PrEP for Women: Prep and PreP-Ception

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Disclosures

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• Research Grant Support - Janssen
PrEP for Women

• 27 yo pregnant female with HIV + partner, tested negative in first trimester of pregnancy. At baby’s 2 week follow-up, mom noted to be positive and baby tested positive.

• 17 yo female victim of commercial sex exploitation referred from JH, tested positive for gonorrhea, chlamydia and HIV.

• 53 yo female, single, dating with 2 partners in last 2 years, tested HIV+ at routine physical exam.
Women at Risk

Lifetime Risk of HIV Diagnosis by Race/Ethnicity

African American Men: 1 in 20
African American Women: 1 in 48
Hispanic Men: 1 in 48
Hispanic Women: 1 in 227
White Men: 1 in 132
White Women: 1 in 880

Source: Centers for Disease Control and Prevention
## 2015 HIV (Cases/100,000)

<table>
<thead>
<tr>
<th>Group</th>
<th>US</th>
<th>California</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>26.2</td>
<td>18.5</td>
</tr>
<tr>
<td>AI/AN</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Hisp/Lat</td>
<td>5.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Asian</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>White</td>
<td>1.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Women at Risk

• In the US, the majority of women get HIV from sex with a man.

• Best known risk factors, injection drug use and male-to-male sex, does not apply to them and many women may not know if it applies to their partners.

• Stigma, fear, discrimination and homophobia may also place many women of color at high risk for HIV
Women at Risk

• Young women:
  – More likely to have partners whose status is unknown
  – More likely to have an STI which facilitates HIV acquisition
  – Immature reproductive tract

• Older women
  – May be unaware their partner has been sexually active with other women or men.
  – May not use condoms as not concerned about pregnancy
• ISIS Study (HPTN 064) n=2099
  – Describe factors that impacted HIV risk
  – Results
    • 1.5% entered study unaware of the HIV infection
    • Annual incidence 0.32% (5x CDC estimate)
    • Factors associated with HIV:
      – Substance abuse
      – Age 27-33; 34+ (compared with 18-26)
      – HIV diagnosis of partner
### Summary of relevant PrEP Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
</table>
| **FEM-PrEP Trial**<sup>3</sup>             | South Africa, Kenya, Tanzania  
Phase 3 randomized, double-blind, placebo-controlled study among heterosexual women  
- 1951 Heterosexual women  
TDF/FTC Vs Placebo | - No Effect  
- Adherence was low  
- TDF detected in fewer than 50%  
- Correlated with low efficacy  
- Trial stopped after interim analysis determined unlikely difference in efficacy between the two groups. |
| **Vaginal and Oral Interventions: VOICE<sup>4</sup>** | Phase 2B randomized, open-label, placebo-controlled study.  
5029 Heterosexual women  
- young: ave age 25  
- single: 79%  
oral TDF or oral TDF/FTC or topical TDF vaginal gel Vs Corresponding placebo | No Effect  
TDF only detected in:  
- 30% in TDF group  
- 29% in TDF/FTC  
- 25% Gel  
Ultimately not assoc w/ risk of reduction.  
- TDF/FTC: 4% increase  
- TDF: 49% increase  
- Gel: 15% decrease (not statistically significant) |
## Summary of relevant PrEP Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Design</th>
<th>Medication</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners Demonstration Project (Partners PrEP)(^1) Africa</td>
<td>Open-label; daily oral PrEP among ART-naïve heterosexual serodiscordant, high-risk couples - 4758 couples - 38% HIV neg female - 68% HIV neg male</td>
<td>TDF/FTC Vs TDF alone Vs Placebo</td>
<td>- TDF- 67% reduction - TDF/FTC- 75% reduction - detectable plasma TDF levels was associated with 90% reduction in risk of HIV acquisition - no drug resistance detected in those infected after enrollment</td>
</tr>
<tr>
<td>TDF2(^2) Botswana</td>
<td>Phase 3 randomized, double-blind, placebo-controlled study in 1,219 heterosexual 55% male 45% female 90% unmarried 90% aged 21-29</td>
<td>TDF/FTC Vs Placebo</td>
<td>- 62% reduction in HIV acquisition (95% CI 22-83; P=0.03) - Adherence was 84% in both arms.</td>
</tr>
<tr>
<td>HPTN 052 Africa, Brazil, India, Thailand</td>
<td>Randomized clinical trial designed to evaluate cART by HIV-infected individuals to prevent sexual transmission of HIV among serodiscordant couples. - 1763 Heterosexual couples 50% HIV neg female</td>
<td>cART- immediate or delayed</td>
<td>cART led to a 96% reduction in transmission of HIV to the uninfected partner.</td>
</tr>
</tbody>
</table>
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</thead>
<tbody>
<tr>
<td>HPTN 069/A5305</td>
<td>Randomized double-blind Women 18+ cohort (188)</td>
<td>MVC containing regimens vs Truvada</td>
<td>MVC containing regimens were safe -adherence 60-65% -no new HIV infections -low number of STI</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>iPrEx</td>
<td>Gay men, other MSM, Transgender women</td>
<td>Daily oral Truvada</td>
<td>44% efficacy</td>
</tr>
<tr>
<td>Brazil, Ecuador, Peru, S.Af, Thailand, US</td>
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</tbody>
</table>
PrEP and women

