What do we know about Safety of Long-acting PrEP during Pregnancy and Breastfeeding?

Elaine J Abrams, MD

ICAP at Columbia University

Advancing HIV Prevention and PrEP
for Pregnant and Breastfeeding Women
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HIV Impact Network for Vertical Transmission Elimination

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Safety of Long-acting PrEP during Pregnancy and Breastfeeding

Antiretroviral (ARV) safety during pregnancy and breastfeeding

- Maternal, pregnancy and infant & child health outcomes

Measurement & Monitoring

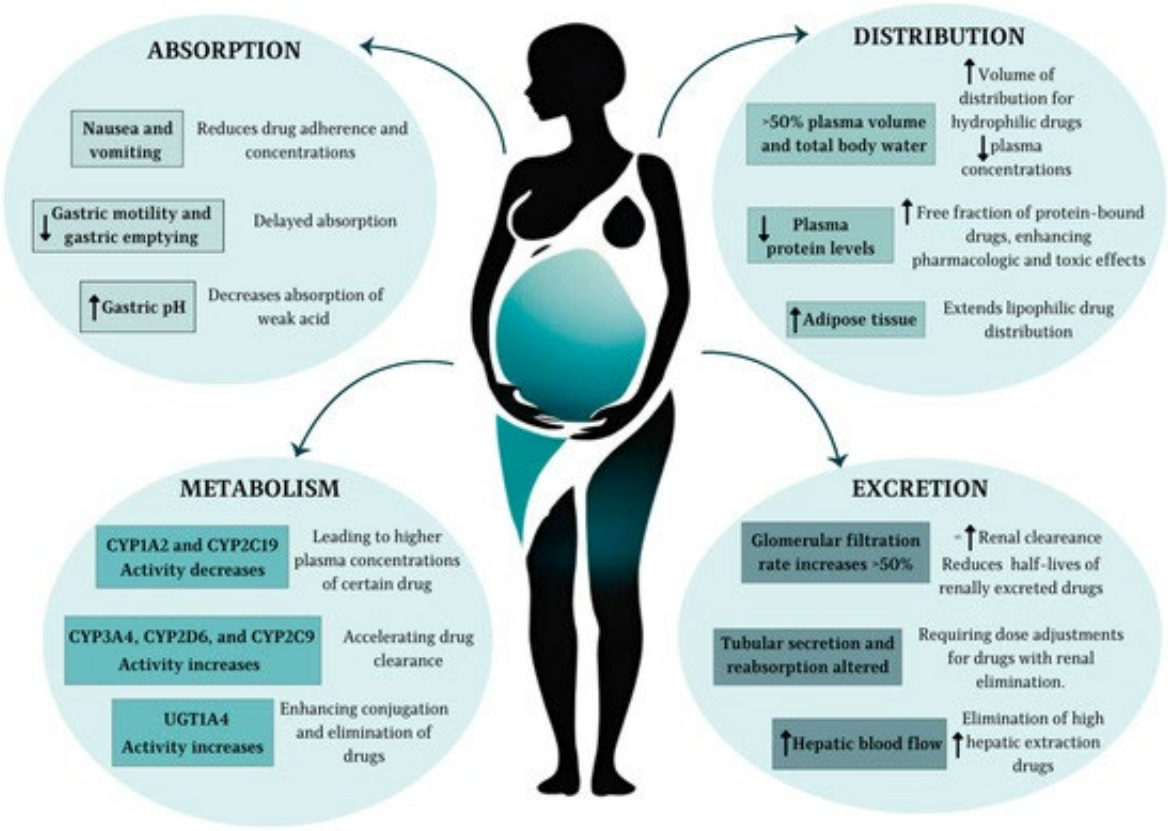
What we know about currently available long-acting antiretroviral agents

- Dapivirine ring (DVR)
- Injectable long-acting cabotegravir (CAB-LA)
- Injectable lenacapavir (LEN)

Conclusions

ARV Safety- How are Pregnant Women Different from Nonpregnant People?

