Prevention of HIV in Pregnant and Lactating People

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University of the Witwatersrand
HPTN annual meeting, June 2023

HPTN HIV Prevention Trials Network

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

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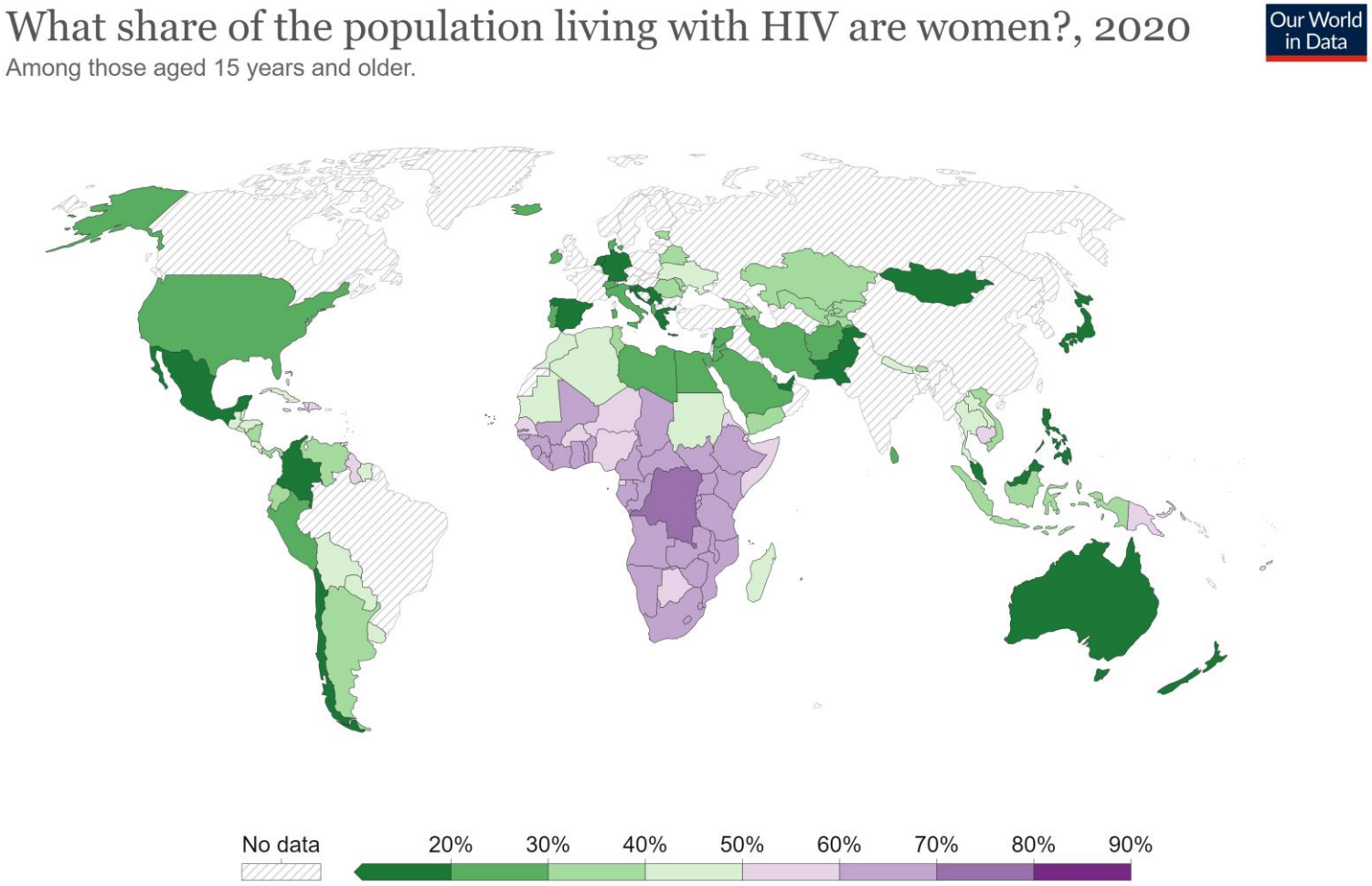

