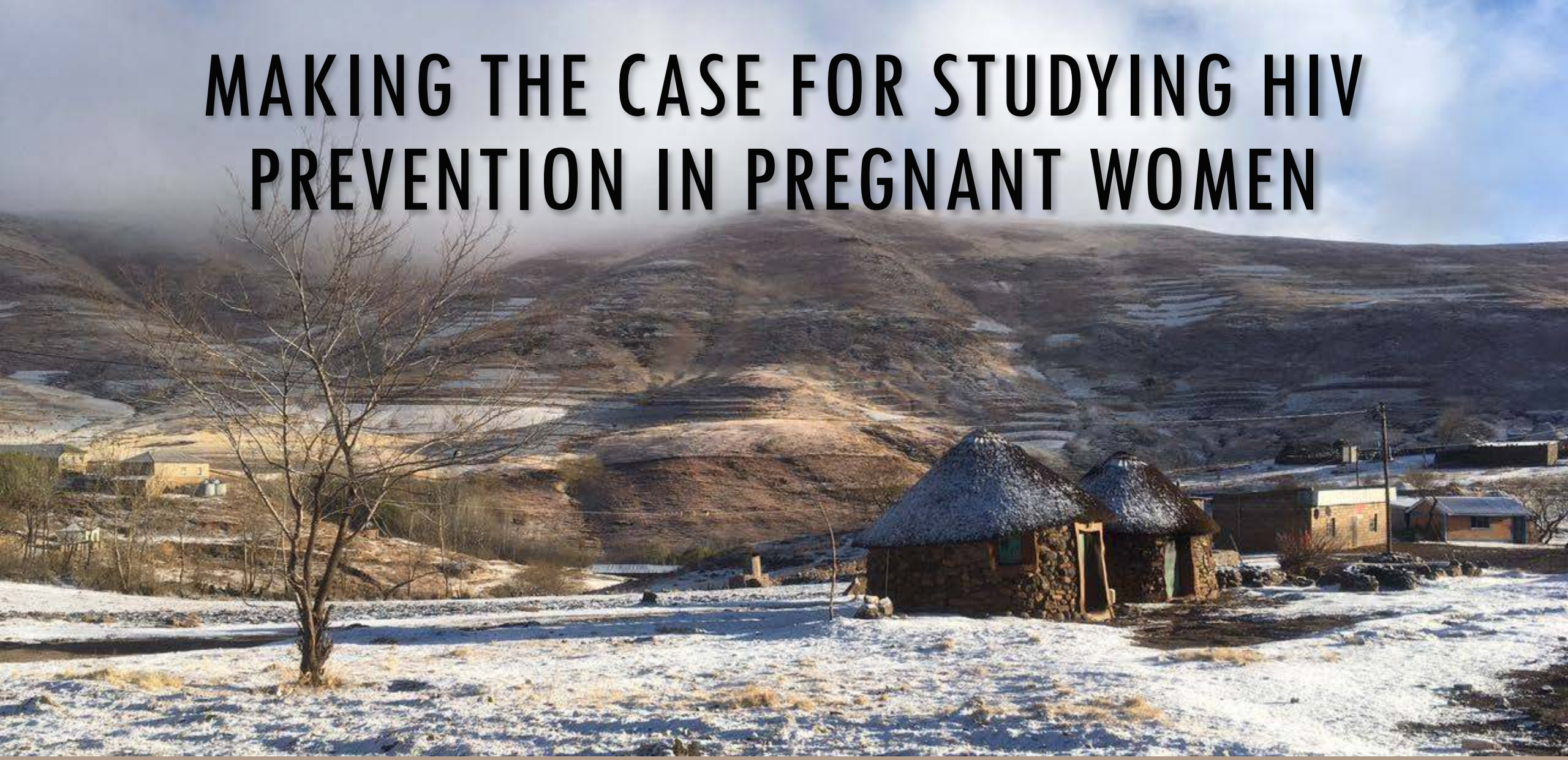
MAKING THE CASE FOR STUDYING HIV PREVENTION IN PREGNANT WOMEN



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University of Washington, Global Health & Epidemiology