- **Physiologic changes of pregnancy can result in changes in absorption, distribution, metabolism and excretion of a drug/therapeutic agent.**
- **These changes can impact drug levels, mechanisms of action, efficacy and toxicities.**
- **Exposures during pregnancy can affect the health of the mother, the pregnancy and the child.**



ARV Safety: Maternal Health

Nonspecific side effects: Overlap with or exacerbation of pregnancy-associated conditions: nausea, vomiting, fatigue

Increased risk of pregnancy-specific complications/comorbidities: gestational diabetes, hypertensive disorders, HELLP syndrome

Mortality during pregnancy, labor and delivery and postpartum

ARV Safety: Pregnancy and Birth Outcomes

Pregnancy outcomes

- Miscarriage*
- Stillbirth*

Birth outcomes

- Preterm Birth (PTB*)
- Small for Gestational Age (SGA*)
- Congenital anomalies
- Low Birth Weight (LBW)

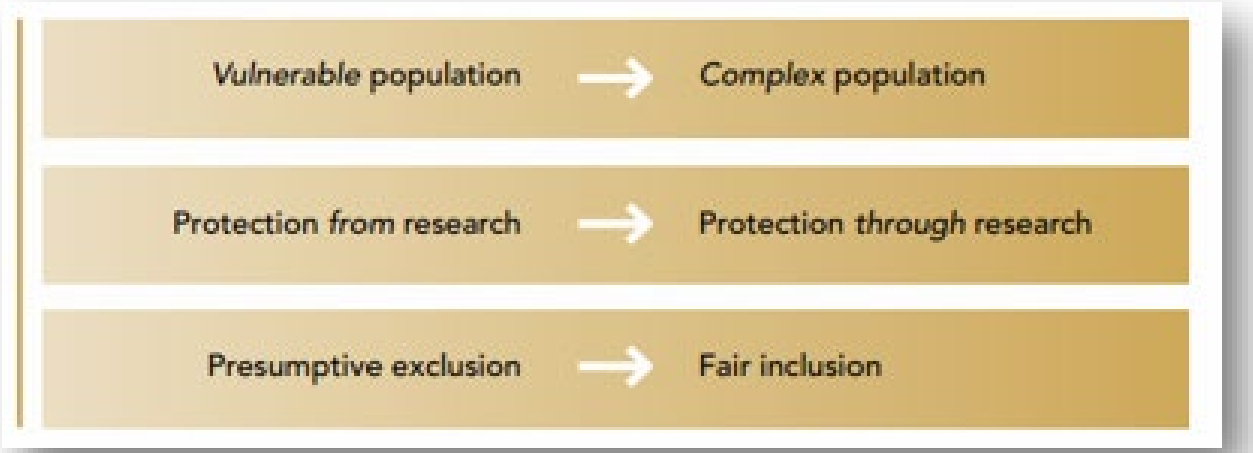
ARV Safety: Infant and Child Health Outcomes

- Neonatal mortality*
- Infant mortality
- Infant growth
- Neurodevelopment

Measuring and Monitoring Safety of New ARVs in Pregnancy

Historically, pregnant women have been excluded from registrational drug trials resulting in delayed study of antiretroviral agents in pregnancy.

- Primarily to protect the fetus/infant from harm
- Paradigm shift to in recent past to include pregnant women in ARV research



https://www.hivpregnancyethics.org/

More on Measuring and Monitoring Safety of New ARVs in Pregnancy

Most of the most critical adverse outcomes occur 'naturally' in pregnancy.

To measure safety, we must determine if the drug exposure increases the risk of the adverse outcome above the background rate for the population.

- Need estimates of the background rate for each outcome
  - With **200** exposures you can rule out ≥ 2-fold more increase in common outcomes, background rate of >10% (miscarriage, SGA, LBW); can be measured in a well-designed clinical trial.
  - Whereas you need **>2000** exposures to determine a 3-fold increase in risk of a rare outcomes (stillbirth, neural tube defects), background rate of >0.1% (1/1000); usually done through active post-marketing surveillance.

https://www.who.int/tools/antiretrovirals-in-pregnancy-research-toolkit/surveillance-studies-and-registries

ARV Safety during Breastfeeding

Few substantial safety issues have been identified during breastfeeding. Maternal metabolism returns to pre-pregnancy state.

