

# Prevention of HIV in pregnant and lactating people

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HPTN Regional Meeting, September 2023

# Key messages

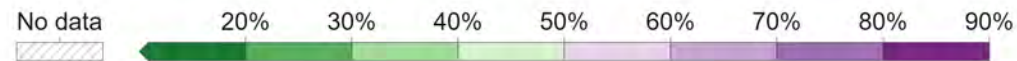
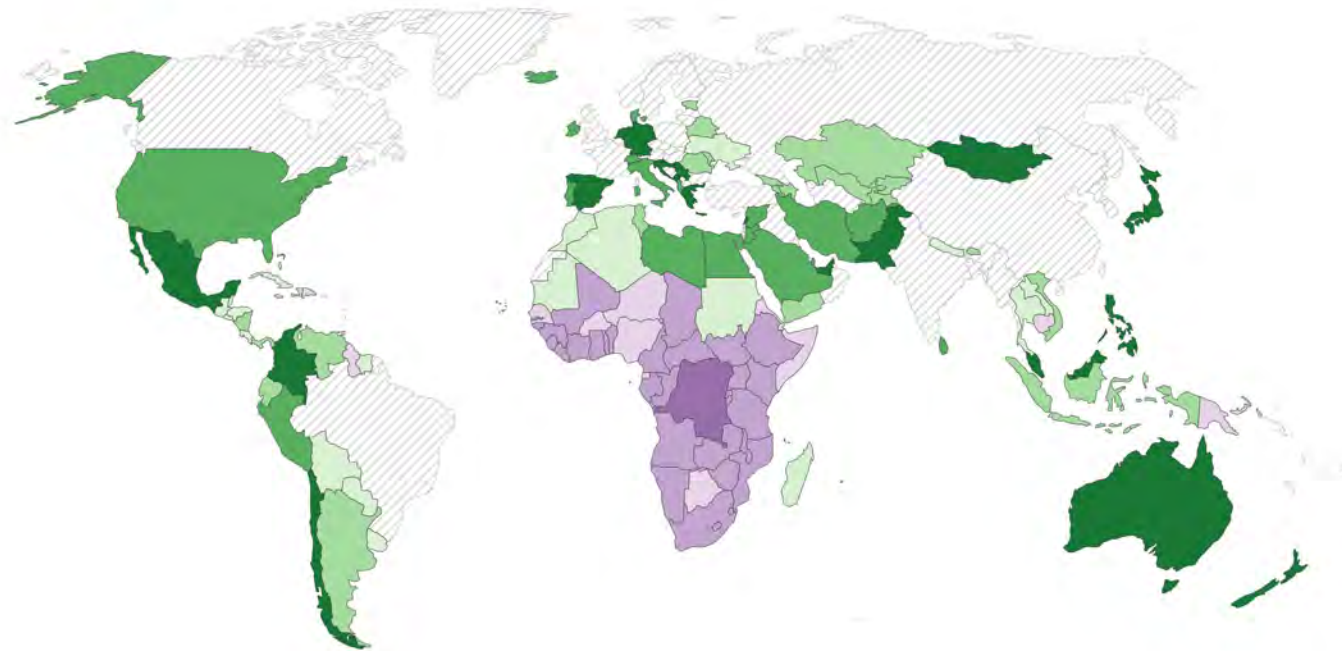
- Women experience overlapping risks for HIV and pregnancy and have need of effective prevention options, but historically have been excluded from pre-licensure trials because of safety concerns
- A paradigm shift is underway, with a call to action to include pregnant and lactating people in pre-licensure trials using a new set of decision criteria
- This change is an opportunity for the HPTN to address the evidence gaps in pregnancy safety data, to educate communities and support participants, and to build the evidence base for current and future products

# Women in sub-Saharan Africa have an unmet need for HIV prevention

What share of the population living with HIV are women?, 2020

Among those aged 15 years and older.