MTN Regional Meeting September 2017
Cape Town, South Africa

Talk outline

Imaginative experience

Framing the discussion

- HIV risk during pregnancy
- Ethics of research among pregnant women

Learning from oral PrEP

Preparing for Dapivirine ring

A couple summary thoughts

Please put yourselves in the mindset of a pregnant woman

Please put yourselves in the mindset of a pregnant woman

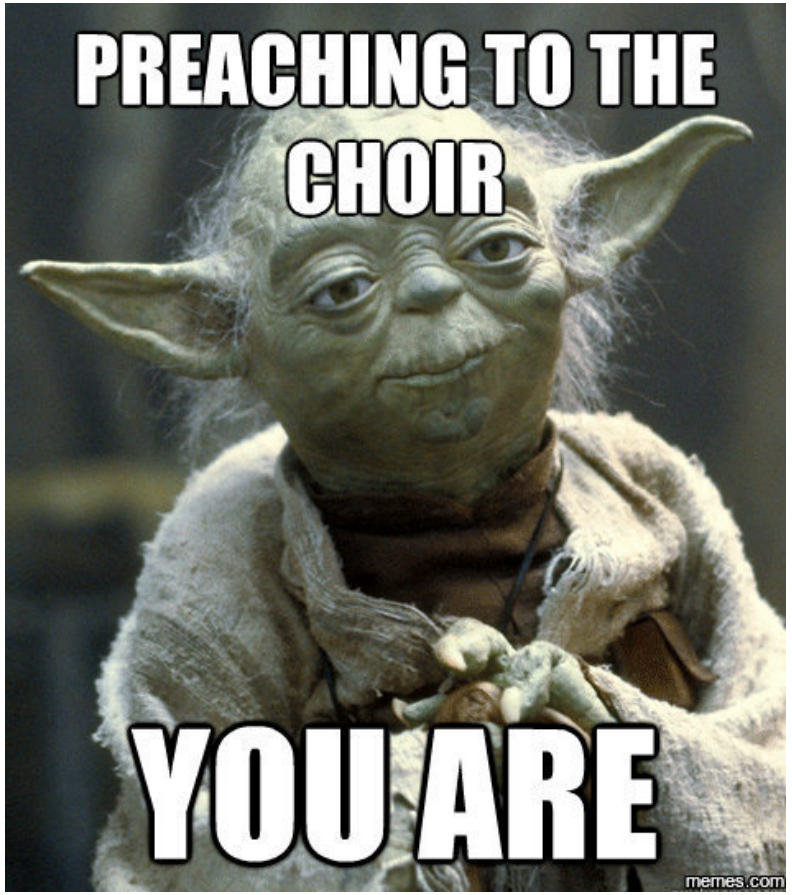
"I did not want to give birth to a child who has HIV" -26 year old Kenyan woman

"I have used PrEP and I haven't sero-converted as they maybe thought someone [in an HIV-serodiscordant couple] could.....I would use it again and again because I think it is effective…" 22-year-old Kenyan woman

"I have not experienced any side effect so I cannot speak about its [PrEP's] disadvantages. I can only talk about the benefits because I have used it and know how good it is. I have only experienced the beauty of it." -27-year-old Kenyan woman