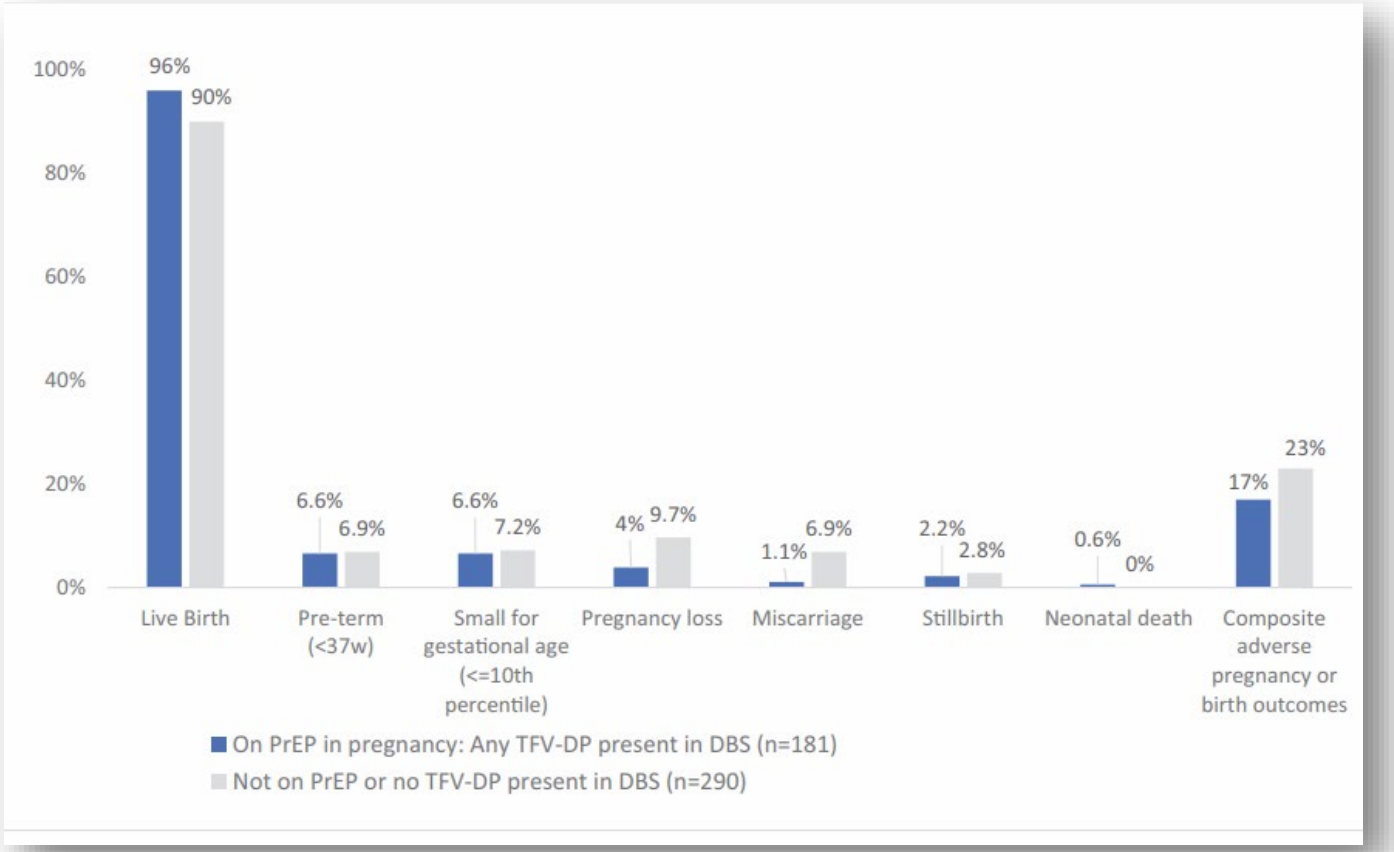
Infant ARV exposure postpartum is through breastmilk.

Most ARVs that have been studied have been detected in breastmilk but at lower levels than maternal plasma.

Very low levels of most currently used ARVs have been detected in breastfed infants.

Daily Oral PrEP (TDF/FTC)

Multiple Studies have confirmed that TDF/FTC as PrEP is Safe in Pregnancy



Birth and pregnancy outcomes in pregnant women taking (blue) oral PrEP and not taking (grey) oral PrEP

Pregnancy & birth outcomes did not differ by PrEP exposure, taking PrEP (confirmed with drug levels) or not taking PrEP

Davey et al; AIDS 2024, 38:75-83

Dapivirine Vaginal Ring (DVR)

Flexible silicone matrix ring containing 25 mg dapivirine, an NNRTI; DPV slowly released from ring when placed in the vagina with limited systemic absorption, is replaced monthly

Studies designed specifically to determine safety, adherence and acceptability of DVR compared to oral PrEP among pregnant (deliver) and breastfeeding (BeProtected) women.

