WHO’s early release guidelines on PrEP: implications for eMTCT

Dominika Seidman, MD
October 13, 2015
Outline

- Evidence behind WHO early release guidelines on PrEP
- PrEP eligibility according to the WHO
- Rationale for PrEP during pregnancy & lactation
- What we know about PrEP during safer conception, pregnancy, lactation & contraception
- Unanswered questions & future directions
WHO: Oral PrEP should be offered to people at “substantial risk”

<table>
<thead>
<tr>
<th>Target population</th>
<th>Specific recommendation</th>
<th>Strength of the recommendation</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-negative individuals at substantial risk of HIV infection</td>
<td>Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches</td>
<td>Strong</td>
<td>High</td>
</tr>
</tbody>
</table>
WHO meta-analysis of PrEP: inclusion criteria

1. RCT or demonstration project evaluating use of oral PrEP (containing TDF) to prevent HIV infection among people at “substantial risk”

2. Measured one or more key outcomes, comparing those randomized to oral PrEP vs. placebo or oral PrEP vs. no PrEP

3. Published before April 2015

## WHO meta-analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of studies</th>
<th>N</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
<th>p-value (meta-regress.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10</td>
<td>17424</td>
<td>0.49 (0.33-0.73)</td>
<td>0.001</td>
<td>--</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;70%)</td>
<td>3</td>
<td>6150</td>
<td>0.30 (0.21-0.45)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate (41-70%)</td>
<td>2</td>
<td>4912</td>
<td>0.55 (0.39-0.76)</td>
<td>&lt;0.0001</td>
<td>0.70</td>
</tr>
<tr>
<td>Low (≤40%)</td>
<td>2</td>
<td>5033</td>
<td>0.95 (0.74-1.23)</td>
<td>&lt;0.0001</td>
<td>0.099</td>
</tr>
<tr>
<td>Mode of Acquisition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>4</td>
<td>3167</td>
<td>0.34 (0.15-0.80)</td>
<td>0.01</td>
<td>0.36</td>
</tr>
<tr>
<td>Vaginal/penile</td>
<td>6</td>
<td>14252</td>
<td>0.54 (0.32-0.90)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Biological sex¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>8706</td>
<td>0.38 (0.25-0.60)</td>
<td>&lt;0.0001</td>
<td>0.19</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>8716</td>
<td>0.57 (0.34-0.94)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Age²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 24 years</td>
<td>3</td>
<td>2997</td>
<td>0.71 (0.47-1.06)</td>
<td>0.09</td>
<td>0.29</td>
</tr>
<tr>
<td>≥25 years</td>
<td>3</td>
<td>5129</td>
<td>0.45 (0.22-0.91)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Drug Regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>5</td>
<td>4303</td>
<td>0.49 (0.28-0.86)</td>
<td>0.001</td>
<td>0.88</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>7</td>
<td>5693</td>
<td>0.51 (0.31-0.83)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Drug Dosing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>8</td>
<td>17024</td>
<td>0.54 (0.36-0.81)</td>
<td>0.003</td>
<td>0.14</td>
</tr>
<tr>
<td>Intermittent</td>
<td>1</td>
<td>400</td>
<td>0.14 (0.03-0.63)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

¹ iPrEx included 313 (13%) transgender women. ² Includes only studies stratified age by <25 and ≥25.

Fonner et al. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis.
WHO meta-analysis: adherence & effectiveness

Regression of Log risk ratio on Adherence

- VOICE
- FEM-PrEP
- Bangkok TDF
- TDF2
- iPrEx
- Partners
- PrEP
- CDC Safety Study

Studies of sexual transmission of HIV that included biologic females
Fonner et al. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis.
Partners PrEP Trial

<table>
<thead>
<tr>
<th></th>
<th>TDF HR</th>
<th>TDF+FTC HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>All women</td>
<td>0.29</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>0.13 - 0.63</td>
<td>0.16 - 0.72</td>
</tr>
<tr>
<td>Women with detectable</td>
<td>0.14</td>
<td>0.10</td>
</tr>
<tr>
<td>drug</td>
<td>0.05 – 0.43</td>
<td>0.02 – 0.44</td>
</tr>
</tbody>
</table>