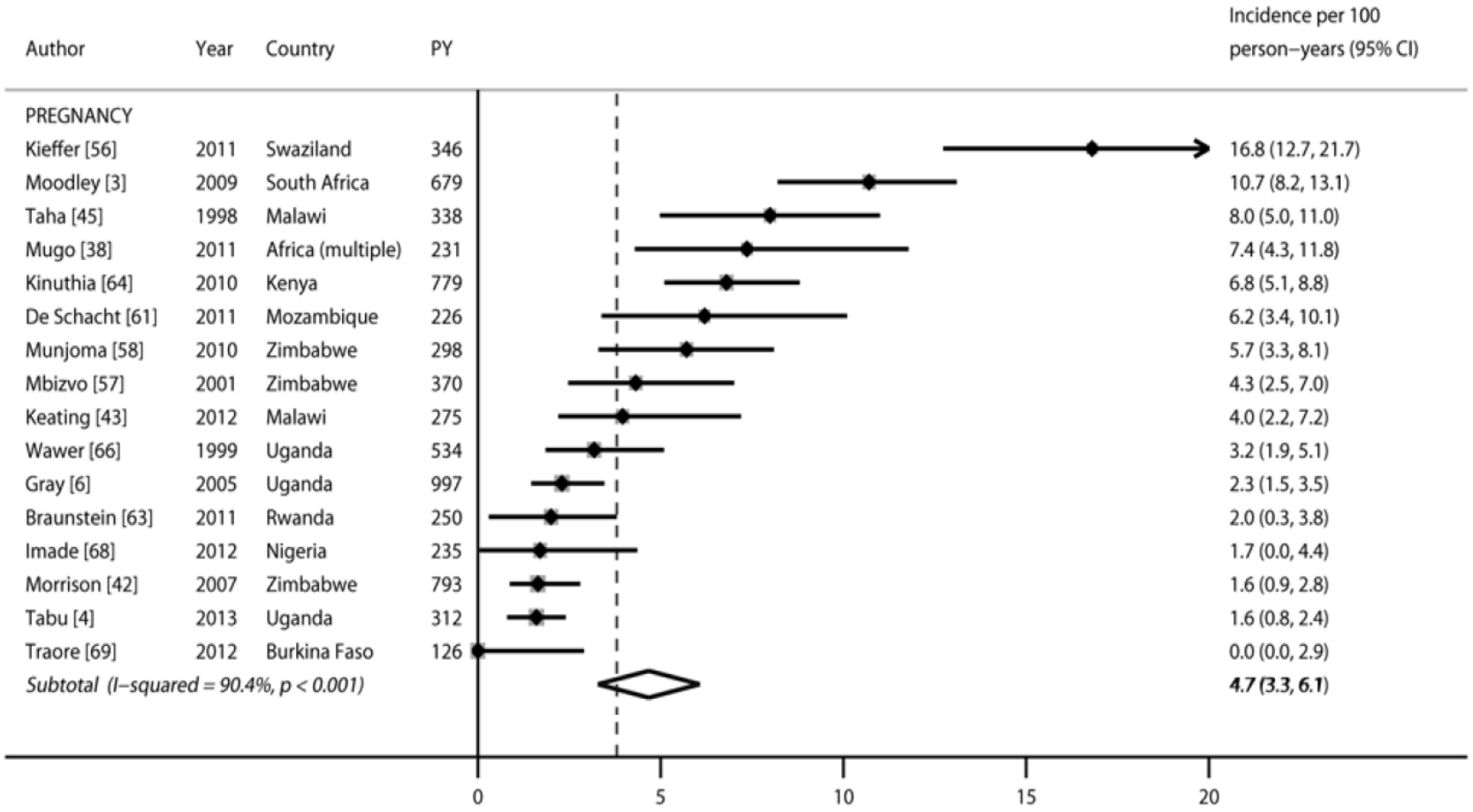
Pintye et al. JAIDS 2017

Framing the discussion



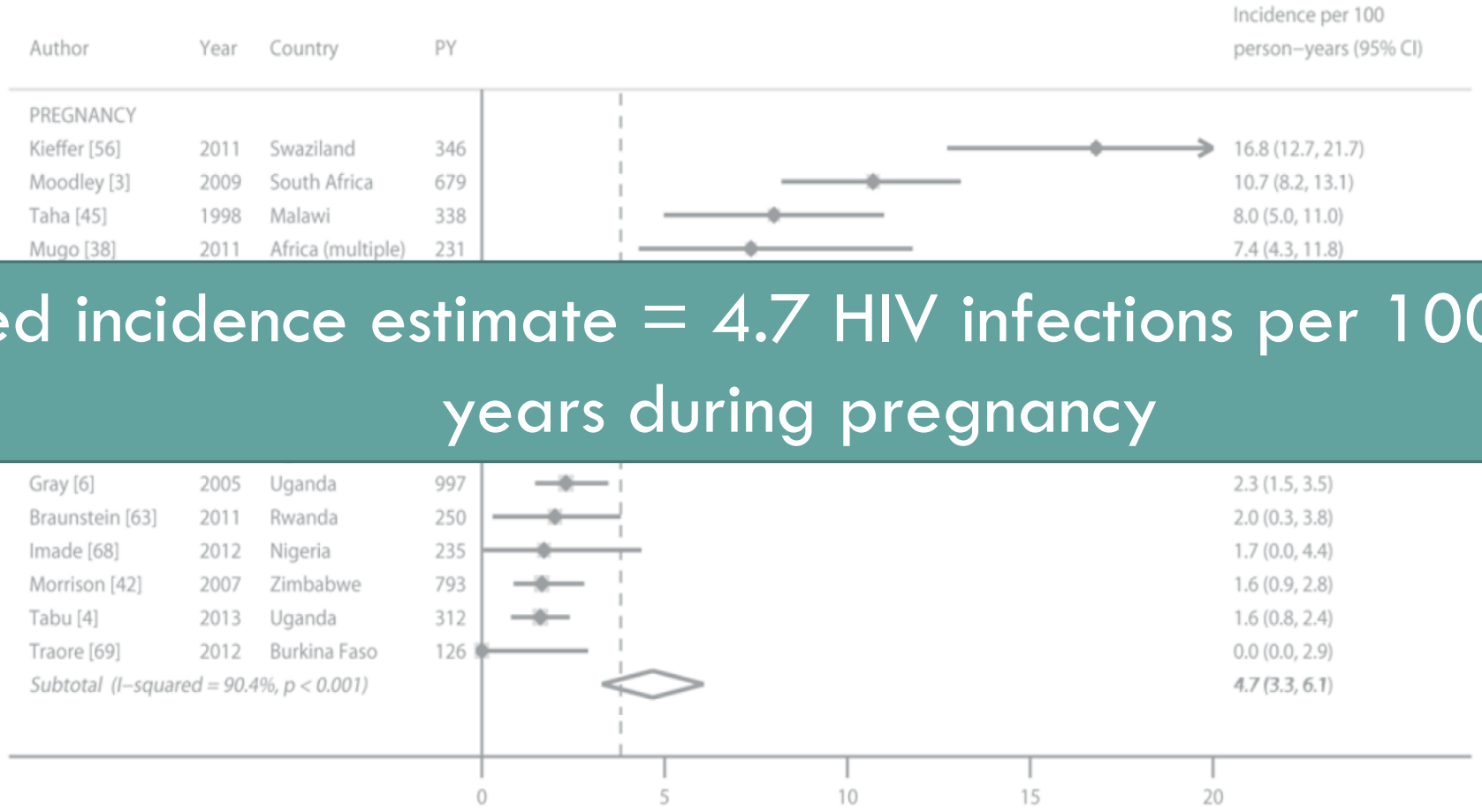
Pregnancy is a time of increased HIV risk