No notable safety concerns with DPV ring used preconception and in early pregnancy (ASPIRE, HOPE).

Excellent safety profile for mothers, newborns and infants through 12 months of life.

No maternal or infant SAEs related to DVR.

Very little dapivirine detected in breastmilk and less in the infant.

ASPIRE
HOPE
Out of ASPIRE, there is HOPE

140 pregnancies during the DVR registrational trial and off label extension

deliver
A Study of PrEP and the Dapivirine Ring in Pregnant Women

BE PROTECTED

200 exclusive breastfeeding mother-infant pairs, randomized to DVR or oral PrEP for 12 weeks

Assessed maternal & infant safety, drug levels, acceptability, adherence

Fairlie L, The Lancet HIV, 2025, Vol. 12, Issue 11, pe763-e773; Bunge K, at at, JAIDS 2024; Ngochi LM, Lancet HIV 2025; 12: e180–90.2025; Mhlanga FG, The Lancet 2026

Similar rates of composite safety outcomes for DVR and TDF

	Cohort 1		Cohort 2		Cohort 3		Total	
	DVR (n=99)	Oral PrEP (n=48)	DVR (n=103)	Oral PrEP (n=51)	DVR (n=196)	Oral PrEP (n=48)	DVR (n=399)	Oral PrEP (n=147)
Sex at birth								
Female	48 (48%)	24 (50%)	62 (60%)	24 (47%)	104 (53%)	25 (52%)	214 (54%)	73 (50%)
Male	51 (52%)	24 (50%)	41 (40%)	27 (53%)	93 (47%)	23 (48%)	185 (46%)	74 (50%)
Gestational age at birth; median (IQR)	40·1 (39·0–41·0)	39·4 (38·3–41·0)	39·7 (38·7–40·7)	39·6 (38·3–40·7)	39·9 (39·1–40·8)	39·6 (38·4–40·5)	39·9 (39·0–40·9)	39·6 (38·4–40·7)
Length of intrauterine product exposure, days*; mean (SD)	24·3 (10·4)	21·1 (11·8)	60·3 (13·8)	58·5 (16·7)	114·6 (29·5)	110·3 (26·6)	78·2 (44·4)	63·3 (41·2)
Preterm births†	1 (1%)	3 (6%)	6 (6%)	4 (8%)	8 (4%)	3 (6%)	15 (4%)	10 (7%)
Available birthweights, n	94	47	101	50	192	48	387	145
Birthweight, kg; mean (SD)	3·19 (0·39)	3·14 (0·42)	3·06 (0·44)	3·12 (0·45)	3·13 (0·47)	3·04 (0·42)	3·13 (0·45)	3·10 (0·43)
Low birthweight (<2·5 kg)‡	2/94 (2%)	3/47 (6%)	6/101 (6%)	3/50 (6%)	12/192 (6%)	3/48 (6%)	20/387 (5%)	9/145 (6%)
Intergrowth-21 weight-for-age severity grade‡								
Mild (≥3rd to 10th percentile)	5/94 (5%)	3/47 (6%)	12/101 (12%)	6/50 (12%)	28/192 (15%)	5/48 (10%)	45/387 (12%)	14/145 (10%)
Severe (<3rd percentile)§	4/94 (4%)	4/47 (8·5%)	8/101 (8%)	2/50 (4%)	11/192 (6%)	2/48 (4%)	23/387 (6%)	8/145 (5%)
Normal	85/94 (90%)	40/47 (85%)	81/101 (80%)	42/50 (84%)	153/192 (80%)	41/48 (85%)	319/387 (82%)	123/145 (85%)

Data are n (%) or n/N (%) unless otherwise indicated. DVR=dapivirine vaginal ring. PrEP=pre-exposure prophylaxis (tenofovir disoproxil fumarate plus emtricitabine). *Time from maternal randomisation to product discontinuation. †Born at less than 37 completed weeks. ‡Percentages are based on the number of available birthweights. §In the Division of AIDS Female Genital Grading Table, no "moderate" grading category exists.