• Effective in Partners PrEP
  – Women were older (mean age 36)
  – All in committed relationship with a partner they knew was HIV positive

• Effective in TDF2
  – Small study size

• Effective in HPTN 069/A5305
  – Adherence was aided by personal motivation and adherence cues and reminders.
  – Few concerns about HIV-stigma or side effects
  – Mixed plans for future PrEP use
• Not effective in FEM-PrEP or VOICE
  – Young age, 59% under age 25
    • Drug detected in 21% of young, unmarried women vs 54% in older, married women (VOICES)
  – 70% perceived themselves at little or no risk of HIV
Lesson learned

- Perceived risk is a big factor for adherence
- Need products women will use.
On going Studies

- Truvada
  - AEGIS- adherence, text messaging, drug level monitoring
- Alternate regimens and modalities.
  - TAF- Oral
  - ÉCLAIR- Injectable Cabotegravir
    - MSM/TGW
  - HPTN 083-injectable Cabotegravir
    - MSM/TGW
  - HPTN 077/084-injectable Cabotegravir
    - Cis women
  - HPTN 076- Injectable Rilpivirine
    - 136 Low risk HIV-uninfected women (NY, NY, ZIM, SA)
  - Immunotherapies- VRCO1
PrEP- C: Guidelines on Safer Conception

- US Public Health Service PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014 A CLINICAL PRACTICE GUIDELINE
  - PrEP use periconception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition.
  - Both the FDA labeling information\(^1\) and the perinatal antiretroviral treatment guidelines\(^2\) permit this use.
  - However, data directly related to the safety of PrEP use for a developing fetus are limited.

Reproductive Health Services for Serodiscordant Couples

- Preconception counseling
- PMTCT services
- Assisted reproductive services
  - Sperm washing
  - IUI/IVF
- Biomedical approaches
  - TasP
  - Prep and Prep-C
  - STI testing and treatment
<table>
<thead>
<tr>
<th>HIV Transmission/goal</th>
<th>Method</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female HIV positive</td>
<td>ARV in the mother</td>
<td></td>
</tr>
<tr>
<td>Goal: decrease perinatal transmission (MTCT)</td>
<td>ARV to child after birth</td>
<td>95-98%</td>
</tr>
<tr>
<td>Male positive</td>
<td>Sperm washing + intrauterine insemination or IVF</td>
<td>100%</td>
</tr>
<tr>
<td>Goal: decrease male to female transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either partner positive</td>
<td>Sex without condoms limited to peak fertility</td>
<td>Unknown</td>
</tr>
<tr>
<td>Goal: decrease transmission to negative partner</td>
<td>ART for infected partner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PrEP (oral, daily FTC/TDF)</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>Treatment of STIs</td>
<td>63-73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>
Risk to HIV negative Woman:

• attempting to get pregnant or are already pregnant increases the risk of getting HIV from the infected partner.
  – risk of transmitting to baby is very high if seroconversion occurs during pregnancy.
  • 8x higher.
Preconception strategies:

Reducing risk of HIV Transmission

- **ARV therapy (TasP)**
  - Goal of sustained, undetectable viral load
  - CD4 count above 350
- **PrEP**
- Are healthy
  - No opportunistic infections
  - Not using drugs or alcohol
- Screen for STI
- Safest options for becoming pregnant
  - Avoid or limit condomless sex

- **No options** have been shown to be **100% effective**, but some can greatly reduce the chance of transmission
Safest:

• Donor sperm from an uninfected HIV man with artificial insemination
• Sperm washing

• Access to sperm washing and IVF can be limited in some settings.
• TDF/FTC is FDA approved for only daily dosing
  – Guidelines: “option for serodiscordant couples during conception and pregnancy”
• Adherence is critical
• The exact time to optimal protection using daily doses of TDF/FTC is not known.
  – maximum intracellular concentrations are reached in cervicovaginal tissues at approximately 20 days
  – rectal tissue at approximately 7 days
HIV treatment and planned unprotected sex

TIMED, PERIOVULATORY UNPROTECTED INTERCOURSE AFTER:

- undetectable viral load for 6 months
- no sexually transmitted infections (STIs)
- Semen analysis- to evaluate for low sperm count, low motility, low semen volume
  - Avoid unnecessary exposure for prolonged periods when likelihood of conceiving is low or nonexistent
- Daily dosing of TDF/FTC beginning one month before conception attempt, continue for 1 month after conception (or longer)
- Condomless sex limited to peak fertility time identified by lab tests for ovulation.