HIV incidence during pregnancy



Drake et al. Plos Med 2014

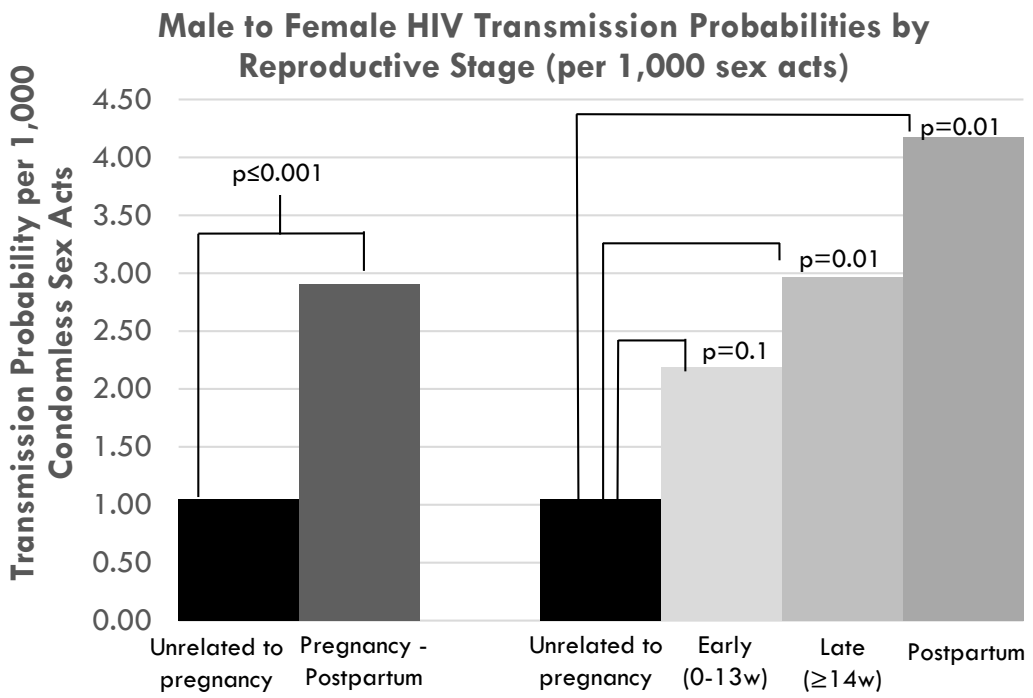
HIV incidence during pregnancy



Pooled incidence estimate = 4.7 HIV infections per 100 person-years during pregnancy

Drake et al. Plos Med 2014

New data: Per act transmission probabilities



	Probability of HIV transmission per condomless sex act (95% CI)	Relative risk of HIV transmission (95% CI) p-value
Early pregnancy through postpartum	0.0029 (0.004, 0.0093)	2.76 (1.58, 4.81) p<0.001
Early pregnancy (0-13w)	0.0022 (0.0004, 0.0093)	2.07 (0.78, 5.49) p=0.14
Late pregnancy (≥14w)	0.0030 (0.0007, 0.0108)	2.82 (1.29, 6.15) p=0.01
Postpartum	0.0042 (0.0007, 0.0177)	3.97 (1.50, 10.51) p=0.01
Time unrelated to pregnancy or postpartum	0.0011 (0.005, 0.0019)	1.00

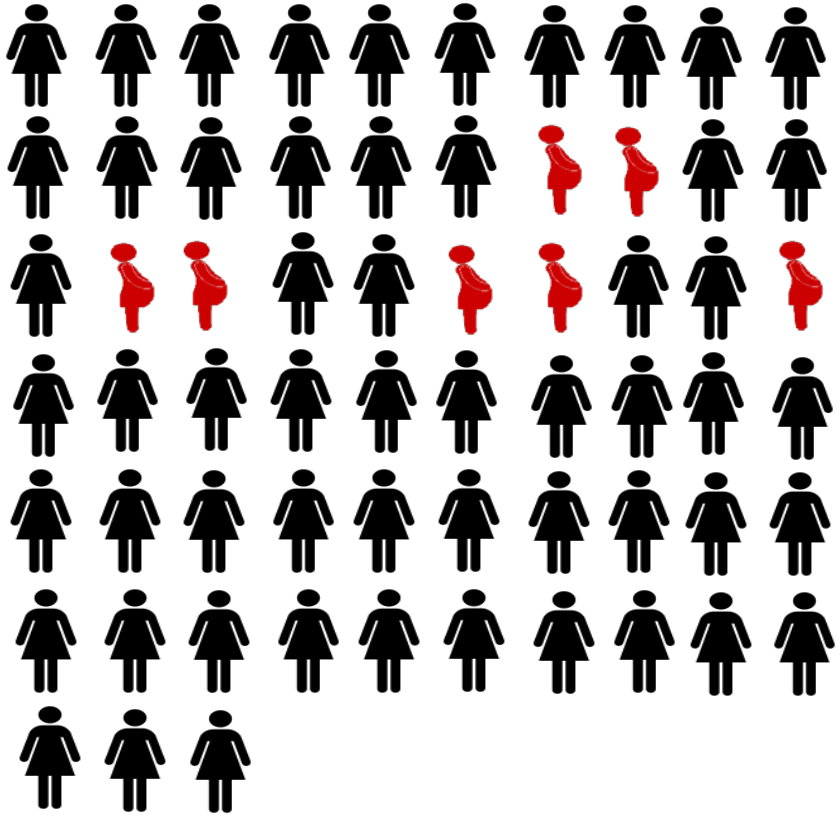
*Adjusted for age, male partner viral load, and PrEP use

Thomson et al, in preparation

Long cumulative duration for maternal HIV risk

= woman year

= pregnant/lactating



Average life expectancy (yrs)

63

Total fertility rate (per woman)

3.9

Years pregnant/lactating (per preg.)