Fairlie L et al. Lancet HIV 2025; 12: e763–73

Long-acting Injectable Cabotegravir (CAB-LA)

Integrase inhibitor with long half-life (40 hours orally, 40 days as injectable long-acting nanosuspension)

CAB-LA Found to be Safe for Pregnant Women and Infants

HPTN 084, the registrational, randomized clinical trial that demonstrated the efficacy of long-acting CAB-LA compared to TDF/FTC in women, excluded pregnant women from enrollment. Women who became pregnant on study stopped drug. Pregnant women were included in the off-label extension (OLE) phase of the study.

- 633 pregnancies with outcomes: 579 pre-conception CAB-LA (*468 active, 111 prior CAB-LA*), 54 no CAB-LA (TDF/FTC)

CAB-LA Found to be Safe for Pregnant Women and Infants

Pregnancy and birth outcomes generally similar between groups

- Pregnancy adverse events uncommon, no maternal deaths
- Pregnancy outcomes with active CAB-LA and no CAB-LA similar by exposure and consistent with background rates.
- Early evidence suggests no increased risk of adverse birth outcomes.
- Early infant growth data reassuring

	Active CAB-LA N (% or IQR)	Prior CAB-LA	No CAB-LA
Live infants	218	35	37
Median gestational age at delivery (weeks)	39 (38-40)	39 (37-40)	37 (38-39)
Median birth weight (kg)	3 (3-3)	3 (3-4)	3 (3-4)
Small for gestational age (≤10%)	23 (11)	2 (6)	4 (11)
Major congenital anomalies*	2	0	0
Neonatal death with 28 days**	7 (3)	0	0
Respiratory distress	5	-	-
Exomphalos	1	-	-
Not specified	1	-	-

* Exomphalos, trisomy 21
**data available for 201 active CAB, 34 prior CAB, 35 no CAB

Delany-Moretlwe S et al. AIDS 2025, Kigali, Rwanda, July 2025, Symposium

HPTN 084 Long-acting Injectable For the Epidemic

Lenacapavir (LEN)

First-in-class HIV capsid inhibitor, given subcutaneously once every 6 months

LEN found to be Safe for pregnant woman and Infants

PURPOSE 1: a phase 3, double-blind, randomized, controlled trial randomized participants in a 2:2:1 ratio to receive subcutaneous LEN every 26 weeks, daily oral F/TAF, or daily oral F/TDF

- PURPOSE 1 purposefully including women who became pregnant and/or who were breastfeeding
  - with pre-specified pregnancy-related and infant outcomes, and pharmacokinetic studies through pregnancy, breastfeeding
- 510 pregnancies in 487 women (193 LEN, 219 F/TAF, 98 F/TDF)
- 277 pregnancy outcomes, 233 pregnancies still ongoing

Bekkar L-G et al . N Engl J Med 2024;391:1179-92. Bekker L-G et al. AIDS 2025, Kigali, Rwanda, July 2025, Abs. OAC0504

PURPOSE 1

No Signals of Increased Adverse Pregnancy Complications or Adverse Birth Outcomes with LEN

	Lenacapavir N=2,138	F/TAF N=2,137	F/TDF N=1,070
# Confirmed pregnancies	193	219	98
Ongoing pregnancies	88 (45.6%)	100 (45.7%)	45 (45.9%)
Completed pregnancies	105 (54.4%)	119 (54.3%)	53 (54.1%)
Gestational hypertension	2	1	1
Pre-eclampsia	0	1	0
Hyperemesis gravidarum	1	0	0
Polyhydramnios	1	0	0
Prolonged labor	0	1	0
Hemorrhage	0	1	0
Fetal distress	1	0	1
Cephalo-pelvic disproportion	0	0	2