Fertility rates are highest in high HIV burden settings

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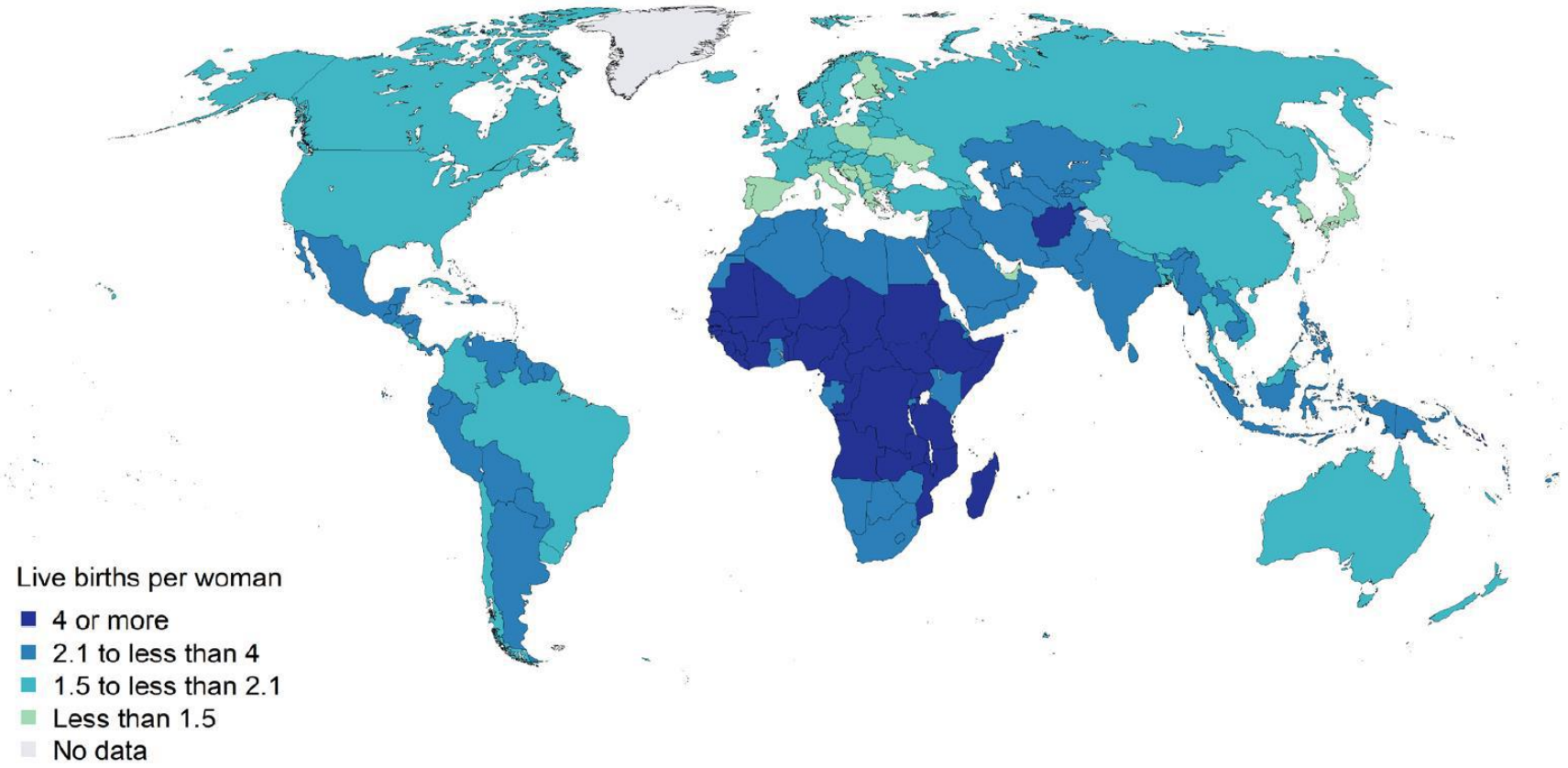
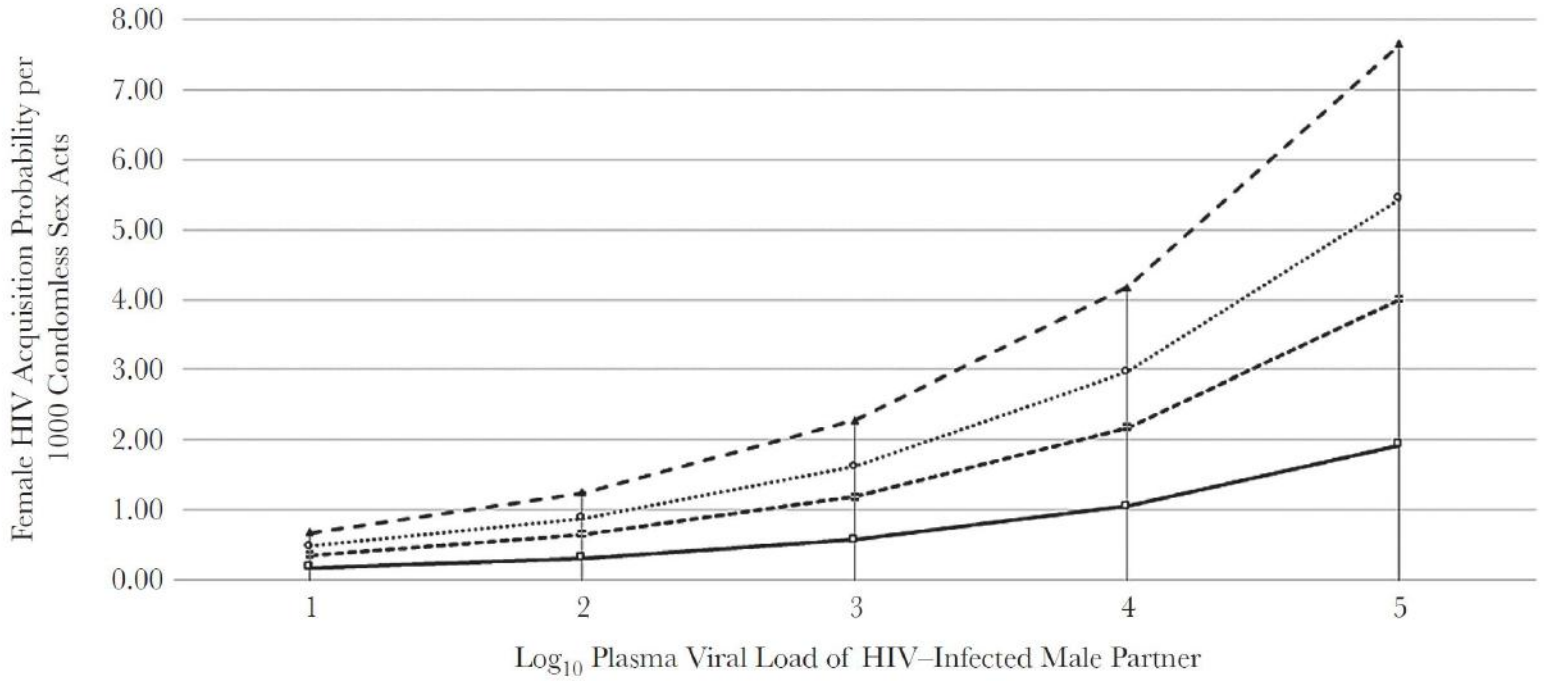
Total fertility rate by country or area, 2019