1.75

Total years pregnant/lactating

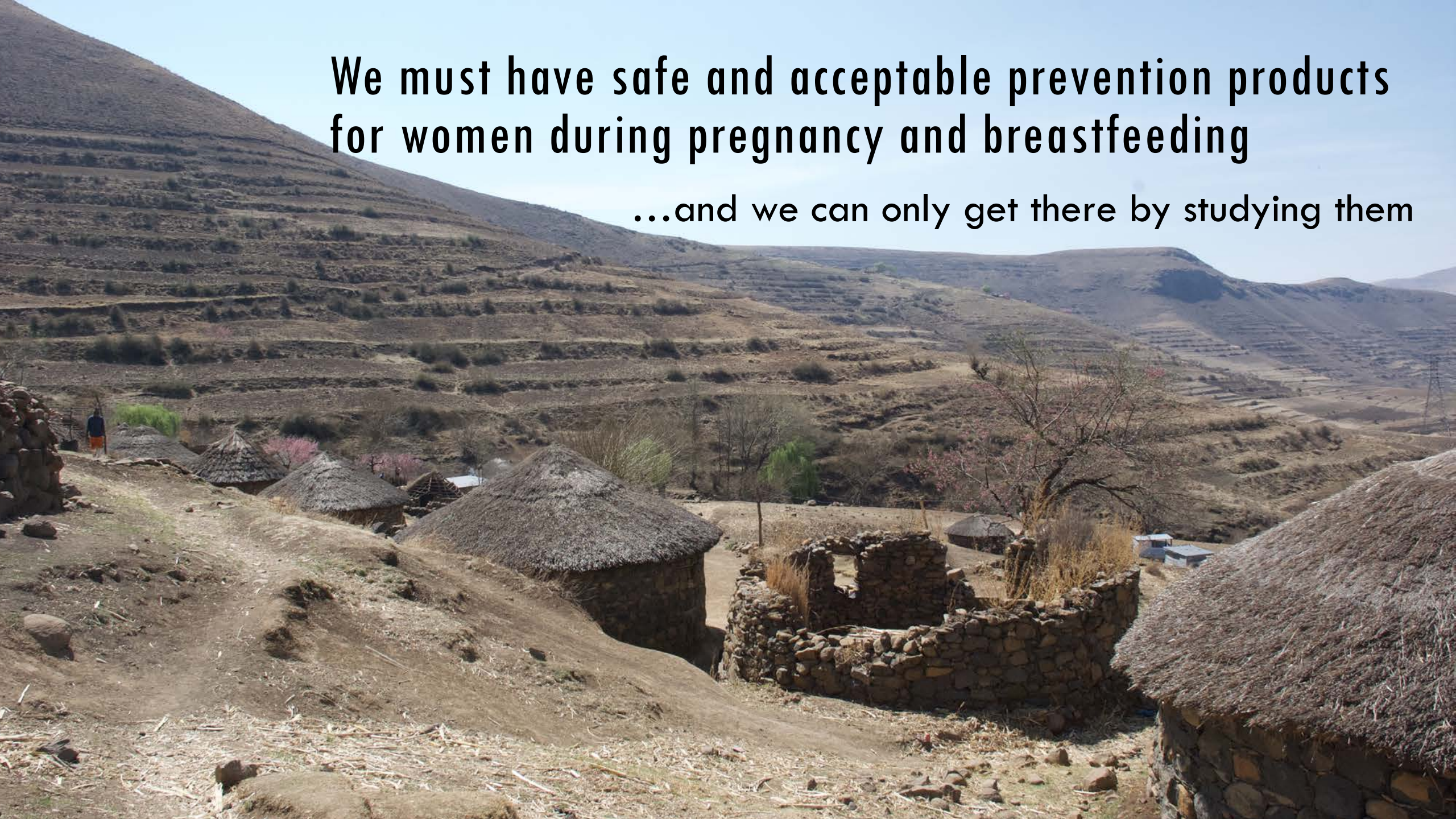
6.8

% of reproductive years spent pregnant/lactating

20%

Slide courtesy of Dr. Alison Drake

Source: Kenya DHS 2014


We must have safe and acceptable prevention products for women during pregnancy and breastfeeding
...and we can only get there by studying them

Is it ethical to study HIV prevention products during pregnancy?

