PrEP in Pregnant Women: current data, experiences, and guidelines

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Outline

- Systematic review
- PROMISE trial results
- New data since the systematic review
- Current experience
- Guidelines

Mofenson systematic review

- Includes data from 33 studies published prior to August 2016
  - 26 TDF-ART
    - 20 comparing TDF-ART versus non-TDF ART (2 randomized trials)
    - 2 comparing TDF-ART versus no ART or ZDV/sdNVP
    - 4 comparing TDF-ART by duration TDF
  - 5 studies among Hepatitis B-infected women (1 randomized trial) encompassing 268 women using TDF
  - 2 randomized trials of PrEP when women used PrEP until the point of pregnancy discovery ~6 weeks of exposure
    - Of the 2, the Partners PrEP Study had good adherence to study drug and FEM-PrEP had low adherence

Mofenson review: pregnancy outcomes

- Stillbirth
  - No significant differences in TDF exposed and non-exposed pregnancies among 4 studies of women living with HIV
- Pregnancy loss
  - No significant differences in 2 placebo controlled PrEP RCT
- Preterm delivery
  - No significant difference in 5 studies among women living with HIV and 6 studies among HIV negative women
- Low birth weight
  - No significant difference in 6 studies among women living with HIV; less frequent in HIV negative women
- Birth defects
  - No significant differences among 7 studies of women living with HIV
- Neonatal death
  - No significant differences in 4 studies among HIV negative women; 1 RCT among HIV positive women with significantly elevated frequency among TDF-exposed concludes that results may be related to the PI-based ART regimen

Mofenson review: infant growth

- Growth parameters at birth
  - All studies show no differences in WAZ, LAZ, HCAZ or slightly larger sizes among TDF-exposed infants
- Growth parameters at 12 months – 4 studies
  - WAZ not different or better in TDF-exposed infants
  - Inconsistent results for LAZ and HCAZ (3 studies, one shows slightly larger children, one shows no difference, one shows slightly smaller children)
- Data are reassuring

PROMISE Study

- 3-arm randomized trial to determine efficacy to prevent early infant HIV and safety
  - Arm 1: ZDV alone, followed by sdNVP+FTC/TDF “tail”
  - Arm 2: ZDV-based ART: AZT, 3TC, LPV/r
  - Arm 3: TDF-based ART: TDF, FTC, LPV/r
- Triple drug ART regimens protected infants from early infection better than ZDV alone (0.8% transmission vs. 1.5%, $p<0.001$)
  - Triple drug ART regimens had more adverse events

Fowler NEJM 2016

PROMISE Study

- Relative to the ZDV-based ART arm, women receiving TDF-based ART had:
  - More severe adverse pregnancy outcomes: 9.2% vs. 4.3%, p=0.02
  - More very preterm delivery before 34 weeks: 6.0% vs. 2.6%, p=0.04
    - But there was no difference between women in the TDF-based arm and the ZDV-only arm
  - More infant deaths: 4.4% vs. 0.6%, p<0.001
    - But there was no difference between women in the TDF-based arm and the ZDV-only arm

PROMISE Study

- Hypothesis for why the TDF-based ART regimen had higher rates of severe adverse events and infant death include:
  - A pharmacokinetic interaction between lopinavir–ritonavir and tenofovir related to protease inhibitor properties
  - An unknown confounder resulting in lower rates of very preterm delivery and infant death in the group assigned to zidovudine-based ART related to study procedures

Conclusion to Mofenson systematic review

- TDF exposure is generally well tolerated in terms of pregnancy outcomes and infant growth
- Most studies among HIV-infected women showed no adverse events with TDF exposure
- Given available safety data, there does not appear to be a safety-related rationale for prohibiting PrEP during pregnancy/lactation or for discontinuing PrEP in HIV-uninfected women receiving PrEP who become pregnant and are at continuing risk of HIV acquisition

Another systematic review

- Includes studies through Feb 2017
- Related to the PROMISE data, this study concludes that: “Tenofovir/emtricitabine is likely to increase stillbirth/early neonatal death and early premature delivery compared with zidovudine/lamivudine, but certainty is low when they are not coprescribed with lopinavir/ritonavir.”