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.

Source: Thomson, JID 2018

Concerns about fetal exposure to medications during pregnancy

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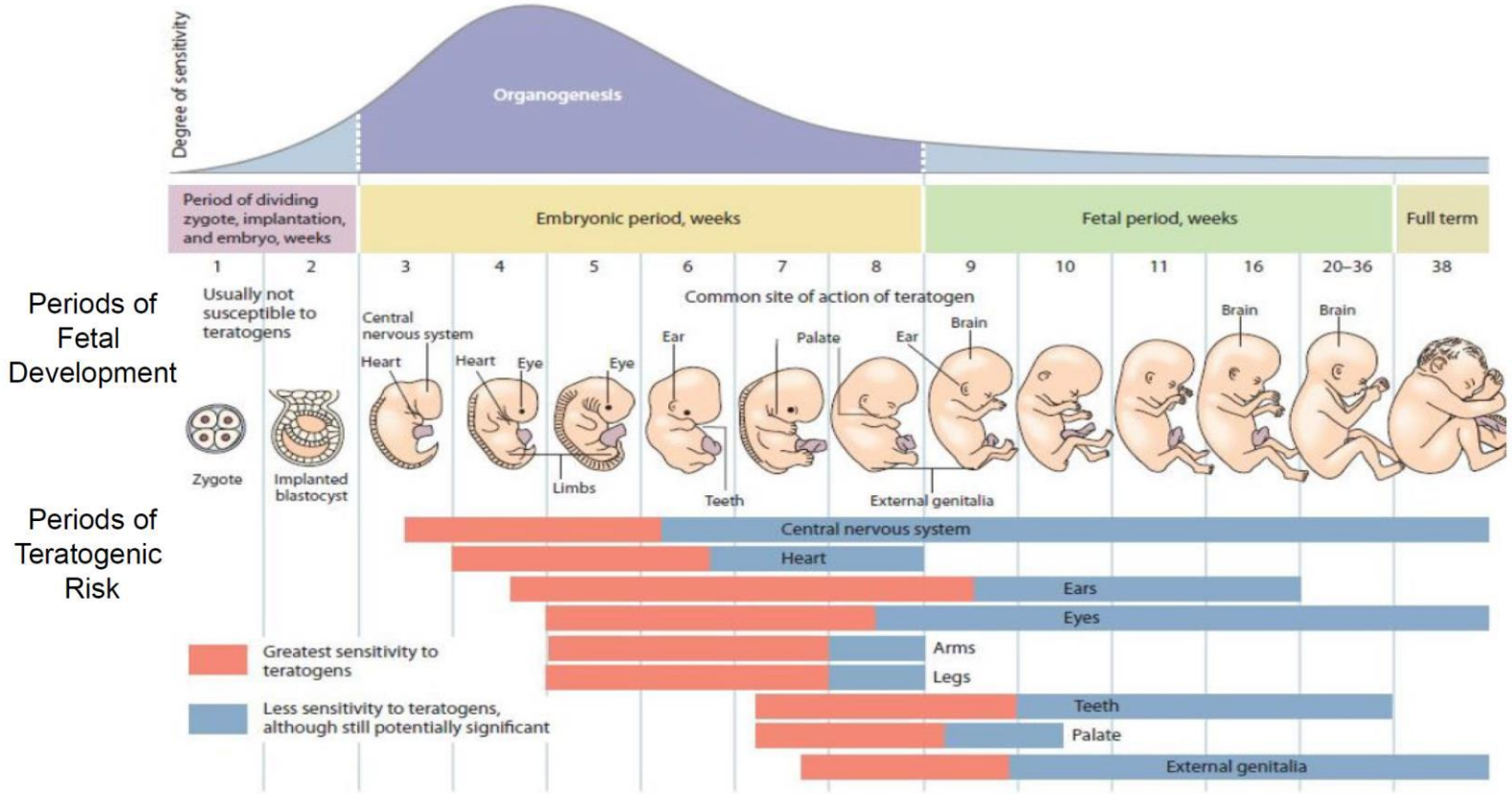
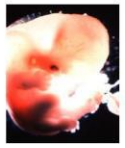
Timing of *In Utero* Drug Exposure and Fetal Risk of Birth Defect