Our World  
in Data

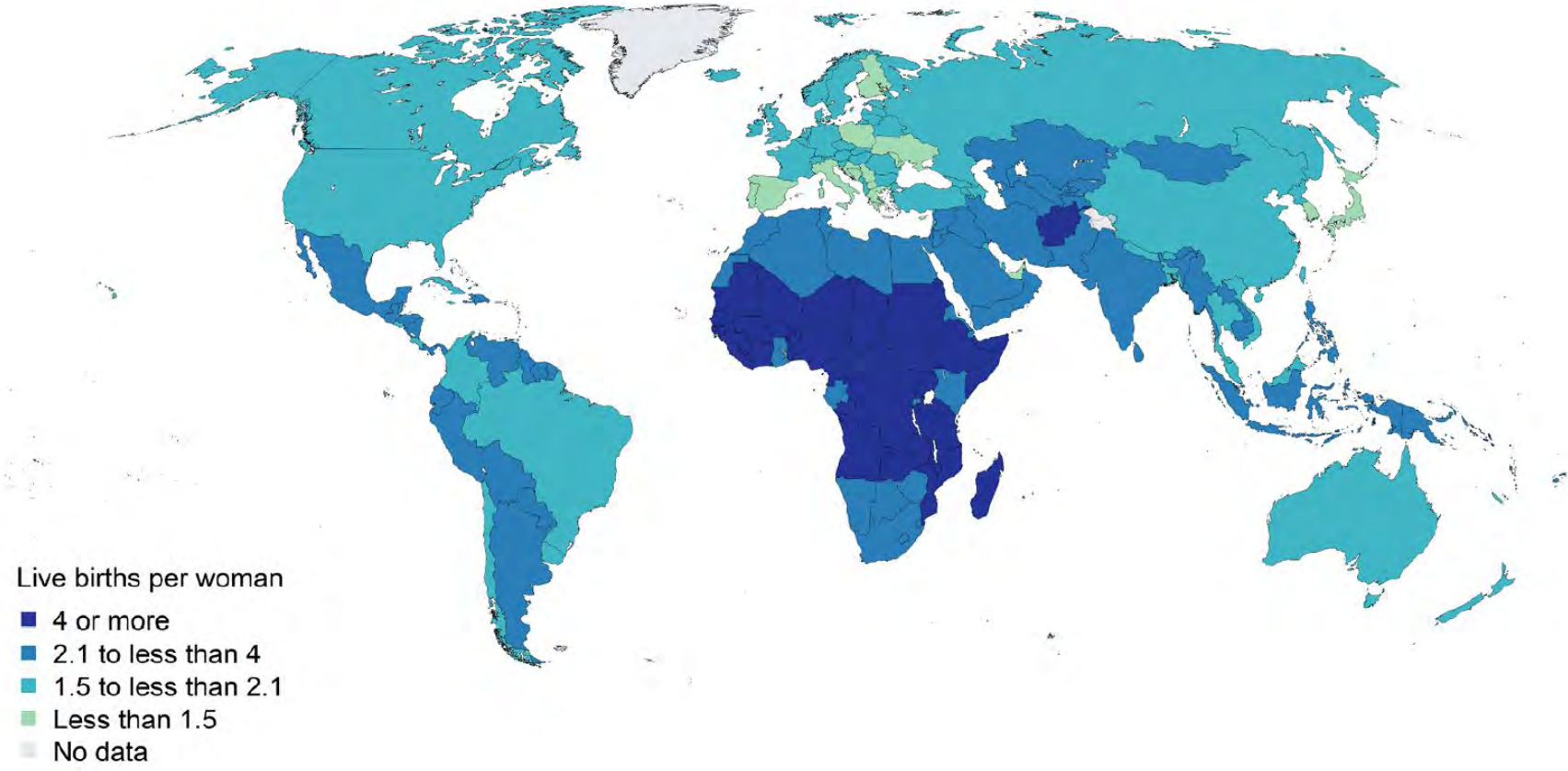


Source: UNAIDS (via World Bank)

OurWorldInData.org/hiv-aids • CC BY

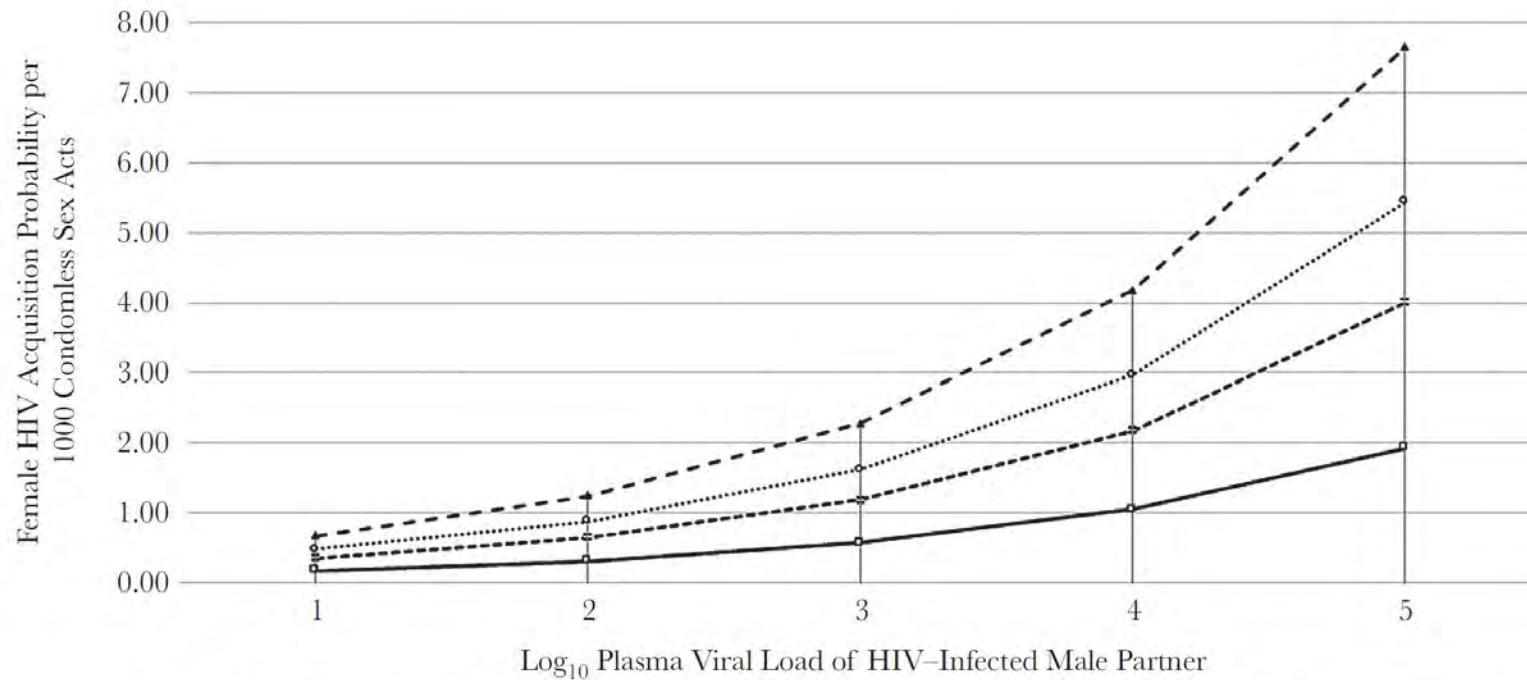
# Fertility rates are highest in high HIV burden settings