Mugo NR. AIDS 2011; 25 (15)
• Switzerland study:
    • Males on cART with undetectable viral load
    • One dose of TDF at peak LH and 2\textsuperscript{nd} dose 24 hours later.
      – No HIV infections
      – High rate of pregnancy- 75% after 12 attempts

• Further studies are needed.
• 267 Women had 288 pregnancies
• Adherence: (CROI 2017,#955 Heffron)

- High adherence to study drug as measured by pill count and plasma tenofovir concentrations
PrEP Risks

• In PrEP trials, follow-up with persons taking medication has been conducted for an average of 1–4 years.
  – Decrease in bone mineral density
    • Return to pre-truvada baseline 6 months after stopping PrEP (iPrex)
    • Women more susceptible to bone loss.

• Long-term safety of PrEP has not yet been determined
• Pregnancy and breastfeeding are not contraindications to PrEP
  – Long term safety during pregnancy or during breastfeeding is not yet determined for HIV negative
    • TFV transferred in milk in very small quantities (3.2 ng/ml or 3% MP conc)
    • Infant plasma, TFV was unquantifiable in 94% of samples
    • BF infant would have exposures <0.01% of proposed infant therapeutic dose (6mg/kg)

## PrEP-C Risk

### Partners PrEP and Partners Demonstration Project pregnancy outcomes in Kenya and Uganda

<table>
<thead>
<tr>
<th></th>
<th>PrEP-exposed</th>
<th>PrEP-unexposed</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of women</strong></td>
<td>30</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td><strong>Number of pregnancies</strong></td>
<td>30</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age (yrs)</strong></td>
<td>25</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Preterm delivery</strong></td>
<td>0</td>
<td>5 (7.7%)</td>
<td>0.4 (0-2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.4</td>
</tr>
<tr>
<td><strong>Pregnancy loss</strong></td>
<td>5 (16.7%)</td>
<td>20 (23.5%)</td>
<td>0.8 (0.3-2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.7</td>
</tr>
<tr>
<td><strong>Congenital anomaly</strong></td>
<td>0</td>
<td>5 (7.7%)</td>
<td>Fisher’s exact p=0.3</td>
</tr>
</tbody>
</table>

No increased poor birth outcomes in women on TRUVADA for PrEP

Heffron R, et al. CROI 2017. Seattle, WA. Poster #934
Challenges: PrEP Uptake In US

• Between 1st quarter 2013-1st Quarter 2016 prescriptions for Truvada rose:
  – 72% for women
  – 1350% for men.

• Kaiser Research (CROI 2017, #874)
  – Cohort study on Northern CA members initiating PrEP July 2012-Dec 2014. N 972
    • 98% men
    • Factors associated with discontinuation:
      – Women: Risk ratio 2.1
      – Drug/alcohol: RR 1.6
      – Copay >$50: RR 1.4

• DHSP PrEP/PEP Centers of Excellence (to date)
  • Enrolled 10 cis-females/12 transgender females
FTC/TDF for PrEP use among AA and Hispanic women was significantly less than that of White women

*These data represent 43.7% (n=21,463) of unique individuals who have started FTC/TDF for PrEP from 2012-3Q2015. Bush S, et al. ASM 2016. Boston, MA. Oral
Challenges: PrEP Uptake In US

MCA

- PrEP
  - Pregnant women in serodiscordant relationships
  - Non pregnant women: age range 14-51
    - Serodiscordant
    - Victims of commercial sex exploitation
- Direct Partnerships: JH, VIP Clinic, Adolescent Clinic and new LGBTQ clinic.
- HIV Education- Treatment and Prevention:
  - Medical Students/Residents/Fellow
  - PAETC trainees
  - “Target Zero”.

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Provider Education
• Educating providers on candidates for PrEP:
  • 26% ever prescribed PrEP
    – 74% MSM; 30% WSM; 23% serodiscordant couples
  – Expand LAC County PrEP guidelines to include specifics on women
  – Normalize sexual health as part of Comprehensive health care.
Challenges and Next Steps

- **Increase women's awareness on PrEP**
  - Most literature and social marketing targets MSM
  - Educate and utilize community stakeholders to deliver messages on PrEP in women.
    - Increase awareness to decrease stigma
  - Recognize and address factors that may interfere with uptake and adherence to PrEP
    - Stigma, intimate partner violence, Immigration status.
  - Normalize sexual health as part of comprehensive healthcare.
Challenges and Next Steps

• Increase number of PrEP Centers of Excellence that focus on women’s care
  – Culturally competent
  – Centers that provide testing and treatment for HIV
  – Expand to family planning clinics and other family clinics were women frequent

• Partner with research institutions and leverage public-private partnerships
  – Knowledge from demonstration projects and real world-experience
  – New modalities for differing needs
  – Build upon locally funded efforts and drug affordability programs
  – Social determinants of health that might impeded HIV prevention programs
    • Interplay between interpersonal, social and structural factors
Special Thanks

- MCA Patients and Community Advisory Board
- MCA Providers and Staff
- LAC Medical Center
- DHSP Staff
- Commission on HIV

- MCA Clinic: PrEP referral
  - Call or text: 323 455-9454
  - Email MCAclinic@usc-mca.org