PRE-EXPOSURE PROPHYLAXIS FOR HIV: EVIDENCE AND GENDER CONSIDERATIONS

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Disclosures

- None
Objectives

• Review the evidence regarding the effectiveness of pre-exposure prophylaxis for HIV prevention
• Discuss concerns, challenges and outstanding questions regarding PrEP
• Address gender considerations and PrEP
Pre- vs Postexposure Prophylaxis

HIV

Postexposure prophylaxis

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

HIV infection
Pre- vs Postexposure Prophylaxis

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

HIV

Pre-exposure prophylaxis

HIV Infection
Pre- vs Postexposure Prophylaxis

Pre-exposure prophylaxis

HIV

0 hr  36 hrs  72 hrs  1 mos  3 mos  5 mos
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004&lt;sup&gt;a&lt;/sup&gt; (coitally-applied TFV 1% gel)</td>
<td>889 heterosexual women (18-40 years)</td>
<td>39% reduced HIV incidence overall; 54% reduction with &gt; 80% adherence</td>
</tr>
<tr>
<td>TDF&lt;sup&gt;b&lt;/sup&gt; (daily TDF/FTC)</td>
<td>1219 heterosexual men and women (~46% women) (90% 21-29 years)</td>
<td>62.2% reduced HIV incidence (&gt; 30% attrition in study)</td>
</tr>
<tr>
<td>Partners PrEP&lt;sup&gt;c&lt;/sup&gt; (daily TDF or TDF/FTC)</td>
<td>4747 heterosexual serodiscordant couples</td>
<td>TDF alone: overall 67% reduced HIV incidence (71% F; 63% M); TDF/FTC: overall 75% reduction (66% F; 84% M)</td>
</tr>
<tr>
<td>FEM-PrEP&lt;sup&gt;d&lt;/sup&gt; (daily TFD/FTC)</td>
<td>2120 heterosexual women (18-35 years)</td>
<td>Stopped for futility April 2011</td>
</tr>
<tr>
<td>VOICE&lt;sup&gt;e&lt;/sup&gt; (MTN 003)</td>
<td>5029 heterosexual women</td>
<td>Oral TDF stopped for futility: September 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF 1% gel stopped for futility: November 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC follow-up completed: no protection with PrEP (≤30% with detectable drug in plasma)</td>
</tr>
</tbody>
</table>

Efficacy of PrEP among High-risk Heterosexuals: Subgroup Analyses from Partners PrEP

- Overall placebo arm HIV incidence 2.0/100 py
- In higher risk subgroups, placebo arm HIV incidence ranged 3.9-6.6/100 py
- In all subgroups PrEP efficacy 64-84%
  - With placebo arm HIV incidence >5/100 py, efficacy estimates 64-84%

Campbell et al. AIDS 2013, 27:2155–2160
FIGURE 7: HIV Prevention Technologies Shown to Be Effective in Reducing HIV Incidence in Randomized Clinical Trials
## Impact of Adherence on PrEP Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Detection in Nonseroconvertors</th>
<th>Efficacy Related to High Adherence</th>
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<tbody>
<tr>
<td>Partners PrEP</td>
<td>81%</td>
<td>86% TDF; 90% TDF/FTC with detectable levels</td>
</tr>
<tr>
<td>TDF2</td>
<td>79% (50% seroconvertors had detectable levels)</td>
<td>78% excluding those with no RF &gt;30 days</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>35-38% at single, 26% at 2 consecutive visits (95% self-report)</td>
<td>Too low to assess efficacy</td>
</tr>
<tr>
<td>VOICE</td>
<td>&lt;30%; ~50% no tenofovir detected in any sample</td>
<td>Too low to assess efficacy Adapted Baeten et al. JAIDS 2013;63 (suppl 2):</td>
</tr>
</tbody>
</table>
Adherence: Not the Only Impact on Efficacy

• Penetration of drug into vaginal tissue: After single dose of tenofovir, cervical and vaginal tissue levels 10-100 times lower for tenofovir and TDF than those achieved in rectal tissue (Patterson et al. Sci Transl Med 2011; 3:112)

• Genital inflammation or breaks in mucosal integrity: Rectal cells exposed to daily TDF gel exhibited downregulation of variety of genes (McGowan et al. 19th CROI 2012)
  • Could daily use be more detrimental to mucosal integrity than sex-dependent use?