Total fertility rate by country or area, 2019



Source: United Nations Population Division, 2020

# Pregnancy and post-partum period associated with increased risk for HIV



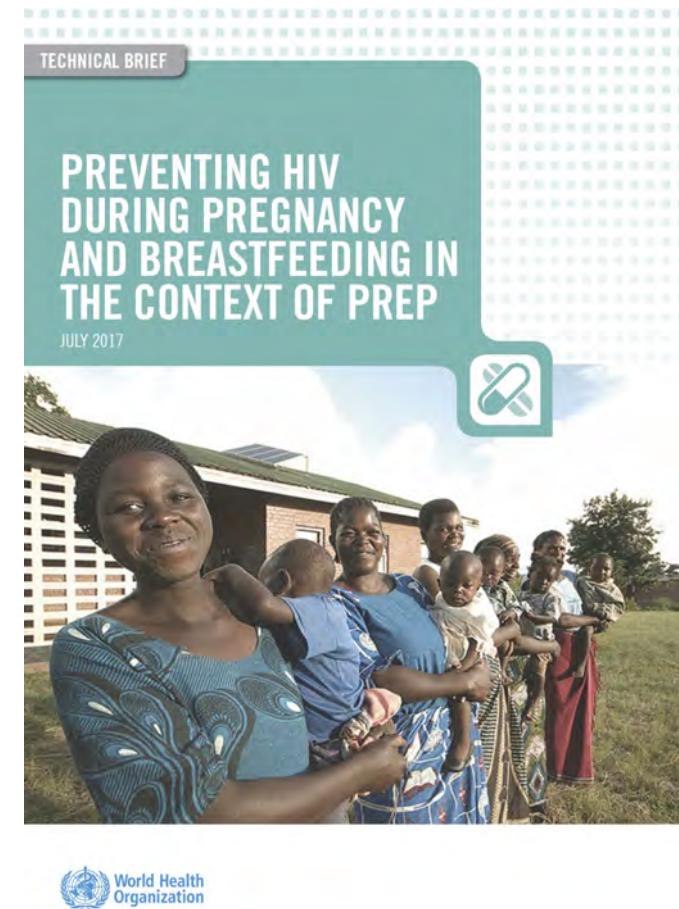
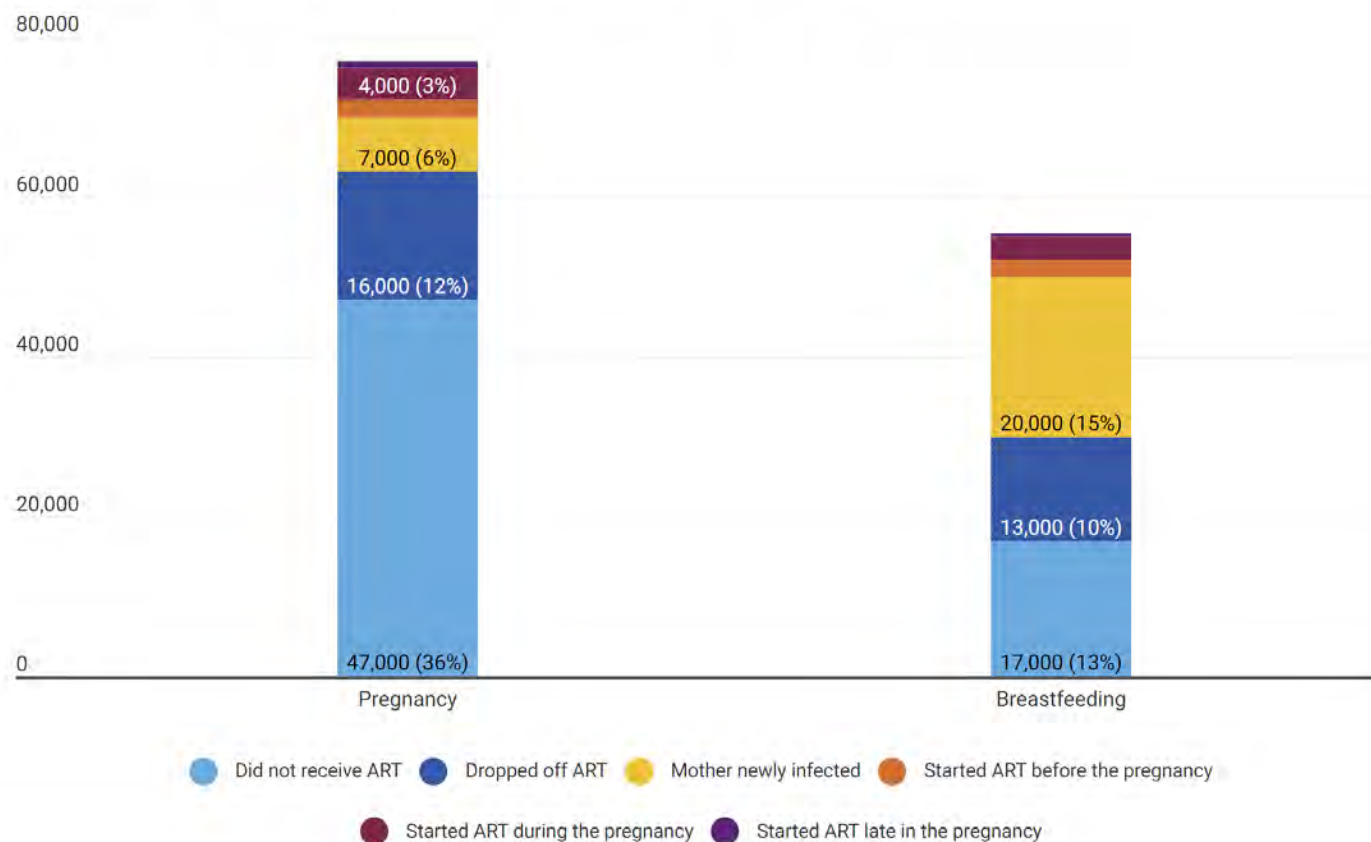
—□—	Nonpregnant	0.17	0.31	0.58	1.05	1.93
- -□- -	Early pregnancy	0.36	0.65	1.19	2.19	4.00
...□...	Late pregnancy	0.48	0.89	1.62	2.97	5.44
- * -	Postpartum	0.68	1.25	2.29	4.18	7.65



Suggests that biological changes during pregnancy and the postpartum period increase HIV susceptibility among women.