Conventional thinking…

Pregnancy is a vulnerable condition

Pregnancy is a normal exclusion criterion for clinical studies

Pregnant women need special protection with respect to research

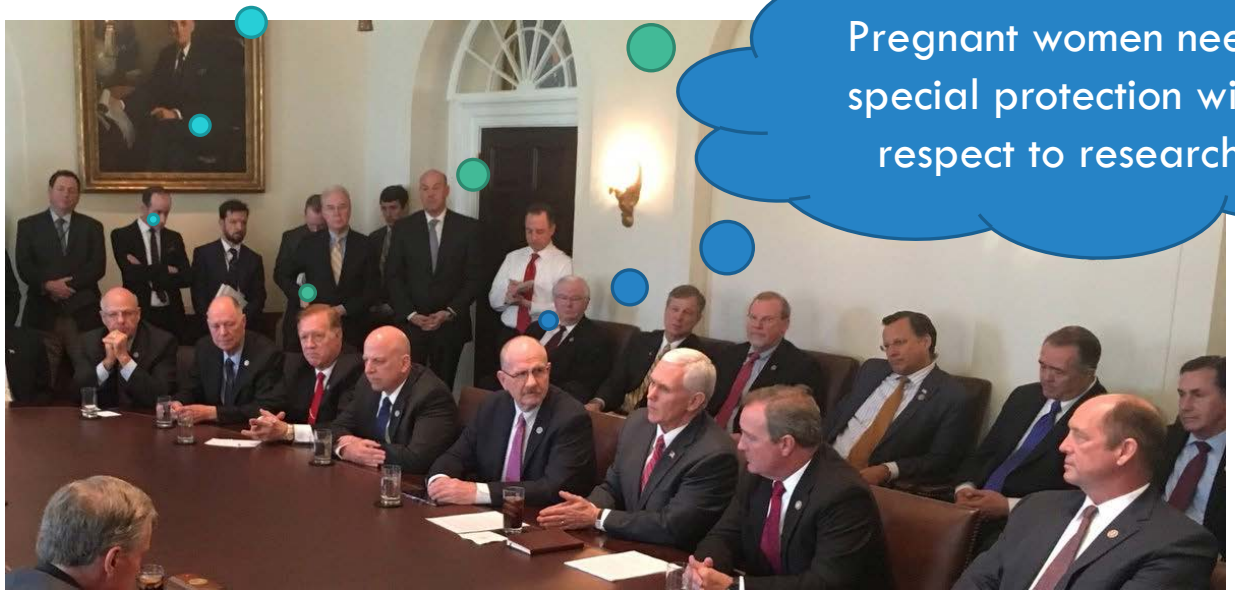


Photo credit: http://www.motherjones.com/politics/2017/03/trump-health-care-summit-white-guys/

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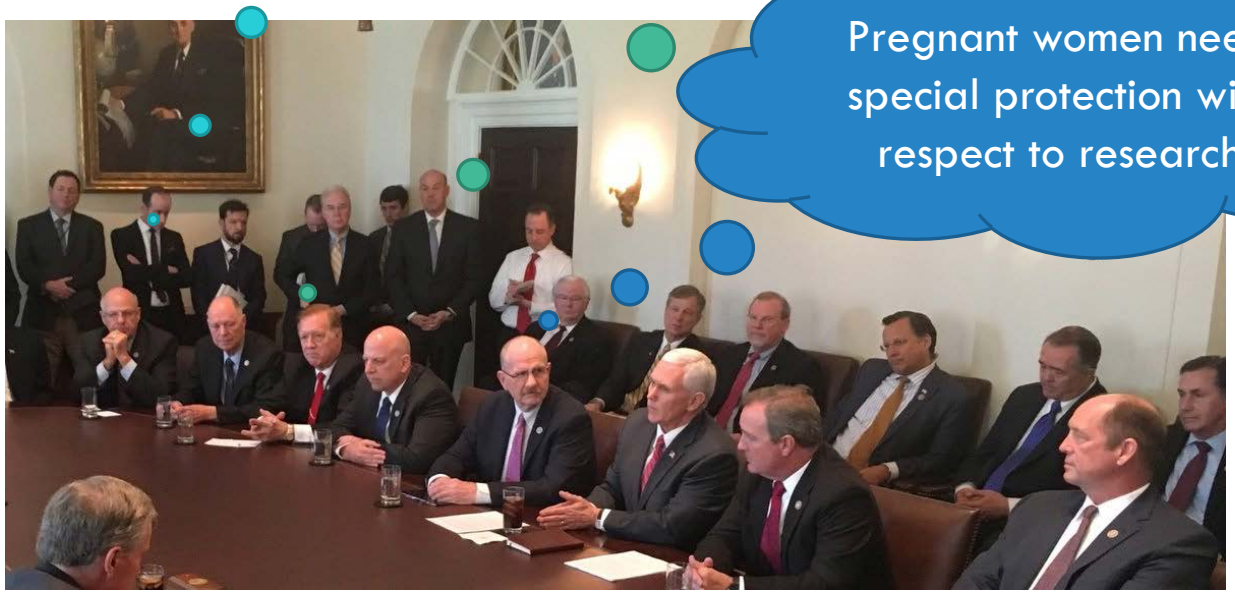

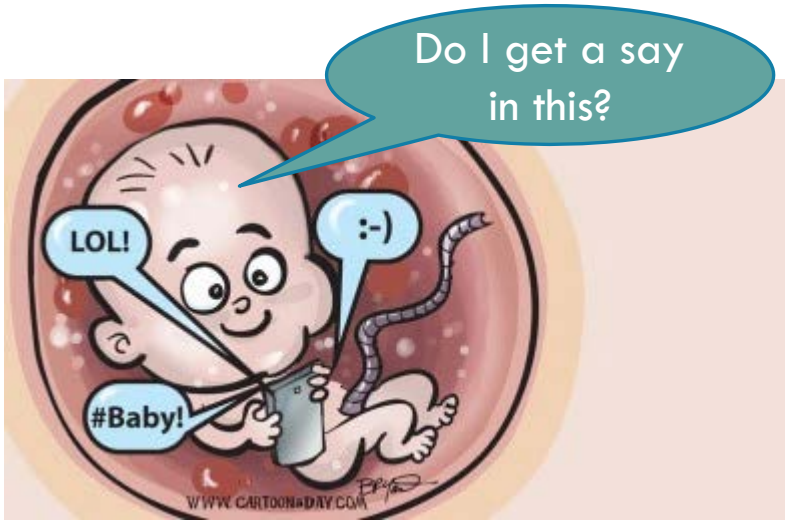

Photo credit: http://www.motherjones.com/politics/2017/03/trump-health-care-summit-white-guys/