Controversy

- BMJ Rapid Recommendation Nov 2017

  "Tenofovir and emtricitabine probably increase the risk of early neonatal death and preterm delivery <34 weeks compared with zidovudine and lamivudine; this is more certain when they are combined with lopinavir/ritonavir" *(Siemieniuk BMJ 2017)*

- British HIV Association

  "We do not support recommendations of 'ART in pregnant women living with HIV: a clinical practice guideline (BMJ, 11/9/17)'" *(http://bhiva.org/BHIVA-response-to-BMJ-article.aspx)*

- PROMISE Investigators

  "the PROMISE team does not agree that the PROMISE trial results support a recommendation against using a TDF-based ART regimen in pregnancy." *(Fowler et al. BMJ 2017)*

New data since the review (not a comprehensive list)

- 1 study among women using TDF as part of ART to treat HIV found no adverse effects of maternal TDF use on perinatal outcomes (Pintye JID 2017)
- 1 study including 168 women randomized to TDF to prevent perinatal transmission of Hepatitis B found no safety concerns but very few safety parameters were studied (Jourdain NEJM 2018)
- 1 study including 30 women using TDF as HIV PrEP throughout pregnancy
  - Compare birth and growth outcomes among FTC/TDF users to placebo arm women from the Partners PrEP Study (Partners Demonstration Project; Heffron et al, under review)

Partners Demonstration Project

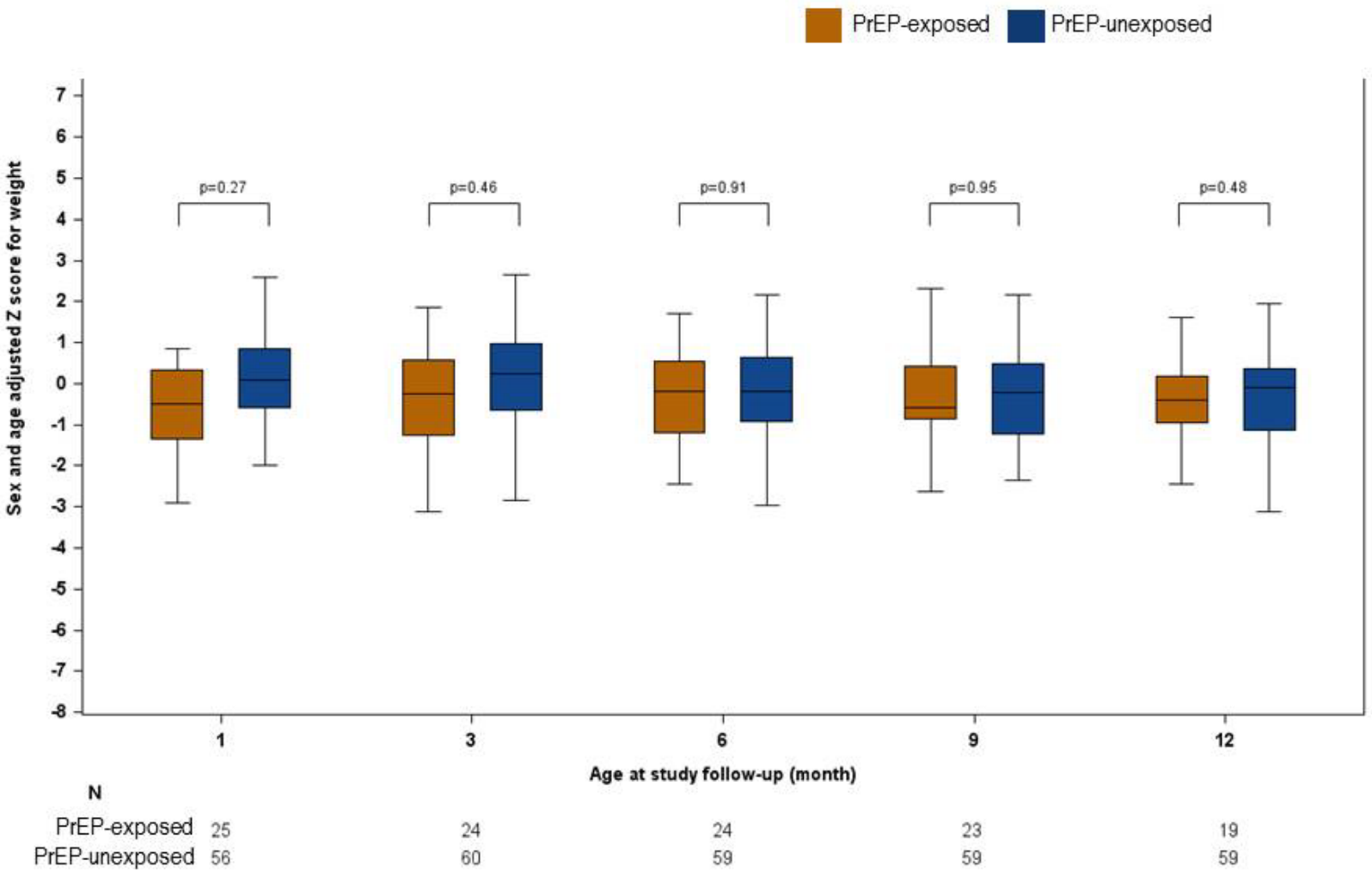
	PrEP-exposed (women chose to continue FTC/TDF during pregnancy)	PrEP-unexposed (placebo arm of Partners PrEP Study)	Odds Ratio 95% CI p-value	Adjusted Odds Ratio 95% CI p-value
Number of pregnancies	30	96		
Number of pregnancies ending with live births	25 (83.3%)	65 (67.7%)		
Number of pregnancies ending in pregnancy loss*	5 (16.7%)	20 (23.5%)	0.42 (0.15-1.19) p=0.103	0.59 (0.15-2.23) p=0.4
Preterm delivery (live births)**	0 (0%)	5 (7.7%)	0.37 (0-2.11) p=0.376	0.54 (0-3.27) p=0.61

