detecting substantial risk of acquiring HIV infection</th>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive injecting partner</td>
</tr>
<tr>
<td>Recent bacterial STI</td>
<td>Recent bacterial STI</td>
<td>High number of sex partners</td>
<td>Sharing injection equipment</td>
</tr>
<tr>
<td>High number of sex partners</td>
<td>High number of sex partners</td>
<td>History of inconsistent or no condom use</td>
<td>Recent drug treatment (but currently injecting)</td>
</tr>
<tr>
<td>History of inconsistent or no condom use</td>
<td>Commercial sex work</td>
<td>Commercial sex work</td>
<td></td>
</tr>
<tr>
<td>In high-prevalence area or network</td>
<td></td>
<td>In high-prevalence area or network</td>
<td></td>
</tr>
</tbody>
</table>

| 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 |

<table>
<thead>
<tr>
<th>Other services</th>
<th>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</th>
<th>At 3 months and every 6 months thereafter, assess renal function</th>
<th>Every 6 months, test for bacterial STIs</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Do oral/rectal STI testing</th>
<th>Assess pregnancy intent</th>
<th>Access to clean needles/syringes and drug treatment services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy test every 3 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STI: sexually transmitted infection
PrEP and serodiscordance

CDC Guidelines

• PrEP should be discussed with heterosexually-active women and men whose partners are known to have HIV infection

• one of several options (IIB)

• Begin one month before conception

• Continue one month after conception
PrEPception

• FDA labeling information
• Perinatal Antiretroviral Treatment Guidelines
  • PrEP for HIV- uninfected partners may offer an additional tool to reduce the risk of sexual transmission (CIII).
  • Utility when the HIV-infected partner is receiving cART has not been studied.

• Limited data on PrEP safety for developing fetus
• Providers should discuss available information about potential risks and benefits
PrEPception

• Small study of periconception use of tenofovir
• 46 uninfected women in HIV-discordant couples
  • no ill effects on the pregnancy
  • no HIV infections
  • decreased anxiety
Breastfeeding and PrEP

• PrEP safety for infants exposed during lactation has not been adequately studied.

• *Infants born to HIV-infected mothers and exposed to TDF or FTC through breast milk suggest limited drug exposure.*

• *World Health Organization recommends TDF/FTC or 3TC/efavirenz for all pregnant and breastfeeding women to prevent perinatal and postpartum mother-to-child transmission of HIV*
PrEPception

• Submit information about any pregnancies in which PrEP is used to

Antiretroviral Pregnancy Registry

• Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to these medications
PrEP Implementation

Ongoing Assessment

• Link HIV-infected sexual partners to care
• Confirm HIV negative
• Monitor renal function
• Screen for hepatitis B infection
  • Vaccinate or treat
• Follow-up every 2–3 months
  • HIV testing
  • Adherence and Risk reduction counseling
• Screen and treat STIs, provide condoms
FDA program
- designed to ensure benefits of a drug outweigh risks
Educate prescribers and individuals
- Importance of adherence
- Importance of regular monitoring of HIV-1 serostatus
- Truvada for PrEP must be part of a comprehensive prevention strategy
PrEP Implementation

• Adherence

• Cost

• Long term drug safety considerations
  • GI side effects
  • 1% BMD loss at the total hip and femoral neck
  • rate of bone fractures was no different
Oral PrEP
Pre-exposure Prophylaxis Initiative Trial (iPrEx)

• Import of Adherence
  – Case-control sub-group analysis
    • Patients with detectable free FTC, TDF, or their intracellular metabolites
    • $\rightarrow$ 92% decreased risk of becoming infected

Grant, RM. et al, NEJM 2010
Oral PrEP: *Importance of Adherence*

**Fem-PrEP**

- RCT ~2000 high-risk women
  - Kenya, South Africa, Tanzania
  - > 1 partner in past month
  - ≥ 1 intercourse in past week
- Daily oral FTC-TDF vs. placebo
- Interim data assessment revealed no difference in the rate of new HIV infections
- Adherence < 40%
  - Only 30% felt themselves to be at risk.
PrEP Implementation Concerns
Drug Resistance

• Potential emergence of drug resistance
  • iPrEx: 10 participants already HIV-infected at the time of enrollment in the window period of acute HIV
    • Most were in the placebo arm
    • 2 randomized to FTC-TDF transmitted or newly-evolved resistance
Objectives

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• Provider perspectives
• Our local experience
PrEP Implementation

- Real world efficacy
- Many at-risk people may not be engaged in care
  - Prescriber
    - “PrEP will empower women” → willing to prescribe
  - Monitoring
- Long term drug safety considerations
  - iPrEx - nausea and mild inadvertent weight loss (in about 1-2% of the study participants)
  - 1% BMD loss at the total hip and femoral neck
  - rate of bone fractures was no different
- Acceptability
Provider Perspectives

- Anonymous on-line survey January to April 2013
  - Conducted among health care providers in Harris Health System (HHS)
    - largest network of public primary care providers in TX.
    - 22 locations staffed by BCM and UTHealth
    - Thomas Street Health Center -> primary care for HIV infected patients.

- 210 providers
  - Mean age - 36
  - 63% female, 48% white

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 to 30</td>
<td>78</td>
<td>41.7</td>
</tr>
<tr>
<td>31 to 40</td>
<td>59</td>
<td>21.9</td>
</tr>
<tr>
<td>41 to 50</td>
<td>34</td>
<td>18.2</td>
</tr>
<tr>
<td>51+</td>
<td>16</td>
<td>8.5</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75</td>
<td>36.7</td>
</tr>
<tr>
<td>Female</td>
<td>129</td>
<td>63.2</td>
</tr>
<tr>
<td>Transgender</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>21</td>
<td>10.5</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>180</td>
<td>89.5</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>67</td>
<td>35</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Black/African American</td>
<td>26</td>
<td>13.2</td>
</tr>
<tr>
<td>Native Hawaiian/ Other Pacific Islander</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>White</td>
<td>94</td>
<td>47.7</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>4.1</td>
</tr>
</tbody>
</table>
What We Found

- HIV specialists had 7.4 times greater odds of agreeing that PrEP is safe and effective (p=.002), compared to other providers.

- HIV specialists had 4 times greater odds of being confident in their ability to identify patients who needed PrEP than other providers (p=0.003).
What Our Results Mean and Why this Matters

• These findings highlight the need for additional training for primary care providers to enhance
  • Knowledge of PrEP safety and effectiveness
  • Ability to identify potential candidates
  • Confidence in PrEP prescribing/referral
  • Willingness to engage patients in the use of PrEP

• Only 18% of providers had received a patient inquiry about PrEP, 80% would be motivated to prescribe PrEP by patient requests.
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Our Local Experience

• Comprehensive HIV Prevention Program at Thomas Street Health Center
  • Incorporate PrEP education into routine counseling and testing for high risk individuals
  • Partners of HIV Positive patients
  • Referred by providers/ counselors/ other staff/self-referral
  • Referrals from health department
  • PrEPception

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Baylor College of Medicine
Comprehensive HIV Prevention at Thomas Street Health Center (TSHC)

Walk-up HIV testing

High Risk
- Px messaging
- PrEP info

Non-High Risk
- Routine counseling and testing

Charlene A. Flash MD MPH
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- Nursing Staff, Medical Assistants and Patient Care Technicians

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- Research Coordinators: Carmen Avalos, MD, Elizabeth Frost
- Medical Students: Katherine Hathaway and Erin Flattery

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Walk-up testing, 1st floor
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References


References