Pregnancy complications uncommon with no difference between groups

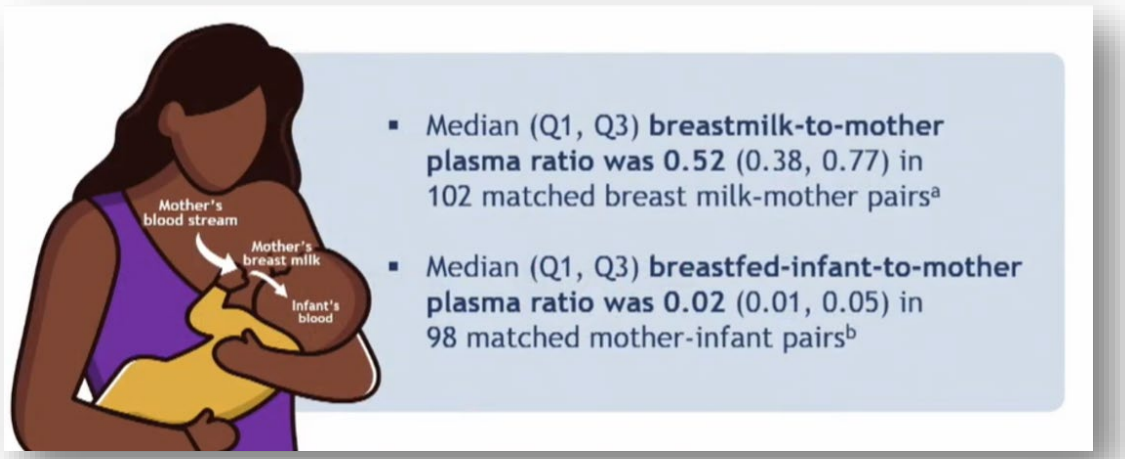
Stillbirths and miscarriage not significantly different for LEN vs oral PrEP; not significantly different than expected background rates

	Lenacapavir N=2,138	F/TAF N=2,137	F/TDF N=1,070
# pt with confirmed pregnancies	184	208	95
# confirmed pregnancies	193	219	98
Ongoing pregnancies	88 (45.6%)	100 (45.7%)	45 (45.9%)
Completed pregnancies	**105 (54.4%)**	**119 (54.3%)**	**53 (54.1%)**
Interrupted Pregnancies	50 (47.6%)	74 (62.1%)	32 (60.4%)
Spontaneous abortion (<20 wks)	20 (19.0%)	34 (28.5%)	12 (22.6%)
Induced abortion	30 (28.5%)	40 (33.6%)	20 (37.8%)
Stillbirths (≥20 wks)	3 (2.8%)	4 (3.4%)	1 (1.9%)
Live births	52 (49.5%)	41 (34.5%)	20 (37.7%)
Birth defect*	1 (1%)	0	0

Bekkar L-G et al . N Engl J Med 2024;391:1179-92

A bit more about LEN and Pregnant and Breastfeeding Women

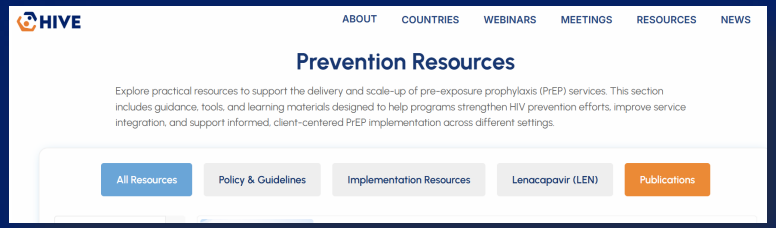
- LEN exposures were similar in pregnant vs non-pregnant persons and 1st, 2nd, 3rd trimesters and postpartum
- LEN pharmacokinetics were similar when injections administered in thigh vs abdomen



Bekker L-G et al. AIDS 2025, Kigali, Rwanda, July 2025, Abs. OAC0504

- LEN was present in breastmilk at levels ~50% of those in maternal plasma
- LEN levels in breastfed infants was extremely low – there was minimal exposure to infant

In summary….



No concerning safety signals for common adverse pregnancy or birth outcomes associated with DVR, CAB-LA or LEN.

- Unusual amount of high-quality data from clinical trials
- No data from trials for women initiating CAB-LA or LEN during pregnancy but no reason to expect different outcomes

Given the high risk of HIV seroconversion in pregnant and breastfeeding women and subsequent high risk of vertical transmission to their infant and the absence of any concerning safety signals, there should be no restrictions on use of these agents during pregnancy or postpartum.

Due diligence requires ongoing surveillance to collect adequate number of observations to rule out an increased risk of rare events

- >2000 exposures to determine a 3-fold increase in risk of a rare outcomes

Thank you!

HIV
Impact Network for
Vertical Transmission
Elimination

Shared knowledge, quality care, mothers thriving, and babies born HIV-free.

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Thanks to Dr. Lynne Mofenson for slides adapted for this presentation