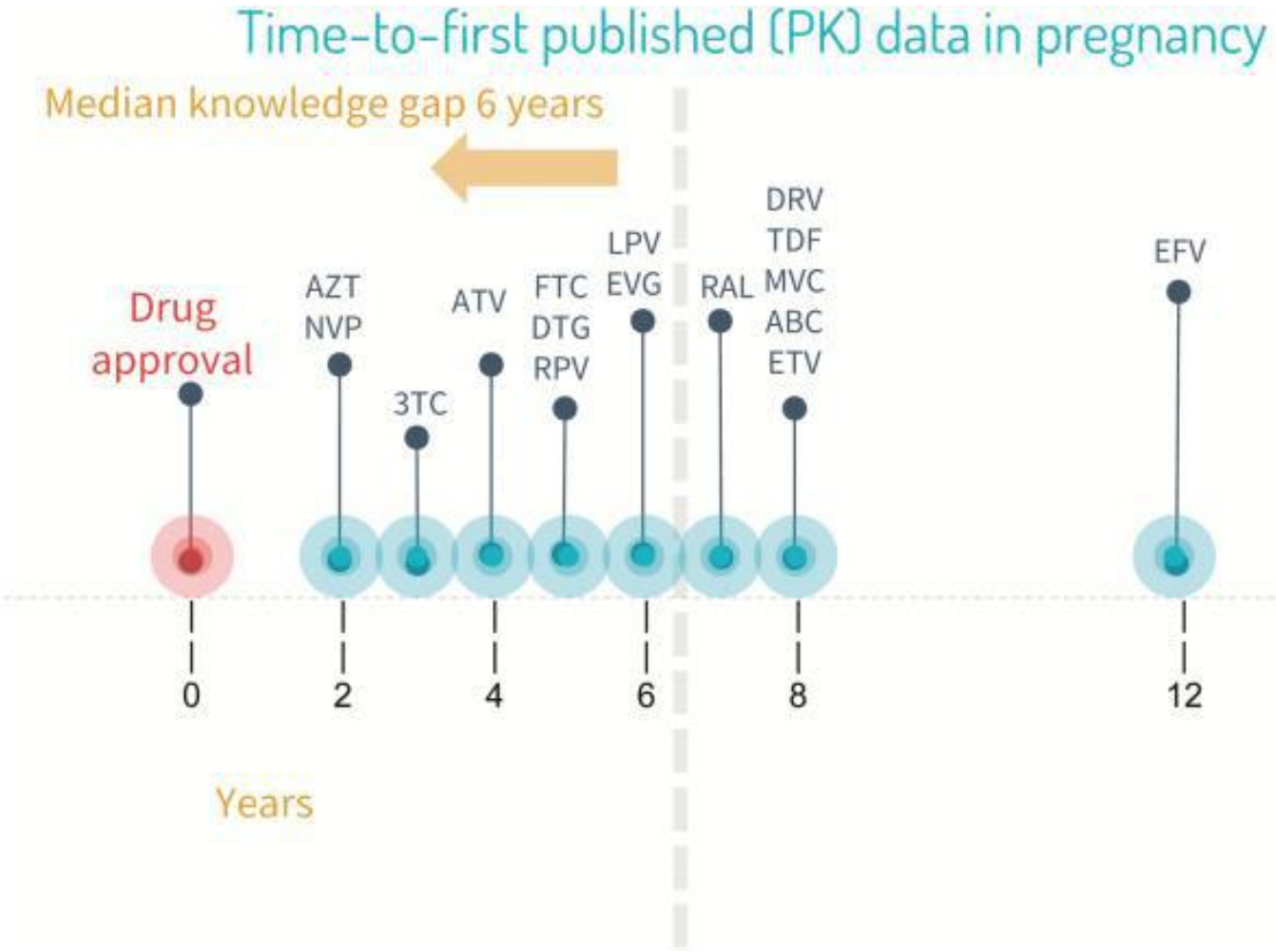




Historically women of childbearing potential are under-represented in trials, are required to use contraception, and required to stop study product if they become pregnant.