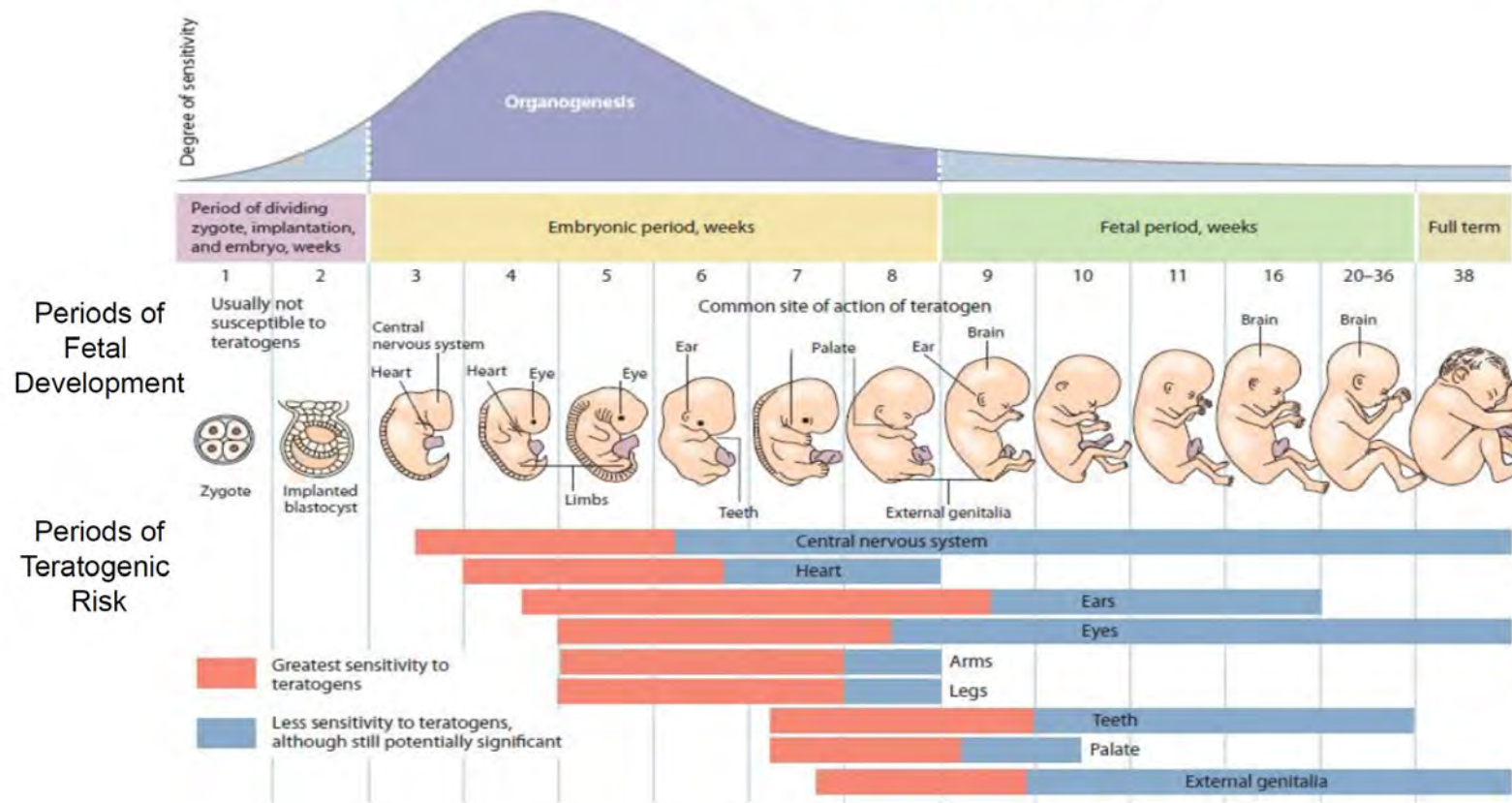
## The majority of paediatric HIV infections are due to new mothers not receiving ART, dropping off ART, or becoming infected during breastfeeding

Number of new HIV infections among children by source of infection, 2022



# Concerns about fetal exposure to medications during pregnancy

## Timing of *In Utero* Drug Exposure and Fetal Risk of Birth Defect

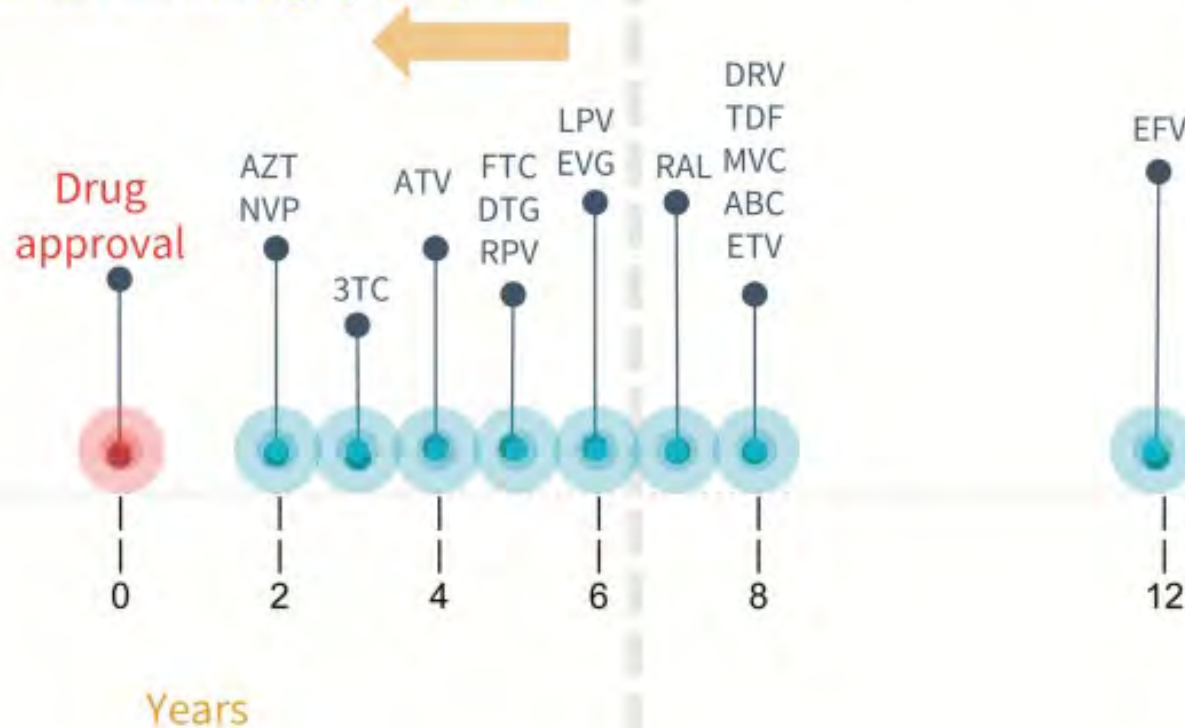


Historically women of childbearing potential are under-represented in trials, are required to use contraception, and required to stop study product if they become pregnant.

# Excluding pregnant women from trials shifts risk of harm

Time-to-first published (PK) data in pregnancy

Median knowledge gap 6 years



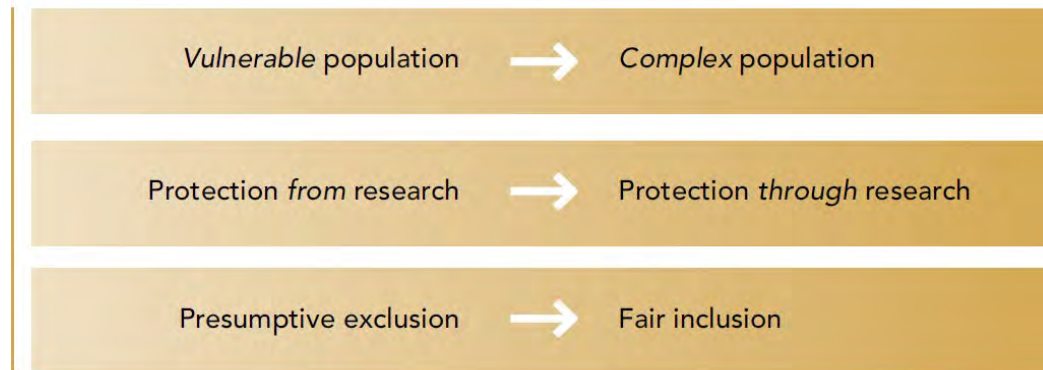
Without research, pregnant people

- May be given drugs in the **wrong dose**
- May be given drugs that carry **unacceptable risk**
- May be **denied access** to critically needed drugs



