Preventing HIV infection in pregnant and nursing mothers: Importance and barriers to study development

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PrEP is effective in women

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Agent</th>
<th>Efficacy</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>889 high-risk South African women</td>
<td>BAT24 TDF gel BAT 24 placebo</td>
<td>39% (54% in those &gt; 80% adherent)</td>
<td>~38% reported &gt;80% adherence</td>
</tr>
<tr>
<td>Partners in PrEP</td>
<td>4747 couples (~1788 HIV neg women)</td>
<td>Daily oral TDF Daily oral Truvada Daily oral placebo</td>
<td>67% TDF, 75% Truvada (Women: 71% TDF; 66% Truvada)</td>
<td>Estimated ~ 97% dispensed doses taken</td>
</tr>
<tr>
<td>TDF2</td>
<td>1200 Heterosexual men (n =656 ) and women (n =544 )</td>
<td>Daily oral Truvada</td>
<td>62% overall; 77% in those taking 80% men;49% women 82% men taking; 75% women taking</td>
<td>Reported 80%</td>
</tr>
</tbody>
</table>
Lack of efficacy is likely related to adherence

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<tbody>
<tr>
<td>FemPrEP</td>
<td>1951 young African women</td>
<td>Daily oral Truvada</td>
<td>Stopped for futility</td>
<td>Reported &gt; 90%; &lt; 50% by drug levels</td>
</tr>
<tr>
<td>VOICE</td>
<td>5000 women (1000 each arm)</td>
<td>Daily oral Truvada, Tenofovir or placebo</td>
<td>TDF gel and oral Tenofovir arms stopped for futility</td>
<td>Not yet reported</td>
</tr>
</tbody>
</table>
High incidence of HIV infection in pregnancy

- Risk of HIV-1 infection may be increased during pregnancy, possibly due to biologic or behavioral factors (Gray Lancet 2005, Mugo AIDS 2011)
- Acute HIV-1 infection during pregnancy associated with 30-50% risk of mother-to-child-transmission

UNAIDS 2010 Report; Moodley JID 2011; Keiffer JAIDS 2011; Moodley AIDS 2009
Pregnancy is a good opportunity for PrEP

- Pregnancy is a period of time during which HIV-infected women have been shown to be more adherent to ARVs

**ARV adherence in pregnant vs. non-pregnant women**

<table>
<thead>
<tr>
<th></th>
<th>Percent with optimal adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ickovics 2002</strong></td>
<td>40</td>
</tr>
<tr>
<td><strong>Rodriguez Vaz 2007</strong></td>
<td>20</td>
</tr>
<tr>
<td><strong>Zorilla 2003</strong></td>
<td>80</td>
</tr>
</tbody>
</table>

- Pregnant
- Postpartum
- Non-pregnant
What about breastfeeding?

- Behaviorally, may be a time of high risk; when women rejoin partners in sexual activity
- In terms of infant risk of HIV acquisition, may be a longer duration than pregnancy
- Hormonally, during exclusive breastfeeding, can be associated with lower estrogen levels, dry vagina and increased risk of trauma during sex
- May be a time of lower adherence to medications due to sleep deprivation, change in perceived risk or competing priorities
Importance

- 2.6 million people were newly infected with HIV in 2009
  - 370,000 of them were children < 5 years old

*Source: UNAIDS.*

Change in HIV-1 incidence between 2001 and 2009

*UNAIDS Global Report 2010*
Possible research questions about PrEP in pregnancy

- **Feasibility**
  - What factors increase adherence to PrEP in pregnancy?
  - Do women want daily or episodic PrEP?

- **Safety**
  - What effects will PrEP have on fetal growth, bones or kidneys?
  - What effects will PrEP have on preterm delivery?

- **Efficacy**
  - Does PrEP work as well (or better) in pregnant women?
  - Is the effective dose the same in pregnant women?
  - Is episodic PrEP effective?
Do we need to study PrEP in pregnancy?

