

# HIV PREVENTION

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ETHICAL CONSIDERATIONS IN DEVELOPING AN EVIDENCE BASE FOR PrEP IN PREGNANT WOMEN

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## HIV & pregnancy

- Approximately 17.8 million women HIV-infected worldwide
- Millions more at risk of becoming infected, most often through unprotected intercourse
- Unprotected sex may also lead to pregnancy
- Circle of risk:
  - many women with HIV become pregnant
  - pregnancy appears to increase risk of acquiring HIV
- Acute HIV infection in pregnancy associated with high rates of vertical transmission

## HIV & pregnancy

- Approximately 1.5 million HIV-infected women give birth worldwide each year
- PMTCT has been focus
- Limited research on treatment and prevention of HIV and co-morbidities in pregnant women

# PHASES

## Pregnancy & HIV/AIDS: Seeking Equitable Study

- Goal: to provide consensus-driven guidance for conducting HIV research in pregnancy
1. Identify scientific **priorities in, perceived barriers to, and novel research designs** for HIV research and pregnancy AND **characterize reasoning** around study participation from the viewpoints of affected women
  2. Conduct scholarly ethical and legal analysis of conditions for responsible HIV research with pregnant women
  3. Develop and disseminate to the HIV research and IRB communities a Concrete, Engagement-Driven Guidance Document delineating when and under what circumstances pregnant women can and should be included in HIV research.

## Roadblocks to research

- Widespread reticence to include pregnant women
  - Ethically and legally complicated
  - Logistic and analytical challenges
  - Research environment and culture

Krubiner, et al, *AIDS*, 2016

- Harms resulting from:
  - Evidence gaps re safety for woman and fetus
  - Evidence gaps re dosing and toxicity
  - Reticence to use beneficial medications
  - Denial of access to direct benefits of research participation

# Pre-exposure prophylaxis (PrEP)

- PrEP = Prevention of HIV through daily pill
    - TDF: tenofovir
    - TDF-FTC: tenofovir-emtricitabine
    - Has been shown to prevent HIV infection in numerous high-risk populations
  - Not studied prospectively in pregnant populations
- **Pregnancy has been an exclusion criteria from all major trials of PrEP in Africa; and women who become pregnant on such trials are required to discontinue medication.**

See e.g.:

Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329(5996):1168-1174

Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367(5):399-410.

## PrEP in pregnancy: What we know

- **Evidence suggests that it is SAFE. No association between PrEP and adverse pregnancy outcomes, including:**
  - Studies of women living with HIV receiving combination ART
    - Majority show no evidence of increases in adverse pregnancy outcomes<sup>1-3</sup>
  - Studies of TDF used by pregnant women for prevention of maternal to child transmission of Hepatitis B<sup>4-5</sup>
    - Adverse events rates **lower** among HBV mono-infected women as compared to HIV-infected women
  - Studies of women who became pregnant on PrEP studies
    - No difference in adverse pregnancy outcomes among women exposed to TDF or TDF/FTC and placebo<sup>6-7</sup>

<sup>1</sup> Wang L, Kourtis AP, Ellington S, Legardy-Williams J, Bulterys M. Safety of tenofovir during pregnancy for the mother and fetus: a systematic review. Clin Infect Dis. 2013 Dec; 57(12):1773–81. 19.

<sup>2</sup> Heffron R, Pintyre J, Matthews LT, Weber S, Mugo N. PrEP as peri-conception HIV prevention for women and men. Curr HIV/AIDS Rep. 2016; 13:131–9.

<sup>3</sup> Zash R, Souda S, Chen JY, Binda K, Dryden-Peterson S, Lockman S, et al. Reassuring birth outcomes with tenofovir/emtricitabine/efavirenz used for prevention of mother-to-child transmission of HIV in Botswana. J Acquir Immune Defic Syndr. 2016; 71:428–36.

<sup>4</sup> Brown RS Jr, McMahon BJ, Lok AS, Wong JB, Ahmed AT, Mouchli MA, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: a systematic review and meta-analysis. Hepatology. 2016; 63:319–33.

<sup>5</sup> Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med. 2016; 374:2324–34.