# A paradigm shift is underway

- Multiple stakeholders have voiced their concerns around the exclusion of pregnant women from pre- and post-registration drug trials and the associated harms and risks of these policies.
- Three major conceptual shifts that will facilitate the inclusion of pregnant women in research:



**Ending the evidence gap  
for pregnant women  
around HIV & co-infections:**

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**A CALL TO ACTION**

# Key principles for studying new antiretrovirals in pregnancy



If the agent is **efficacious in non-pregnant adults** (viral load suppression) and **adequate drug exposures** are achieved in pregnancy, then **efficacy can be assumed** in pregnancy without additional trials.



If the agent is efficacious in non-pregnant adults (viral load suppression) and adequate drug exposures are achieved in pregnancy, **efficacy for prevention of vertical transmission can be inferred**.



**All new agents** must be studied in pregnant woman for **pharmacokinetics/optimal dosing and short-term safety**.



**Dedicated pregnancy safety studies assessing pregnancy, birth and infant outcomes** should be conducted for all **new ARVs with expected broad use** in pregnant women and women who may become pregnant.

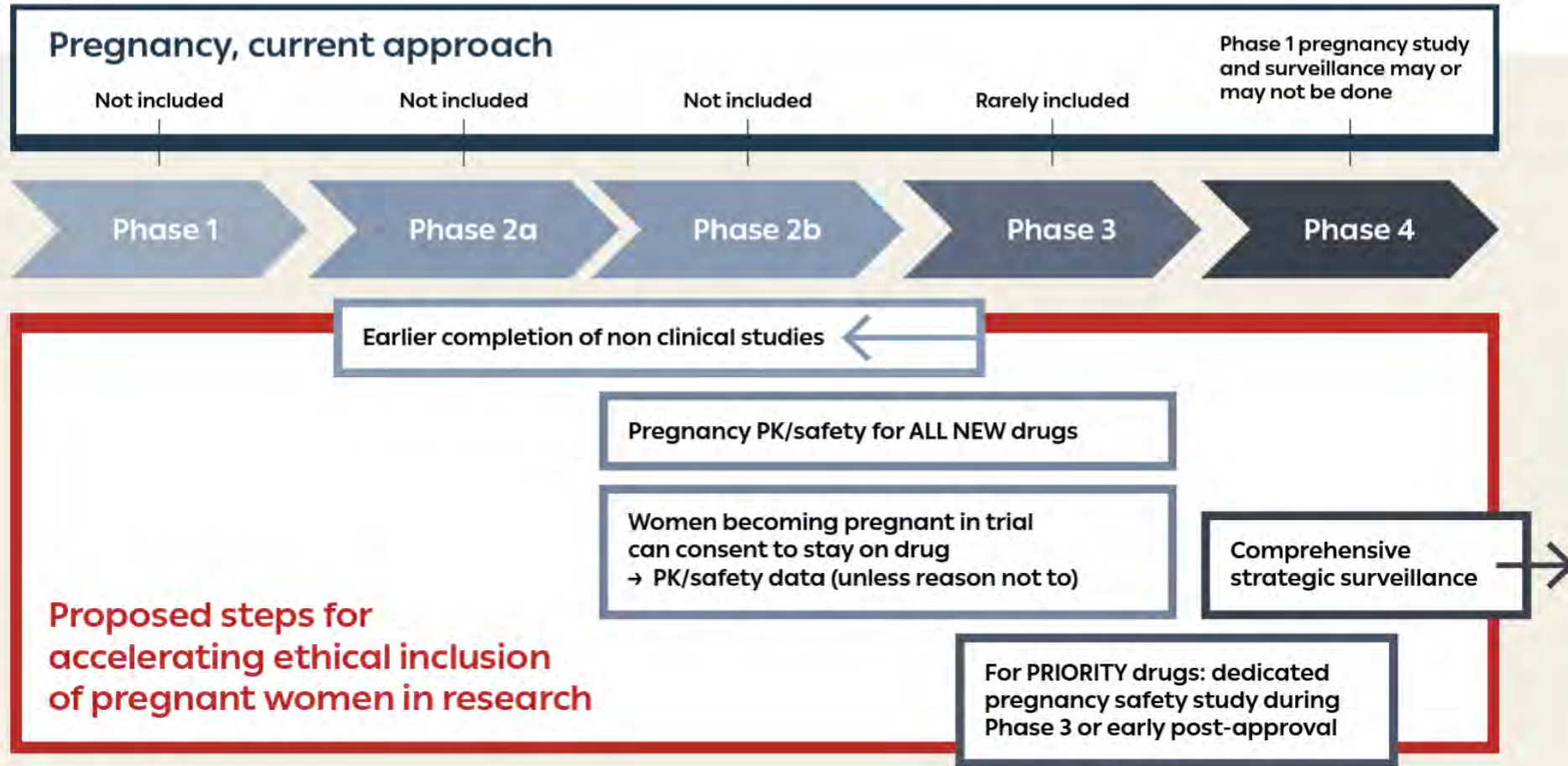


There is **no expectation to have meaningful clinical information about teratogenicity risk before registration**; Large numbers of observations with exposure at conception/early pregnancy are needed to identify increased risk of rare events and will only come through active surveillance/Phase 4 studies.



Once **pharmacokinetic/dosing and short-term safety** in pregnancy are determined to be adequate, there should be no restrictions to access during pregnancy once the ARV is licensed.