• Degree of HIV exposure?
a) RIGHT DRUG AT RIGHT PLACE

- Oral
- Topical
- FGT: Virucidals, Env binding, RT integrase, protease
- Lymph node: cell + drug, naive cell, virus trans
- Sub-mucosa lumen, epithelial barrier

b) RTI KINETICS

- Vag. fluid
- Local cell: NRTI-P
- Recruited cell
  - Single drug:
    - NRTI
    - NNRTI
  - Combination:
    - NRTI
    - NNRTI

Protection, partial protection (exit kinetics), susceptibility

Kiser PF et al. AIDS Res Hum Retroviruses 2012;28:1373
### TABLE 2. Antiretroviral Resistance in PrEP Trials

Demonstrating Efficacy of PrEP for HIV Prevention

<table>
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<tr>
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<tbody>
<tr>
<td>Individuals With Seronegative Acute HIV Infection at Enrollment</td>
<td>Individuals Who Acquired HIV After Enrollment</td>
</tr>
<tr>
<td>iPrEx</td>
<td>2/2</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>2/8</td>
</tr>
<tr>
<td>TDF2</td>
<td>1/1</td>
</tr>
</tbody>
</table>

In iPrEx, the 2 subjects with seronegative acute HIV infection at the time of PrEP initiation both developed M184I/V mutations, conferring resistance to FTC. In Partners PrEP, of 8 subjects with seronegative acute HIV infection at the time of PrEP initiation, 2 developed antiretroviral resistance: 1 K65R substitution (conferring resistance to TDF) and 1 M184V substitution. In TDF2, 1 subject, also with seronegative acute HIV infection at the time of randomization to the FTC/TDF PrEP arm, developed both the K65R and M184V substitutions.
Other PrEP Considerations

• Safety (individuals with pre-existing renal conditions excluded from trials):
  • Both TDF and TDF/FTC well-tolerated
  • Rate of both mild and serious adverse events generally balanced between PrEP and placebo
  • Nausea most prominent side effect (10% or less)-mild, self-limited
  • Small increases in Crt seen in some, no correlation with clinical events or other consistent lab abnormalities
  • Small but significant decrease in BMD but no association with clinical findings
Other PrEP Considerations

- Risk compensation: no evidence of increase in sexual risk behaviors but:
  - Validity of self-reported behavioral data?
  - Applicability to real-world setting?
- Use in pregnancy: Antiretroviral Pregnancy Registry experience sufficient to rule out at least a two-fold increase in birth defects related to 1st trimester exposure to TDF +/- FTC
CDC Interim Guidance on PrEP

- **Before initiating PrEP:**
  - Document HIV-negative status, ask about acute HIV symptoms
  - Provide adherence and risk-reduction counseling and condoms; test and treat for STI as needed
  - Screen for sexually transmitted infections
  - Assess for pregnancy plans, current pregnancy, breastfeeding (no PrEP if breastfeeding)
  - If partner HIV+ determine whether receiving ART; assist with linkage to care

- **Beginning PrEP:**
  - Prescribe TDF [300 mg] plus FTC [200 mg]) daily, 90-day supply
  - Refill after documenting HIV-negative status
  - Risk-reduction and PrEP adherence counseling and condoms

Consult the complete CDC Interim Guidance on PrEP if this HIV prevention strategy is being considered.

CDC Interim Guidance on PrEP

- **Every 2-3 months on PrEP:**
  - Document HIV-negative status; assess adherence, risk behaviors, STI symptoms
  - Pregnancy test at every visit

- **Every 6 months on PrEP:**
  - Test for bacterial STIs and treat as indicated
  - Check serum creatinine and calculate creatinine clearance-3 months after initiation then every 6 months

Consult the complete CDC Interim Guidance on PrEP if this HIV prevention strategy is being considered.


- Survey of 1790 potential users (FSWs, MSMs, IDUs, SDCs and young women) in 7 countries (Peru, Ukraine, India, Kenya, Botswana, Uganda and South Africa)
- 61% reported they would definitely use PrEP
- Results maintained with consideration of side effects, need to combine condoms with PrEP, and need for regular HIV testing
- Across populations, route of administration most important
US and Canadian Provider Opinions on PrEP (Karris et al. CID 2013; Dec 30)

- Survey of 573 adult ID providers
- 74% support provision of PrEP
  - Only 9% had actually provided PrEP
- 14% have not or would not provide PrEP
  - 77% worried about adherence and risk of future resistance
  - 57% concerned about cost/reimbursement
  - 53% did not want to use potentially toxic drugs in healthy persons
  - 53% felt insufficient evidence for efficacy
- Great variability in real-world practice of PrEP
Gender Considerations

- Risk and vulnerability
  - Physiologic vulnerability (anatomic, hormonal, STIs)
  - Psychosocial vulnerability (intimate partner violence and sexual coercion, economic dependence, lack of power, etc)