*Odds ratios are from GEE estimating the association between PrEP exposure and pregnancy loss; adjusted OR controls for maternal age at study enrollment, history of pregnancy loss and preterm delivery

**Exact logistic regression was used to evaluate the association between PrEP exposure and pregnancy loss; adjusted OR controls for maternal age at study enrollment, and history of pregnancy loss.

Heffron et al., under review

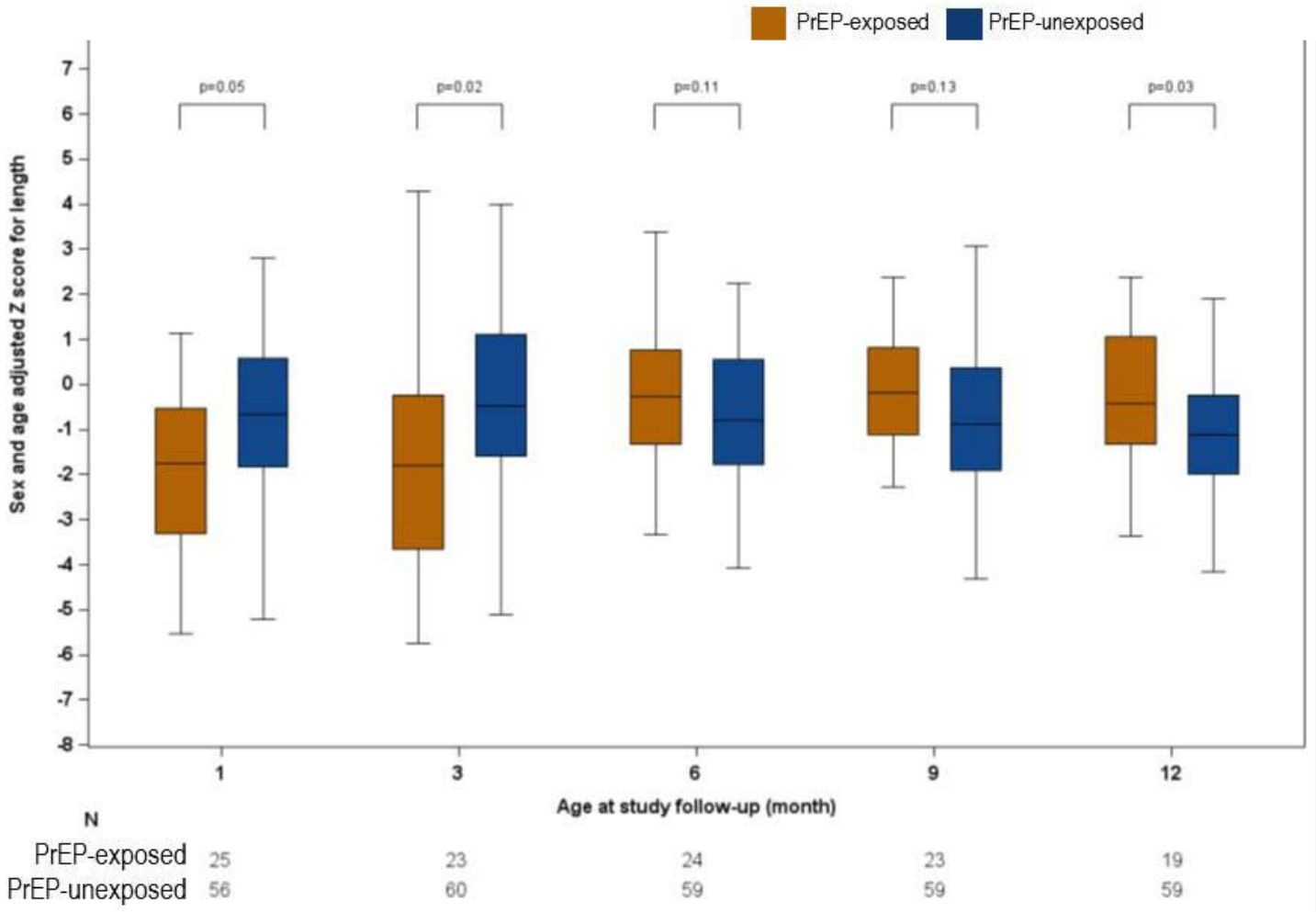
Infant growth: Weight



Adjusted z-scores were similar between PrEP-exposed and PrEP-unexposed at every visit