# A framework for accelerating inclusion in pre-licensure clinical trials



Research for informed choices: Accelerating the study of new drugs for HIV in pregnant and breastfeeding women

### A call to action



Trials of DVR, CAB, LEN, ISL all include pregnant and lactating people

# Congenital anomalies are not the only (nor even the most important) safety endpoint related to medications taken in pregnancy

## Pregnancy outcomes, including

Preterm delivery (**PTD**, birth <37 weeks)

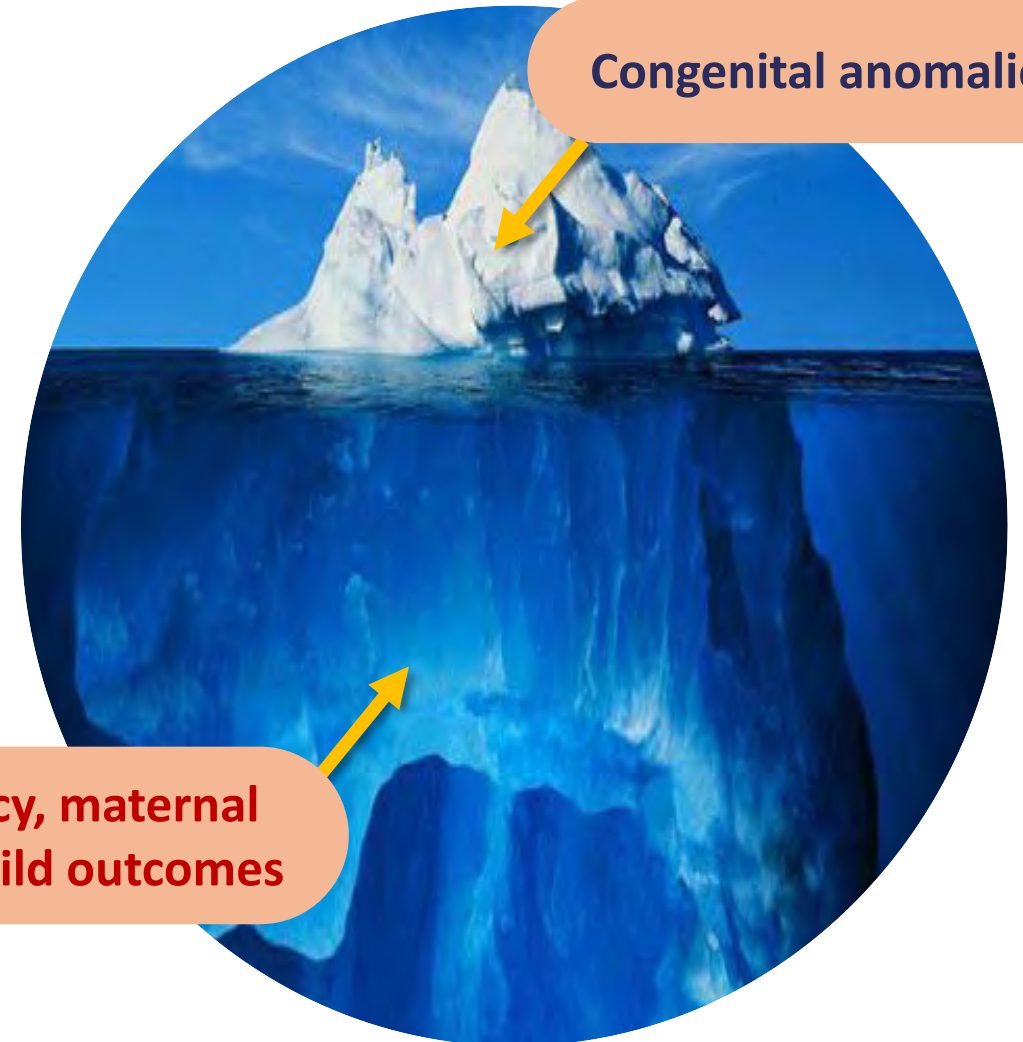
Low birthweight (**LBW**, <2500g)

Small for gestational age (**SGA**, <10<sup>th</sup> %ile)

Fetal loss (miscarriage, stillbirth)

## Maternal health outcomes

## Child outcomes



# Congenital anomalies are not the only safety endpoint related to medications taken in pregnancy

Assessing pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe:  
Results from a systematic chart review

	Malawi N = 2442	Uganda N = 3835	South Africa N = 1936	Zimbabwe N = 2213	Overall N = 10426
Place of delivery					
Current health facility	2282 (93.4)	3607 (94.1)	1858 (96.0)	2032 (91.8)	9779 (93.8)
At a different health facility	131 (5.4)	180 (4.7)	26 (1.3)	71 (3.2)	408 (3.9)
At a home (private residence)	28 (1.1)	33 (0.9)	48 (2.5)	109 (4.9)	218 (2.1)
Not documented	1 (0.0)	15 (0.4)	4 (0.2)	1 (0.0)	21 (0.2)
Mode of delivery					
Vaginal delivery	1819 (74.5)	2726 (71.1)	1258 (65.0)	1819 (82.2)	7622 (73.1)
Cesarean delivery	592 (24.2)	1082 (28.2)	674 (34.8)	362 (16.4)	2710 (26.0)
Other	28 (1.1)	9 (0.2)	0 (0.0)	32 (1.4)	69 (0.7)
Not documented	3 (0.1)	18 (0.5)	4 (0.2)	0 (0.0)	25 (0.2)
Pregnancy outcome					
Full term live birth	2094 (85.7)	3192 (83.2)	1387 (71.6)	1775 (80.2)	8448 (81.0)
Premature live birth (<37 weeks)	261 (10.7)	400 (10.4)	400 (20.7)	258 (11.7)	1319 (12.7)
Still born/intrauterine fetal demise (≥20 weeks)	75 (3.1)	152 (4.0)	64 (3.3)	122 (5.5)	413 (4.0)
Outcome not documented	12 (0.5)	91 (2.4)	85 (4.4)	58 (2.6)	246 (2.4)
Birthweight (grams) <sup>2</sup>	2934±533 (600–5000)	3027±633 (500–5400)	2946±659 (500–5570)	2977±592 (400–4960)	2979±608 (400–5570)
Low birthweight (<2500 g) <sup>2</sup>	353 (15.1)	574 (15.9)	324 (17.4)	288 (13.8)	1539 (15.5)
Neonatal death <sup>3</sup>	61 (2.6)	42 (1.2)	24 (1.3)	65 (3.2)	192 (2.0)

<sup>1</sup>Statistics are N (%) for categorical variables and mean ± SD (range) for continuous variables.

<sup>2</sup>Birthweight reported for livebirths only.

<sup>3</sup>Livebirths only. Missing data for N = 118 (1.2%) included in the denominator.