Opinions from HIV experts on the ethics of conducting research among pregnant women

Ethical concerns are real

- Need a framework for guiding clinical research during pregnancy that is based on ethical and legal analysis of the conditions for responsible research conduct with pregnant women and is responsive to the needs and concerns of those who would conduct and participate in the research

Regulatory bodies also need guidance

Investigators need incentives that encourage research among pregnant women

"Creative designs" have a role – registries, opportunistic studies, combination Phase I/II studies

Many success stories in the field of PMTCT

Krubiner et al. AIDS 2016

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Krubiner et al. AIDS 2016

Making the Case for Studying HIV Prevention in Pregnant Women

Pregnancy is a time of heightened HIV risk

It is right to study HIV prevention during pregnancy

Learning from the experience with oral PrEP

Available data to generate safety information about PrEP during pregnancy

When we want to study safety, we conduct a randomized trial with sufficient numbers of women to generate powered comparisons

When an agent is demonstrated to be efficacious and safe, placebo-controlled studies are not usually viable

For tenofovir, alternative designs and populations contribute to recommendations about PrEP use during pregnancy:

- Women using tenofovir to treat HIV infection
- Women using tenofovir to treat Hepatitis B infection
- Women using tenofovir to prevent HIV infection prior to pregnancy
- Women using tenofovir to prevent HIV infection during pregnancy

Current state of the evidence

Systematic review by Mofenson, Baggaley and Mameletzis, published in AIDS (2017)

Comparative studies included (N=33):

- 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 Hepatitis B mono-infection (1 randomized trial)
- 2 PrEP studies (2 randomized trials)

Current state of the evidence: 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 is still undergoing investigation to understand findings

Current state of the evidence: 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

Conclusion to 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

What happens when safety data during pregnancy are not available

TRUVADA package insert, 2012-present

Pregnancy Category B

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TRUVADA, an Antiretroviral Pregnancy Registry (APR) has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

TRUVADA has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

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TRUVADA package insert, 2012-present

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What
pregn

TRUVAD

What happens when safety data during pregnancy are not comprehensive

Kenya antiretroviral guidelines, 2016

Pregnancy or breastfeeding	Pregnancy and breastfeeding are not contraindications to provision of PrEP. Pregnant or breastfeeding women whose sex partners are HIV positive or are at high risk of HIV infection may benefit from PrEP as part of combination prevention of HIV infection. PrEP is also indicated for HIV-negative in discordant partnerships who wish to conceive. PrEP in these situations can be prescribed during the pre-conception period and throughout pregnancy to reduce risk of sexual HIV infection

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South African guidelines on the safe use of PrEP, 2016

"In South Africa, the use of TDF/FTC as PrEP in pregnant or breastfeeding women is **contra-indicated.** However, as the risk of seroconverion 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."

What happens when you try to collect these data after efficacy is established

Data from women in the Partners Demonstration Project who became pregnant and chose to continue PrEP

Compared to the placebo arm of the Partners PrEP Study

	PrEP-exposed	PrEP-unexposed	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 generalized estimating equations 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

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N=30!

A historical cohort from a similar, but not identical study

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Heffron et al., under review

Preparing for dapivirine

How to advance safety and delivery of the dapivirine ring during pregnancy

Data for safety of tenofovir during pregnancy come from:

- Women using tenofovir to treat HIV infection
- Women using tenofovir to treat Hepatitis B infection
- Women using tenofovir to prevent HIV infection prior to pregnancy
- Women using tenofovir to prevent HIV infection during pregnancy

Data for safety of dapivirine during pregnancy could come from:

- ~~Women using dapivirine to treat HIV infection~~
- ~~Women using dapivirine to treat another infection~~
- Women using dapivirine to prevent HIV infection prior to pregnancy
- Women using dapivirine to prevent HIV infection during pregnancy

Dapirivine use prior to pregnancy

Data from ASPIRE/MTN-020

Table 3. Pregnancy outcomes by arm

	Dapivirine N=86		Placebo N=94	
Full term live birth	52	(60%)	53	(56%)
Preterm birth	0	(0%)	9	(10%)
Stillbirth/Intrauterine fetal demise	2	(2%)	2	(2%)
Spontaneous abortion	18	(21%)	21	(22%)
Therapeutic/elective abortion	13	(15%)	8	(9%)
Ectopic pregnancy	1	(1%)	1	(1%)

Table 4. Congenital anomalies by arm[1]

	Dapivirine N=48	Placebo N=59
Any anomaly	4 (8%)	4 (7%)
Physical defect	1 (2%)	3 (5%)
Cranio-facial	1 (2%)	0
Other	2 (4%)	1 (2%)

[1]Data available for 107 of 114 live births

No differences in pregnancy rates, outcomes, or frequency or location of congenital anomalies

Makanani et al. Abstract #935, CROI 2017

What do we know about dapivirine and safety during pregnancy?