<sup>6</sup> Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, et al. Partners PrEP Study Team. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA. 2014; 312:362–71.

<sup>7</sup> Bunge K, Balkus J, Noguchi L, Pan J, Piper J, Kabwigu S, et al. Pregnancy incidence and outcomes in women receiving tenofovir-based PrEP in the VOICE trial. International AIDS Conference. July 2015, Vancouver, Canada. Abs. MOPEC480.

## PrEP in pregnancy: Conflicting guidelines

### World Health Organization<sup>8</sup>

Permissive of PrEP in pregnancy:

PrEP is recommended as, “an additional prevention choice for people **at substantial risk of HIV infection**”

and ... “**further research is needed** to fully evaluate PrEP use during pregnancy and breastfeeding”

### South Africa<sup>9</sup>

PrEP is contraindicated in pregnancy:

“...**PrEP in pregnant or breastfeeding women is contra-indicated.**”

However, as the risk of seroconversion during pregnancy is high, the risks and benefits of PrEP should be discussed with potential PrEP users, allowing these women at high risk of HIV acquisition to make an informed decision regarding PrEP use.”

<sup>8</sup> World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection—recommendations for a public health approach—second edition, 2016. Geneva, Switzerland: World Health Organization, 2016. <http://www.who.int/hiv/pub/arv/arv-2016/en/>.

<sup>9</sup> Bekker L-G, Rebe K, Venter F, Maartens G, Moorhouse M, Conradie F, et al. Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection. Southern African Journal of Hiv Medicine [Internet]. 2016 Mar 9 [cited 2016 Oct 16];17(1). Available from: <http://www.sajhivmed.org.za/index.php/HIVMED/article/view/455>



## Proposed case

- A prospective study of oral PrEP for pregnant women at risk for HIV
  - Adapted from a study being developed by the IMPAACT network (IMPAACT 2009), an observational cohort study comparing pregnancy outcomes between: 1) women at risk for HIV taking oral PrEP and 2) women at risk for HIV who decline PrEP during the antenatal period
    - Would be the first large prospective study of PrEP in pregnant women

<http://impaactnetwork.org/studies/IMPAACT2009.asp>

## Proposed case

- Sites: Malawi, South Africa, Uganda, and Zimbabwe
- HIV-negative pregnant women offered PrEP at their first antenatal visit
- Target: 300 women (200 women receiving PrEP/100 women refusing PrEP)
- Monthly clinic visits during pregnancy and for 6 months following
- Outcomes:
  - Woman:
    - Pregnancy outcomes, e.g., pre-term delivery, miscarriage/stillbirth
    - PrEP adherence over time measured by plasma drug concentrations
    - Liver function, HIV status
  - Infant:
    - Health/development for first 6 months of life, e.g., congenital abnormalities, weight, length, head circumference, liver function, serum chemistries

## Ethical issues: Prospect of Direct Benefit

- **Prospect of Direct Benefit (PDB)**

- Potential maternal benefit
  - Purpose of PrEP is to prevent maternal disease
- Potential benefits to the fetus if successful in preventing maternal infection
  - Prevent potential fetal HIV infection
  - Not gestated in potentially compromised environment of woman infected with HIV
- PDB is greater for woman than fetus
  - Fetal transmission occurs in a subset of maternal infections

## Ethical issues for consideration

1. Are there are ethically relevant differences between risks of interventions in trials in the context of prevention of fetal disease (as in PMTCT, which is widely seen as acceptable) versus the context of prevention of maternal disease (which is the case with PrEP)?
2. Can an increment of prospect of maternal benefit justify potential risk to the fetus?
3. When in the development of new interventions should pregnant women be included in trials?

## Summary

- Given urgent need for HIV preventives during pregnancy, a prospective clinical trial of PrEP in pregnant women is an important step
- Ethical issues needing consideration include:
  - ethically relevant differences between risks of intervention aimed at maternal versus fetal disease;
  - the appropriate standard for acceptable fetal risk in trials holding the prospect of benefit;
  - the appropriate timing of studies including pregnant women in research and development of new interventions
- Through this case study discussion we hope to further inform the development of ethically responsible, action-guiding recommendations for addressing evidence gaps through research in pregnancy.

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