Pre-term birth complications are the leading cause of death among children under 5 years

Pre-term neonates who survive are at greater risk of short and long-term morbidities

LBW associated with worse health outcomes

# Pre-term birth and low-birth weight associated with negative outcomes

- **Pre-term birth**
  - Preterm birth complications = leading cause of death among children under 5 years (35% of deaths among neonates)
  - Pre-term neonates who survive has greater risk of short-term and long-term morbidities
  - Poor long-term outcomes including cognitive disability, impaired hearing/vision, neurological complications, infections, and chronic pulmonary, cardiovascular, metabolic, and renal disorders (especially in very preterm babies)
  - Associated with significant costs to the health system, and families
- Low-birth weight (or small for gestational age) babies are at significantly higher risk of poor health outcomes (including mortality), particularly in low-income settings

# A need for harmonised safety outcomes

Birth outcomes	Maternal health outcomes	Neonatal/infant outcomes
Stillbirth	Mortality (during pregnancy, L&D)	Mortality (early neonatal)
Preterm birth (and whether spontaneous vs indicated)	Prolongation of hospitalization or re-hospitalization	Neonatal mortality (28 days)
Birthweight	Blood pressure, hypertensive disorders of pregnancy	Infant mortality (first year)
Small for gestational age (SGA) (<10 <sup>th</sup> percentile)	Weight gain in pregnancy	Growth (first year)
Major congenital anomaly (with neonatal surface exam and <u>fetal anatomic ultrasound</u> )	Caesarean section (with indication)	Congenital anomalies (6 months)
Early fetal loss/miscarriage	Gestational diabetes	Hospitalization (first year)
	Pregnancy and labor/delivery complications	Liver, renal, full blood count (if breastfeeding, and dep. on drug)
	Liver, neuropsychiatric, renal, bone toxicity (depending on drug)	Neurodevelopment

# Importance of a comparator group

- Very important to collect contemporary outcomes data in medication-unexposed comparator group in the same locations/populations
  - Cautious use of “Background” rates from the most comparable population are a far less desirable alternative, if contemporaneous data from comparator group not feasible



## Safety

- Are the **maternal, pregnancy and infant** safety outcomes similar between CAB exposed vs. non-exposed, with active dosing in OLE?

## Pharmacology

- Do we need **dose adjustment** during pregnancy?
  - PBPK model predictions suggest bimonthly long-acting cabotegravir is likely to maintain antiviral efficacy throughout pregnancy.
- What can we say about infant exposure to CAB during **lactation**?
  - Data on CAB in breastmilk limited
  - Data from DTG suggests low concentrations in breastmilk
    - median ratio of DTG in breast milk to maternal plasma was 0.03 (median 66.7 ng/mL)
    - In DTG elimination by newborn infants is prolonged but no AEs have been reported
  - Additional virology questions

HIV/AIDS > HIV/AIDS

# FDA Warns of Birth Defects from HIV Drug Dolutegravir

— Safety signal seen in Botswana trial data

by John Gever, Managing Editor, MedPage Today May 18, 2018

# Community considerations

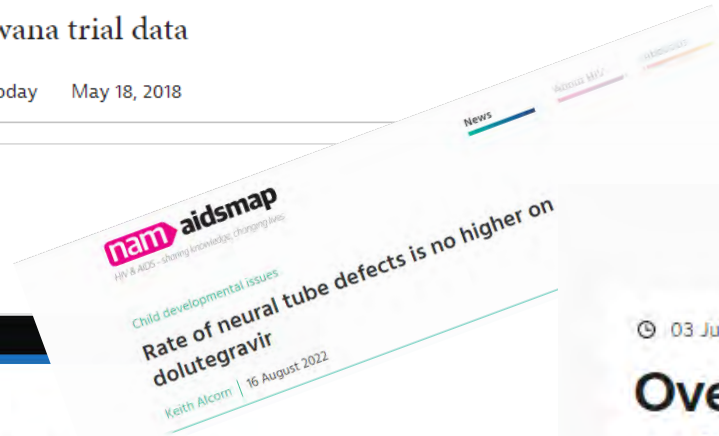


Home > Drug Safety Update

**Dolutegravir (Tivicay ▼, Triumeq ▼, Juluca ▼): signal of increased risk of neural tube defects; do not prescribe to women seeking to become pregnant; exclude pregnancy before initiation and advise use of effective contraception**

New safety recommendations have been issued while an EU review evaluates cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir.

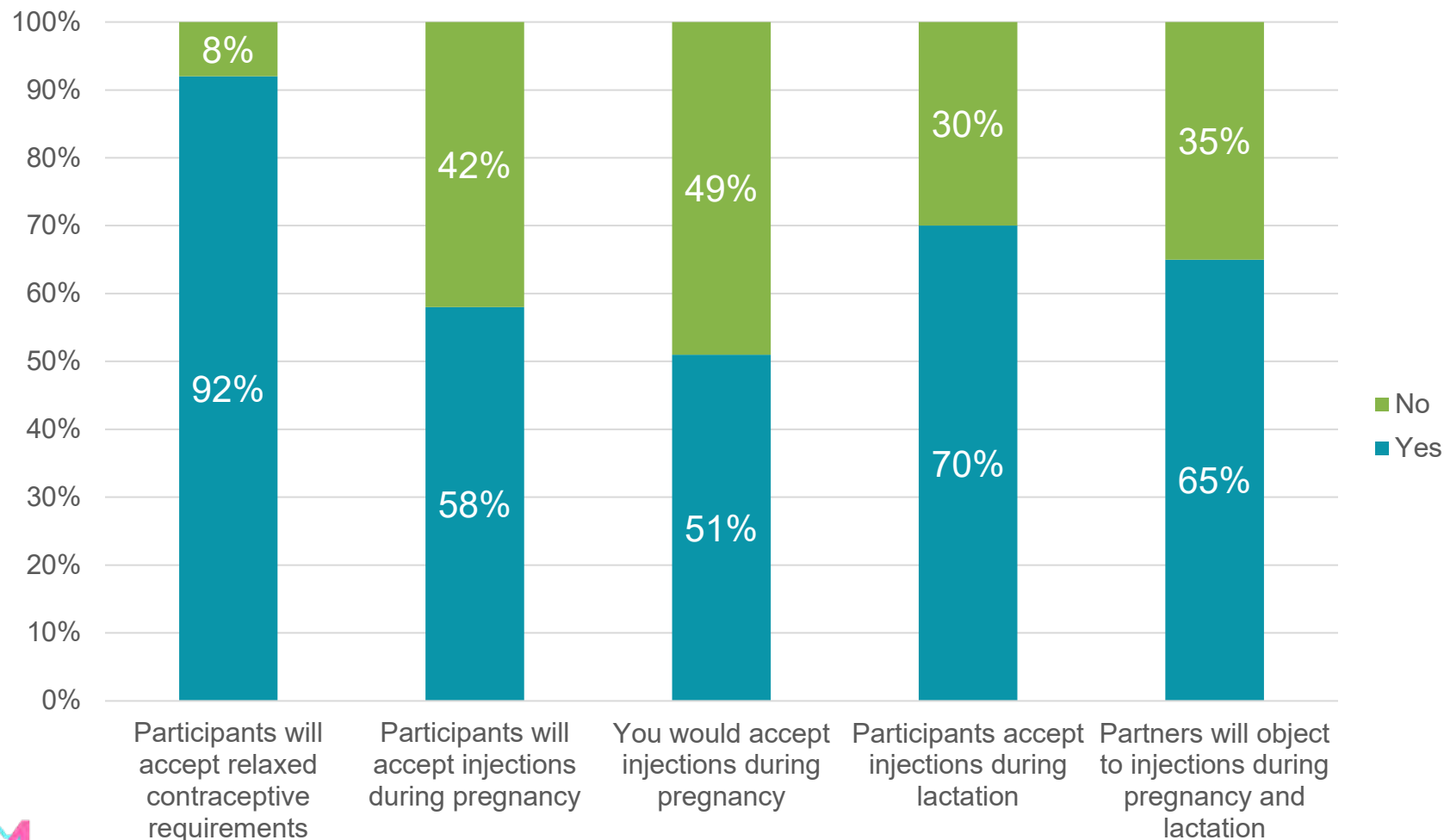
From: [Medicines and Healthcare products Regulatory Agency](#)  
Published 22 June 2018