Heffron et al., under review

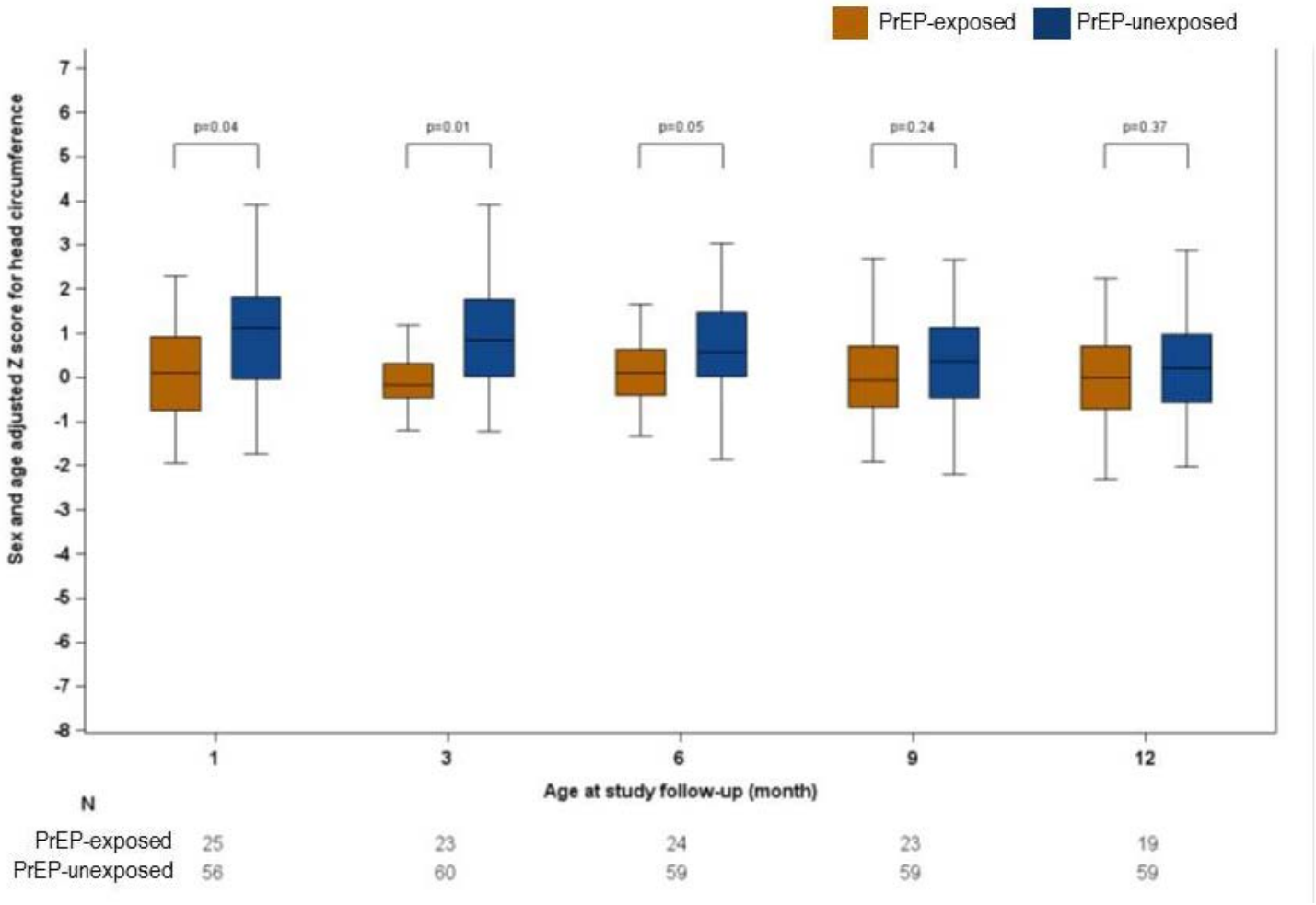
Infant growth: Length



Lengths are slightly lower for PrEP-exposed infants at month 1 and month 3
By 12 months, lengths were higher for PrEP-exposed infants

Heffron et al., under review

Infant growth: Head circumference

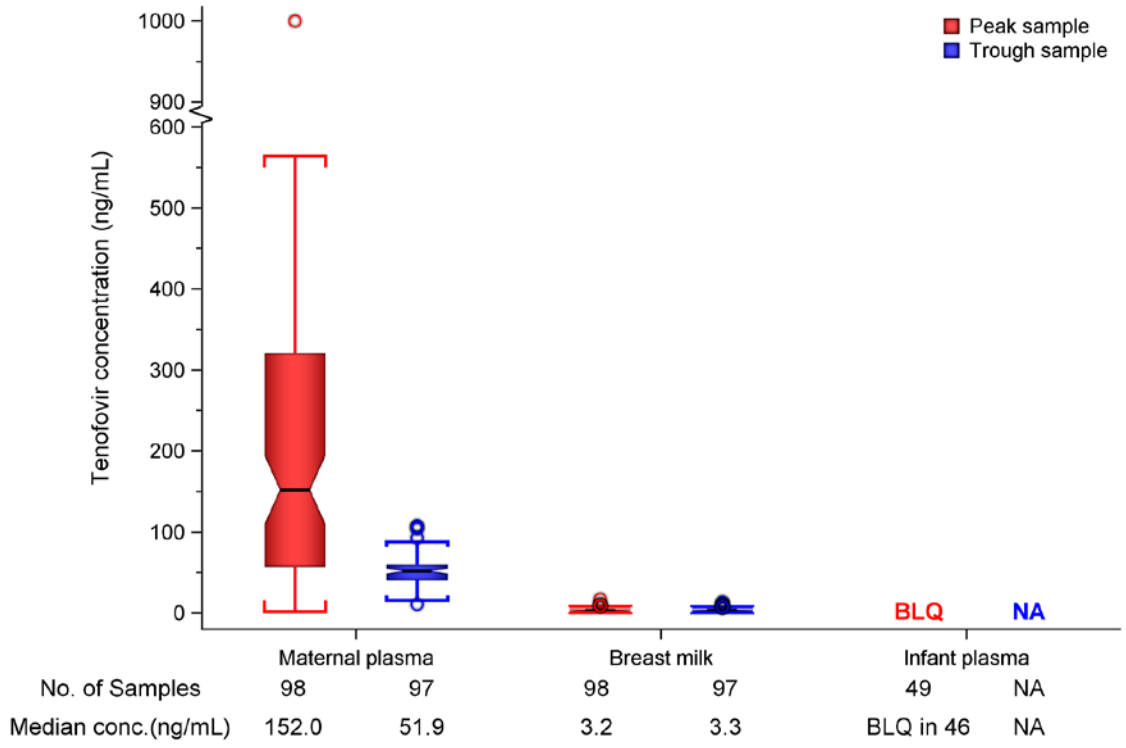


PrEP-exposed infants had a slightly lower adjusted z-score at birth

No difference in head circumference at 12 months

Tenofovir levels in breastmilk and infant plasma among HIV-negative women

- DOT FTC/TDF for 10 days at 1-24 weeks postpartum among 50 women in Uganda and Kenya
- Tenofovir concentrations were minimal in breastmilk and not detectable in infant plasma