Baeten et al. et al, Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. NEJM 2012
Open-label studies

Partners Demo Project
- 1,000 sero-different couples in Kenya & Uganda; ~50% HIV-negative women
- PrEP as bridge to ART
- 1 HIV infection (expected: ~21)

ADAPT
- 179 young women in Cape Town
- Randomized to daily, twice weekly + boost, and event-driven dosing
- Highest adherence & coverage of sex acts with daily dosing; no difference in HIV infections

# Drug resistance in setting of PrEP

<table>
<thead>
<tr>
<th>Study</th>
<th>Infected at Entry</th>
<th>Incident Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Drug Resist/Tot</td>
<td>Placebo Resist/Tot</td>
</tr>
<tr>
<td>iPrEx</td>
<td>2/2</td>
<td>1/8</td>
</tr>
<tr>
<td>Partners</td>
<td>1/3</td>
<td>0/6</td>
</tr>
<tr>
<td>PrEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF2</td>
<td>1/1</td>
<td>0/2</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>VOICE</td>
<td>2/9</td>
<td>0/1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6/16</strong></td>
<td><strong>1/18</strong></td>
</tr>
<tr>
<td><strong>% (95% CI)</strong></td>
<td><strong>37.5% (18 to 61%)</strong></td>
<td><strong>5% (1 to 26%)</strong></td>
</tr>
</tbody>
</table>

11 infections with resistance occurred in active arms

**Overall risk of resistance = 11/9222 or 0.1%**

Adapted from Liegler and Grant in *Drug Resistance*, Springer, in press
FEM-PrEP resistance data

- Analysis of seroconversions: 35 in placebo and 33 in drug arm
  - Seroconversions in setting of low or undetectable drug levels → little resistant virus
  - Seroconversions in setting of detectable drug → resistant virus, but suggestive of seroconversion prior to initiation of PrEP

WHO: safety data

• 10 RCTs presented data on adverse events

• Risk of any adverse events did not differ between PrEP vs. placebo (RR 1.01, 95% CI 0.99-1.03, p=0.27).
  – No differences in sub-groups based on sex, age, mode of acquisition, drug regimen or dosing

• Subclinical decline in renal function and bone mineral density; no clinical events & no decline with time

Fonner et al. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis.
WHO: PrEP eligibility

- Offer PrEP to anyone at “substantial risk” of HIV

- Individual-based vs. group-based risk assessment

- Discuss risks/benefits/alternatives of PrEP with pregnant & breastfeeding women
Defining “substantial risk”

- Incidence threshold: incidence at which cost of PrEP is less than cost of ART to treat averted infection

“Substantial risk” incidence in control arms of PrEP trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Incident HIV Infections</th>
<th>Person Years</th>
<th>HIV Incidence Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BKK TDF</td>
<td>IDU</td>
<td>33</td>
<td>4823</td>
<td>0.7</td>
<td>0.47 to 0.96</td>
</tr>
<tr>
<td>FEM PREP</td>
<td>Women</td>
<td>35</td>
<td>n/a</td>
<td>5.0</td>
<td>n/a</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>60</td>
<td>1308</td>
<td>4.6</td>
<td>3.5 to 5.9</td>
</tr>
<tr>
<td>iPrEx RCT</td>
<td>MSM and TGW</td>
<td>83</td>
<td>2113</td>
<td>3.9</td>
<td>3.1 to 4.8</td>
</tr>
<tr>
<td>Partners PrEP RCT</td>
<td>Men and women in SDC</td>
<td>52</td>
<td>1578</td>
<td>2.0</td>
<td>n/a</td>
</tr>
<tr>
<td>TDF2</td>
<td>Men and Women</td>
<td>24</td>
<td>n/a</td>
<td>3.1</td>
<td>n/a</td>
</tr>
<tr>
<td>PROUD</td>
<td>MSM</td>
<td>19</td>
<td>214</td>
<td>8.9</td>
<td>6.0 to 12.7</td>
</tr>
<tr>
<td>Ipergay</td>
<td>MSM</td>
<td>14</td>
<td>n/a</td>
<td>6.6</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Van Damme NEJM 2012; Baeten NEJM 2012; Marrazzo NEJM 2015; Thigpen NEJM 2012; Choopanya Lancet 2013; Grant CROI 2013; Grant Lancet Infectious Diseases 2014.
WHO: PrEP eligibility