## A district perspective

Dr Josephine Otchere-Darko, programme head of Wits RHI's HIV/TB care and treatment programme in Ekurhuleni, says that initially there were mixed emotions and slow uptake, due to fears around the usage of TLD, particularly in pregnancy. Yet uptake started to increase a little after the studies that essentially “nullified the neural tube defect issue”.

# Community consultation, May 2021



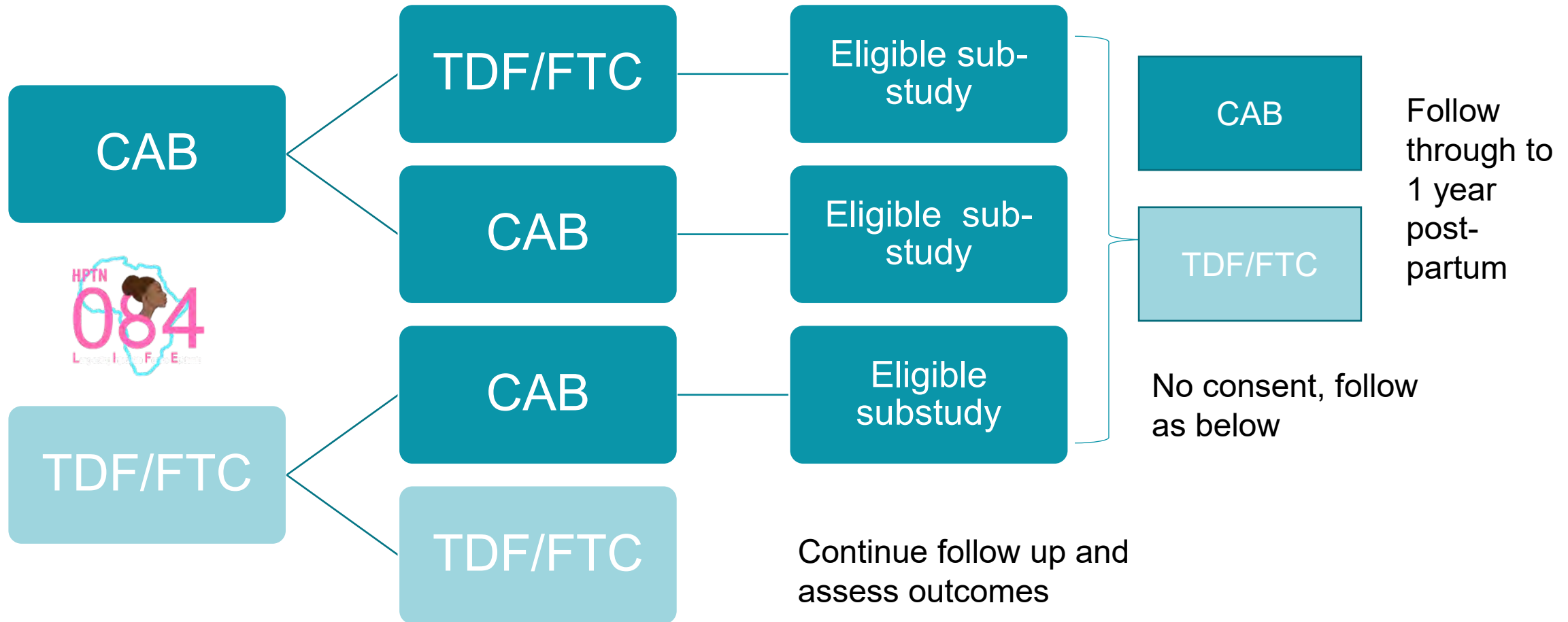
N=101 participants,  
mainly community  
stakeholders

Emphasized safety  
concerns and need  
for information +++

Pregnant women part  
of social network with  
many stakeholders in  
a safe pregnancy  
outcome

# HPTN 084 design, OLE period

No LARC requirement



# Progress to date

- Pregnancies during OLE
  - N=268
  - 161/207 eligible for substudy consented (79%)
    - Both prevalent and incident pregnancies
    - Participants starting CAB and those at steady state
  - Follow up ongoing
  - 44 participants have at least one post-partum visit
- Cumulatively since start of HPTN 084
  - 465 pregnancies, 394 CAB exposed, 71 no CAB exposure
  - 232 live births, 191 CAB exposed, 41 no CAB exposure

# Key messages

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# Acknowledgments

## Sponsor

- U.S. National Institute of Allergy and Infectious Diseases (NIAID), all components of the U.S. National Institutes of Health (NIH)

## Additional funding support

- ViiV Healthcare
- Bill & Melinda Gates Foundation
- National Institutes of Mental Health

## Pharmaceutical support

- Gilead Sciences
- ViiV Healthcare

## HIV Prevention Trials Network

- Leadership and Operations Centre, FHI360
- Laboratory Centre (Johns Hopkins)
- Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchison Cancer Research Center
- HPTN Leadership

## HPTN 084 Study team

- 20 sites in 7 countries in sub-Saharan Africa
- Community advisory boards and partners
- Pregnancy advisors: Friday Saidi, Lynda Stranix-Chibanda

... and our study participants!

UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).



/HIVptn

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