Slide courtesy of L. Mofenson

Excluding pregnant women from trials shifts risk of harm



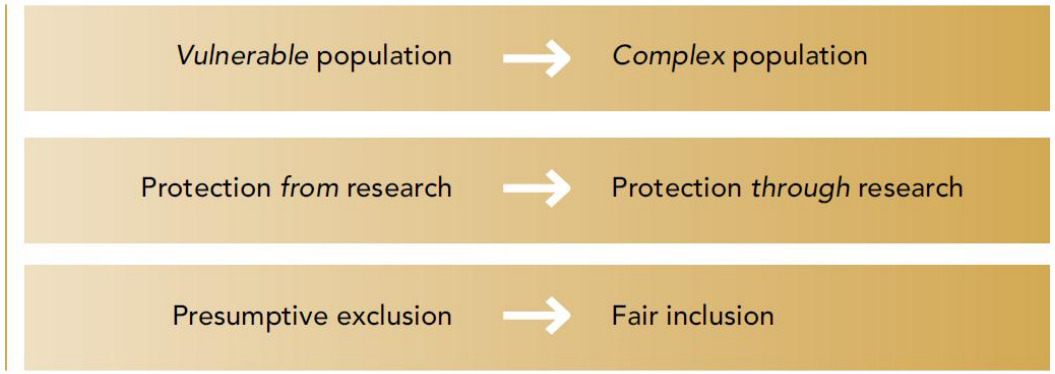
Without research, pregnant people

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

Source: Colbers, 2019; PHASES working group, 2020

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:



Key principles for studying new antiretrovirals in pregnancy

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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

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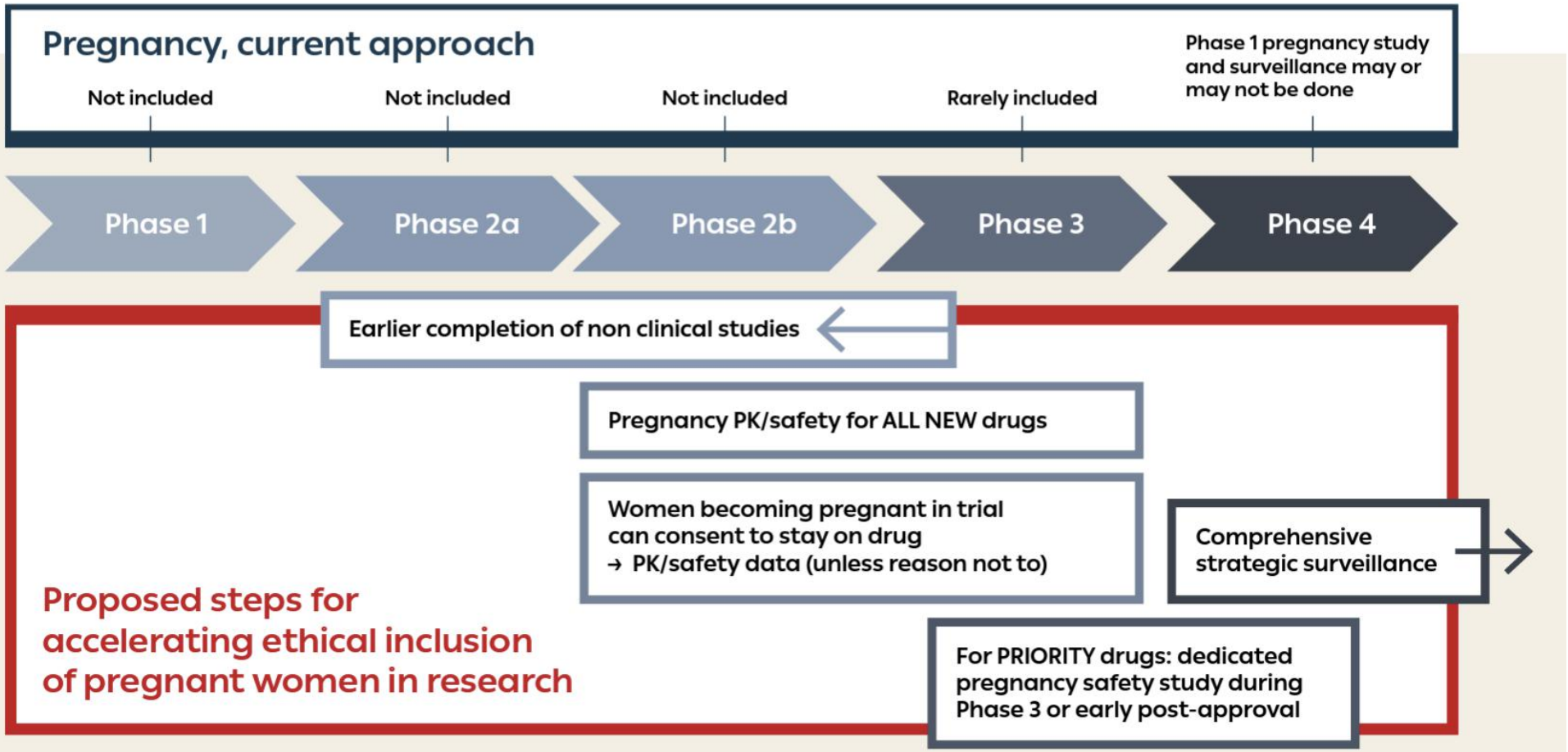