- Offer PrEP to anyone at “substantial risk” of HIV

- Individual-based vs. group-based risk assessment

- Discuss risks/benefits/alternatives of PrEP with pregnant & breastfeeding women
Rationale for PrEP during pregnancy & lactation

• Pregnancy is associated with ~2X increased risk of HIV acquisition

• Acute HIV during pregnancy associated with ~8X increased risk of perinatal transmission

• Acute HIV during breastfeeding associated with ~4X increased risk of neonatal transmission

Singh et al. HIV seroconversion during pregnancy and mother-to-child HIV transmission: data from the enhanced perinatal surveillance projects, United States, 2005–2010. CROI 2013, Atlanta, GA.
Rationale for PrEP during pregnancy & lactation

Risk of HIV acquisition by pregnancy & postpartum status

Rationale for PrEP during pregnancy & lactation

Effect of ART on perinatal HIV transmission in setting of incident infection during pregnancy

Safer conception with PrEP: safety

- Partners PrEP: PrEP discontinued when pregnancy detected, mean 5 wks gestation
- No difference in pregnancy incidence, birth outcomes, and infant growth
- “Signal” for PrEP associated with pregnancy loss?
  - 42.5% for FTC+TDF vs. 32.3% for placebo (difference 10.2%; 95% CI, −5.3% to 25.7%; p = 0.16)
- CIs for pregnancy outcomes were wide → definitive statements about safety of PrEP periconception cannot be made

TDF in pregnancy

- APR: adequate 1st trimesters exposures to detect 1.5X risk of overall birth defects
- No impact on intrauterine growth
- Conflicting data on birth outcomes
- DART: no dif. in growth, fractures at 2 yrs
- IMPAACT: no dif. in growth at 6 months
- PHACS (US): decreased length (0.4 cm) and head circumference (0.3 cm) at 1 year

TDF exposure and infant BMC

- SMARRT: 12% decreased bone mineral content \((p=0.002)\) in TDF-exposed infants; no long-term data available

- PHACS: no association between meconium TDF concentration and birth weight, length or bone mineral content

TDF during lactation

- Little data

- TDF/FTC is secreted in breast milk, but infant levels are extremely low (<2% proposed infant doses)

PrEP & Contraception

• No difference in PrEP’s efficacy among women using DMPA vs. no hormonal contraception (adjusted $p_{interaction} = 0.65$, comparing aHR 0.35 versus aHR 0.25)

• No change in contraceptive efficacy in women using PrEP and combination oral contraceptives, injectables, and implants

PrEP in adolescent women

- ~140,000 15-19 yo women living in areas with HIV prevalence ≥3%

- Research agenda for young women:
  - Drug safety, acceptability & use patterns
  - Long-term impact of multiple cycles of starting/stopping PrEP
  - Implementation strategies in sub-populations
  - Address ethical/legal/regulatory barriers to PrEP use in young people

Next steps

• Implementation science & expanded access
  – Anticipate WHO implementation guidelines in 2016
• Improve understanding of female reproductive tract biology
• Pharmacokinetic data in women
• Studies in pregnancy & breastfeeding
• Changing risk/benefit ratios in setting of universal ART recommendations
• Alternate dosing regimens
• Alternate modes of delivery
• Drug-drug interactions
• Multipurpose prevention technologies
Acknowleggements

- Shaffiq Essajee
- Bob Grant
- Jessica Rodrigues