- **Feasibility & acceptability**
  - Adherence has varied widely in different PrEP studies
  - Needs to be evaluated in many populations, with multiple strategies to optimize adherence and risk perception

- **Safety**
  - Data on fetal anomalies with Tenofovir and Truvada in ~1700 HIV-1 infected mothers is available from pregnancy registry, but no data on growth or renal function
  - One of the primary concerns of most women taking medication in pregnancy

- **Efficacy**
  - If pregnancy is a higher risk time biologically, PrEP may be less effective
  - Episodic PrEP may be less effective compared to daily PrEP
Special considerations for studies in pregnancy

- Regulations in the US require that studies in pregnancy offer direct benefit to the mother or the fetus
- Can infants be followed long enough to assess neuro-developmental outcomes?
- In many low-resource countries women do not access prenatal care until later in gestation
- Many communities and regulators have a higher threshold for risk in studies during pregnancy
Feasibility

- Adherence has been identified as a key component of PrEP effectiveness
  - In CAPRISA 004 motivational interviewing and individualized counseling increased adherence
  - Measurements of adherence are imperfect
- Risk perception is a critical part of adherence
  - In Fem-PrEP only ~25% of women thought they were at risk for HIV acquisition
  - One of the most successful PrEP studies to date is Partners, in which participants knew that their partner is HIV-infected
- Studies of cell phone text messaging reminders, peer counseling, etc might identify strategies to increase adherence
Efficacy

- Given mostly positive results of PrEP trials to date, would be difficult to justify a placebo-controlled trial
  - Stepped wedge design could be used to provide a comparison
- N would be several thousand women
- Drug levels would be needed to assess biologic efficacy, which is the most pressing scientific question
- A study of effectiveness would be more similar to a feasibility study, related to whether women actually take the medication
Safety

- Questions remain about effects of Tenofovir and Truvada on fetal growth and renal function

- Studies in pregnant monkeys dosed SQ daily with 30mg/kg from 2nd trimester showed:
  - Lower birthweight compared to historical controls
  - Growth restriction in 2/6 PMPA-treated infants (normal in utero growth)

- Studies in HIV-infected pregnant women (TDF dose 300mg po daily) show:
  - Infant size < 10th percentile same in TDF-exposed and unexposed infants (n = 68 exposed)
  - No difference in structural or genetic anomalies (n = 1092 1st trimester exposures, 639 2nd trimester exposures)
  - No difference in stillbirth, birth weight, growth to 2 years, creatinine, phosphate, fractures (at 2 years). (n = 120 exposed, 62 unexposed)

Safety

- MTN 019 is a “roll-back” design; initial participants enrolled late in gestation; if safe, will enroll earlier in gestation
  - Total N = 391, randomized to TDF gel vs. placebo
  - Allows 90% power for detection of a RR of 2.0 associated with study drug (compared to a baseline risk of 12%)

- Using a stepped-wedge design with oral PrEP compared to standard of care, and using a composite fetal outcome measure, the following N would be needed:

<table>
<thead>
<tr>
<th>Baseline rate</th>
<th>Unacceptable rate</th>
<th>RR</th>
<th>N</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>12%</td>
<td>18%</td>
<td>1.5</td>
<td>2592</td>
<td>89%</td>
</tr>
<tr>
<td>12%</td>
<td>24%</td>
<td>2.0</td>
<td>768</td>
<td>90%</td>
</tr>
<tr>
<td>12%</td>
<td>30%</td>
<td>2.5</td>
<td>400</td>
<td>90%</td>
</tr>
</tbody>
</table>
Safety

- In HIV-infected patients, TDF can cause renal impairment and osteoporosis (though these can also be related to HIV infection)
- In most PrEP studies, people with renal dysfunction are excluded
- Pregnant women have an increased GFR and often a lower Cr – should there be different cut-offs for inclusion/exclusion?
Ultimate Goal