Trials of DVR, CAB, LEN, ISL all include pregnant and lactating people

WHO/IMPAACT, 2022

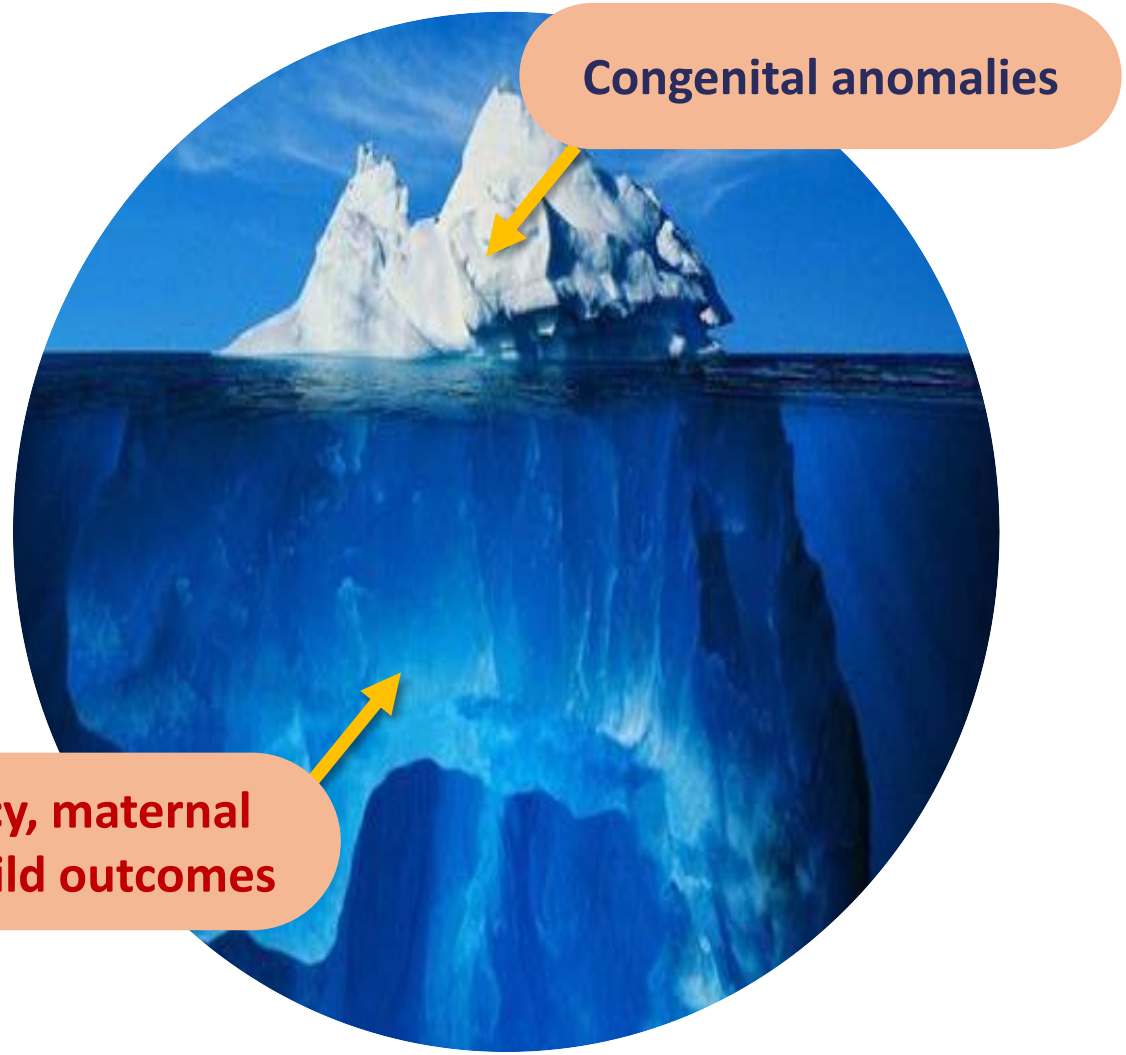
Congenital anomalies are not the only (nor even the most important) safety endpoint related to medications taken in pregnancy