Current experience

- When given a choice to continue/discontinue, 88% of PrEP-experienced women with known HIV-positive partners chose to continue PrEP (Partners Demonstration Project, Heffron et al. AIDS & Behavior 2017)
- In US antenatal care program, 67% of 24 women offered PrEP chose to take it (Seidman AJOG 2016)
- Multiple reports of PrEP use as part of safer conception strategies (in discordant couples and others trying to conceive) with varying uptake in South Africa (Schwartz JIAS 2017), Kenya and Uganda (Heffron AIDS Behav 2017)

Serum levels of TFV may be lower during pregnancy

TFV ng/mL in stored plasma					
	Non-Pregnant (n=83 women, 226 samples)	Pregnant (n=33 women, 163 samples)	1st Trimester (n=23 women, 42 samples)	2nd Trimester (n=23 women, 59 samples)	3rd Trimester (n= 23 women, 62 samples)
Mean doses per month, MEMS	23.1	22.2	23.6	22.0	21.5
Recent dose in past 2 days, MEMS	93.4%	89.0%	90.5%	88.1%	88.7%
Mean TFV ng/mL	86.5	34.7	45.5	36.6	25.5
Adjusted Difference (95%CI)		-50.4 (-68.3, -32.5) p<0.001	-40.0 (-66.8, -13.3) p=0.004	-49.4 (-69.5, -29.2) p<0.001	-59.2 (-77.7, -40.7) p<0.001

Pyra et al. Under review

Risk to benefit calculus

- Given the option to use PrEP during pregnancy, women have a lot to consider:
  - HIV exposure
  - Side effects – pregnancy will add its own set of symptoms
  - Few safety data from women using TDF throughout pregnancy as PrEP
  - PrEP clinic visits plus antenatal visits
  - Postpartum retention

- For healthy women with an unknown amount of HIV exposure, the risk to benefit calculus is likely different than women making decisions about therapeutic TDF use

WHO Guidance

"The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection"

"…active surveillance of mother and infant outcomes during PrEP use in pregnancy and breastfeeding should be part of a PrEP programme"

1. Maternal adverse outcomes
2. Adverse birth outcomes
3. Adverse infant and child outcomes

Review of national PrEP policy guidance with regards to pregnancy guidance

- See the AVAC handout in meeting packets

Review of national PrEP policy guidance with regards to pregnancy guidance

- Countries with generalized HIV epidemics
  - Few have pregnancy-specific guidance
  - Among the 4 that do, (South Africa, Kenya, Swaziland, and Uganda), 3 recommend PrEP to be used during pregnancy
  - South Africa: “TDF/FTC is contra-indicated for use as PrEP in pregnant or breastfeeding women. 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.”
  - Zimbabwe & Malawi: Recognize pregnant women as a high risk group but no specific guidance for PrEP/PrEP use during pregnancy
- Countries with concentrated HIV epidemics
  - PrEP can be used during pregnancy, consideration should be given to whether there is an added benefit of PrEP in the context of ART use and viral suppression.

Davies and Heffron, under review

In Summary…

- Oral PrEP is recommended by WHO as safe to use during pregnancy
- Data from women using TDF as part of ART regimens for HIV treatment are difficult to interpret – there is a lot going on with multiple ARVs and HIV itself
- Studies of women using TDF for HIV prevention are few and quite small (N=30) – MTN-042 will markedly increase this number
- National guidelines are often permissive of PrEP use in pregnancy with options for women to weigh personal preferences BUT not all countries with large HIV epidemics among women have adopted WHO recommendations
- Mixed experiences with levels of uptake, especially between women PrEP-experienced and inexperienced prior to pregnancy