- Perception of risk
  - VOICE: Despite ongoing counseling and provision of free condoms, unmarried women <25 had infection rate of 9%/yr but <30% had detectable drug levels when randomized to drug
  - FEM-PrEP: 70% of women reported feeling at little risk for HIV, despite almost 5% annualized HIV incidence
ISIS/HPTN 064: High HIV Incidence Among At-Risk Women in US

- 2099 women recruited from US communities with high HIV prevalence[1]
  - 88% black, 12% Hispanic, 8% white
  - 1.5% of women newly diagnosed with HIV at baseline

- Annual HIV incidence 5 x higher than CDC’s 0.05% estimate for black women[2]
  - Comparable to adult incidence rates in sub-Saharan Africa (0.28% for Congo and 0.53% for Kenya)[3]

<table>
<thead>
<tr>
<th>Events Analyzed</th>
<th>Women Analyzed, n</th>
<th>Events, n</th>
<th>Window Period</th>
<th>Annual Incidence Estimates, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infection at enrollment</td>
<td>2064</td>
<td>2</td>
<td>2 wks</td>
<td>2.52</td>
<td>0.60-10.7</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>1951</td>
<td>4</td>
<td>--</td>
<td>0.24</td>
<td>0.09-0.65</td>
</tr>
</tbody>
</table>

Gender Considerations

• Fertility
  • Pregnancy desires and reproductive decision-making: most studies show that these are similar between HIV-infected and HIV-uninfected women (Chen 2001, Craft 2007, Finocchiaro-Kessler 2012)

• Pregnancy
HIV Serodiscordance

- High rates of HIV serodiscordance (SDC) among sexual partnerships
  - Approximately 50% of HIV+ individuals are in SDC relationships and ~20% in relationships with partner of unknown HIV status (Fam Plann Perspect 2001; 33:144)
  - Estimated ~140,000 HIV SDC heterosexual couples in US, about half of whom want more children (Am J Obstet Gynecol 2011;204:488)
Live Births Among HIV+ Women Before and After HAART Availability

• WIHS
  • Comparison of live birth rates 1994–1995 (pre-HAART era) and 2001–2002 (HAART era) in HIV+ and HIV- women aged 15–44 years
  • In HAART era, 150% increase in live birth rate among HIV+ women versus 5% increase among HIV- women
    • Live birth rate higher in all age categories with largest difference (306%) seen in women >35 years
    • Birth rate higher in HAART era within each category of CD4 cell count

CD = cluster of differentiation.
Acute HIV in Pregnancy

  - Analysis of 2144 HIV+ women giving birth in NY: only 1.4% were seroconversions, but these accounted for 23.4% of all MTCT 2002-2004
  - CDC analysis of 10 states: 1.4% seroconversion rate among 4006 HIV+ pregnancies; MTCT rate 29.3% vs 4.8%
Periconceptional PrEP?

• 53 serodiscordant couples (male HIV+)
  • Viral suppression (HIV-RNA <50 copies/mL) of male partner for at least 6 mo
  • Daily determination of LH-peak in urine to optimize timing of intercourse
  • Two doses of tenofovir (300mg) taken 36 and 12 hours before intercourse by the HIV- woman

• 244 documented unprotected events of vaginal intercourse with 0 seroconversions

• Pregnancy rates: 1st attempt- 26%; 5 attempts- 60%; 12 attempts- 75%

Vernazza et al. AIDS 2011; 25:2005
Global Challenges to Implementation of PrEP

- Financial and resource limitations
  - Health system and work force capacity
- Need for national and global guidelines
- Competing priorities
- Identification of high risk populations and ways to engage them
- Stigma
- Potential risk compensation
- Support and appropriate measurement of adherence
Global Challenges to Implementation of PrEP

- Identification of optimal provider cadre, locations for provision of PrEP
  - Demonstration projects ongoing
- Need better understanding of relationship between drug concentration and effect
- Need better understanding of determinants of behavior related to PrEP
Mathematical Modeling

• PrEP could be at least as cost-effective as earlier ART initiation by infected partner, provided annual cost of PrEP is <40% cost of ART and PrEP effectiveness >70% (Hallett et al. PLoS Med 2011;8:e1001123)

• Impact and cost-effectiveness of PrEP in South Africa: most cost-effective if utilized before ART reaches 65% HIV+ persons; above this level, C-E decreases rapidly (Pretorius et al. Plos One 2010; 5:e13646)
On the Horizon

- Studies of alternatives to daily dosing
- Studies of alternative ARV drugs (MVC, RPV, Dapivirine)
- Studies of alternative formulations: intravaginal rings, films, injectables
Conclusion

• PrEP is another tool for HIV prevention, but should be part of a comprehensive risk reduction package

• Good adherence is critical to PrEP effectiveness-need better measures, better support and more forgiving regimens

• In women use of PrEP must take into account risk and risk perception and fertility plans and desires