Pregnancy outcomes, including

- Preterm delivery (**PTD**, birth <37 weeks)
- Low birthweight (**LBW**, <2500g)
- Small for gestational age (**SGA**, <10th %ile)
- Fetal loss (miscarriage, stillbirth)

Maternal health outcomes

Child outcomes



Slide courtesy S. Lockman

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) (<10th percentile)	Weight gain in pregnancy	Growth (first year)
Major congenital anomaly (with neonatal surface exam and fetal anatomic ultrasound)	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

WHO Pregnancy and Therapeutics Work Group, 2023

Understanding background rates of select pregnancy outcomes in sub-Saharan Africa/LMICs

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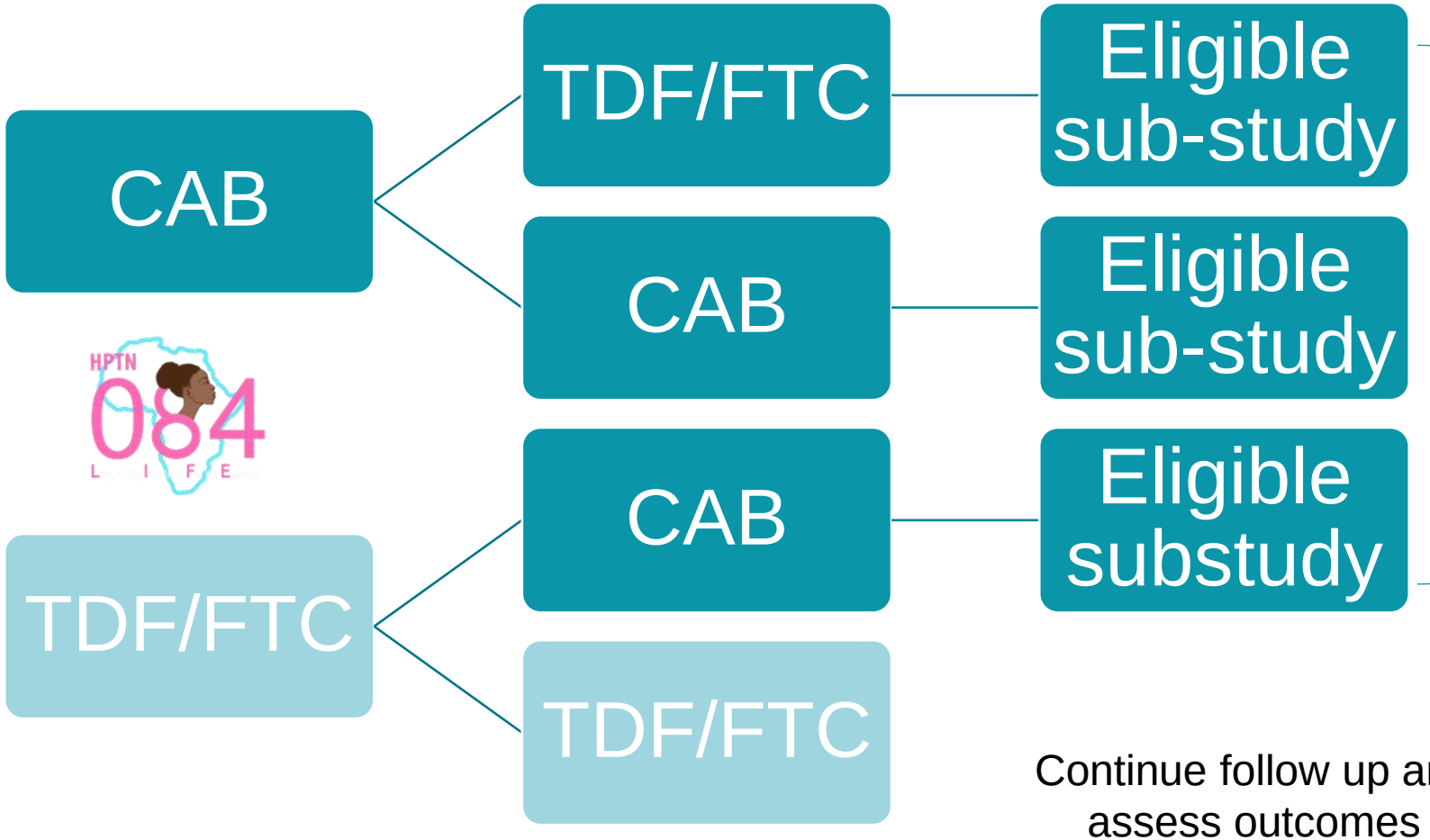
Very important to collect contemporary outcomes data in medication-unexposed comparator group in the same locations/populations