No direct studies yet – MTN-041, MTN-042, and MTN-043 will be critical to understand women's preferences and safety of dapivirine IVR in pregnancy and breastfeeding

Dapivirine is an NNRTI, as is Efavirenz

- EFV is now recommended are part of a first line regimen for women initiating ART during pregnancy (as part of TDF + FTC/3TC + EFV)
- Early concerns about neural tube defects and congenital anomalies with EFV have been assuaged by a large meta-analysis including data from >11,000 pregnancies with EFV and non-EFV exposure (Ford et al. AIDS 2014)

Dapivirine ring is different from oral Efavirenz

- Topical versus systemic administration
- Composition of dapivirine is different – unknown how this will impact effects

As we learn more and more about antiretrovirals, it seems critical to evaluate each one individually and not generalize across a class of agents

The risk-benefit calculus

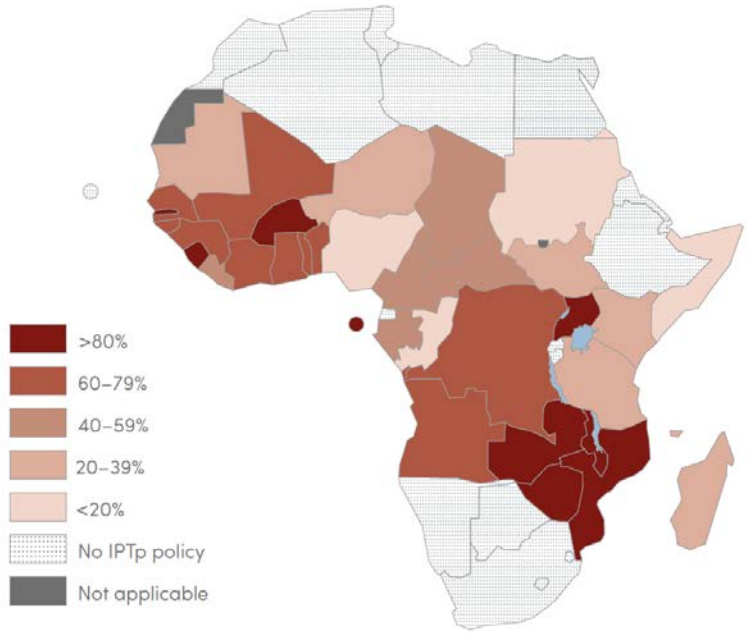
Likely different for preventive therapies than for treatment – we can learn from studies of preventive malaria treatment during pregnancy

- IPTp is a highly effective intervention to prevent an illness with severe consequences (maternal anemia, stillbirth, low birth weight)
- IPTp uptake is low – supply side barriers likely outweigh demand side barriers
- Demand side barriers include general concerns about medication taking during pregnancy, but these concerns may be overcome by health worker recommendations:

"***Another one is not to use drugs unnecessary. If you are pregnant, you should use drug prescribed to you in the health facility. Don't buy drugs from the vendor and swallow like that." – pregnant woman in Uganda***

Rassi, Malaria Journal, 2016

Figure 3.7 Proportion of pregnant women receiving at least one dose of IPTp, sub-Saharan Africa, 2013–2014



The following country-years are shown in the map due to missing data for 2013 and 2014: Gabon (2011), Somalia (2011), Sudan (2009).

Source: *WHO estimates using national malaria control programme reports and United Nations population estimates*

WHO. World Malaria Report 2015

Does adherence to FTC/TDF wane during pregnancy? Do systemic TVF levels change during pregnancy?

Pre-pregnancy adherence of TDF/FTC appears similar to adherence among women who don't get pregnant (Matthews et al. JAIDS 2014)

Work ongoing to explore adherence patterns and systemic TFV levels during pregnancy

PrEP adherence during pregnancy, Partners Demonstration Project

	Months since pregnancy discovery at research clinic				
	1	3	6	9	Total
PrEP dispensation possible, N women	30	28	22	14	212
Drug dispensed, N (% of expected dispensing)	22 (73.3%)	21 (75.0%)	20 (90.9%)	11 (78.6%)	167 (78.8%)
Women with ≥80% expected MEMs cap openings	12 (54.5%)	12 (57.1%)	11 (55%)	4 (36.4%)	87 (52%)
Plasma available for TFV testing	20	17	17	12	154
TFV detected, N (% of samples tested)*	14 (70.0%)	12 (70.6%)	14 (82.4%)	8 (66.7%)	115 (74.7%)
TFV ≥35 ng/ml, N (% of samples tested)**	10 (50.0%)	9 (52.9%)	3 (17.6%)	3 (25.0%)	62 (40.3%)

*p-value from a chi-square test for trend=0.5.
**p-value from a chi-square test for trend=0.6.

Heffron et al., under review

Summary

We have a lot to learn about HIV prevention– and dapivirine IVR specifically – during pregnancy

Ethical principals suggest that we ***have an obligation*** to gather data from pregnant women using dapivirine ring – and give them the autonomy to choose to participate in research or not

Questions for studies during pregnancy span from clinical to behavioral and pharmacological considerations

- Safety – pregnancy and infant growth outcomes
- Behavior – adherence
- Dosing

Acknowledgements

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Kerry Thomson for sharing preliminary data from her PhD dissertation

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Thank you for your attention

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