Outcome	Prevalence (95% CI)
Preterm	12.7% (11.2, 14.3) (Lokken, FRH 2021)
Very preterm	3.5% (Caniglia BMJ Open)
SGA	19.3% (Lee BMJ 2017, INTERGROWTH 21)
Very SGA	6% (Caniglia BMJ Open)
Stillbirth	2.5% (2.2, 2.7) (Lokken, FRH 2021)
Composite of any of the above	29% (Caniglia BMJ Open)
Neonatal death	1.7% (1.4, 2.1) (Lokken, FRH 2021)
Miscarriage	10-20%, if pregnancy diagnosed/known (as high as 30% of all pregnancies end in miscarriage by 20 weeks—80% of these by 12 weeks)
Any congenital anomaly	3%
Neural tube defect	0.1%

Slide courtesy F. Saidi

HPTN 084 design, OLE period

No LARC requirement



Follow through to 1 year post-partum

No consent, follow as below

Continue follow up and assess outcomes

Key questions about safety, need for dose adjustment in pregnancy, and safety during lactation

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

Community considerations

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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

GOV.UK

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

03 Jun

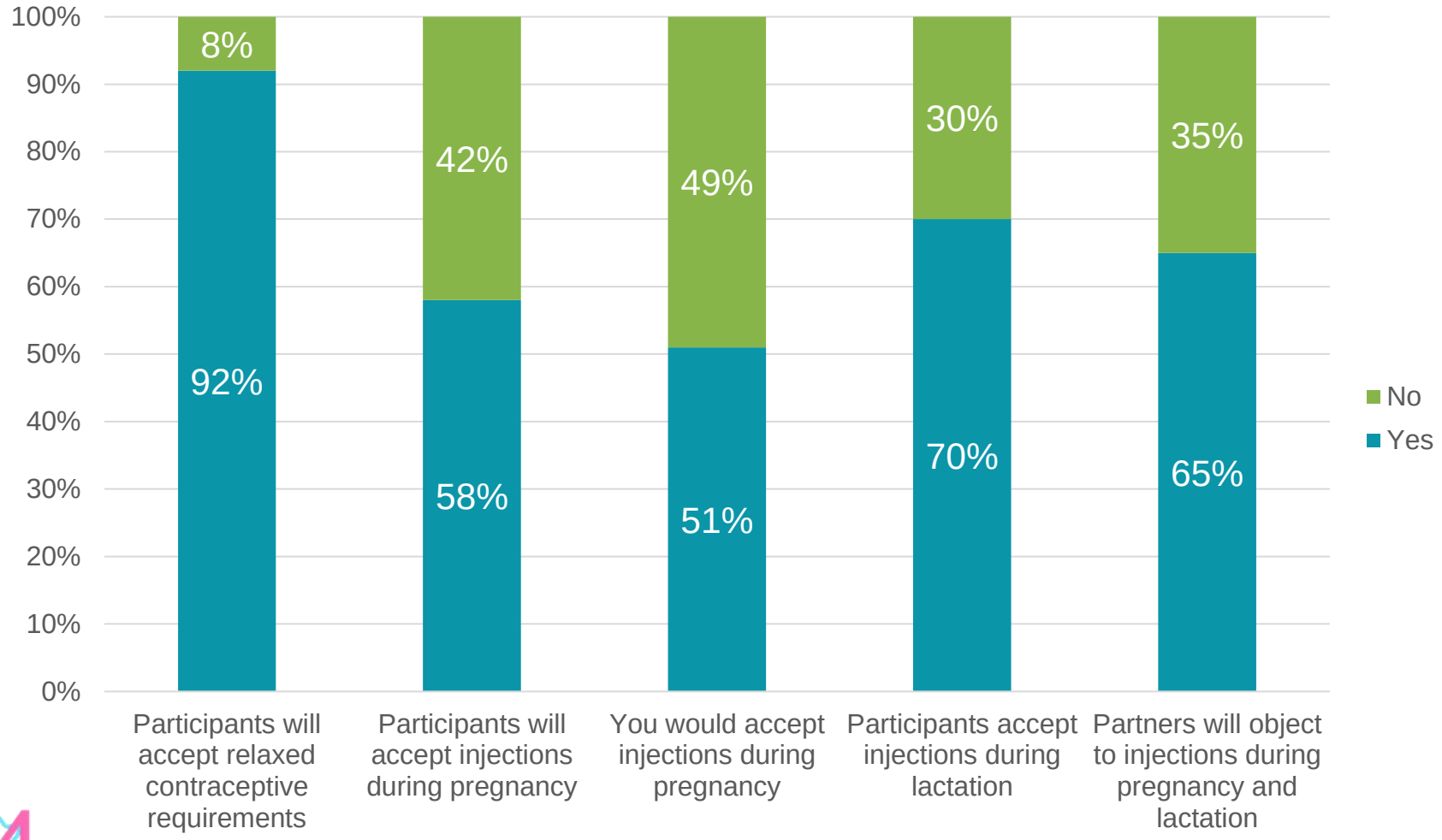
Over 3 million people on new HIV drug, but not all smooth sailing

spotlight Elri Voigt SHARE

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



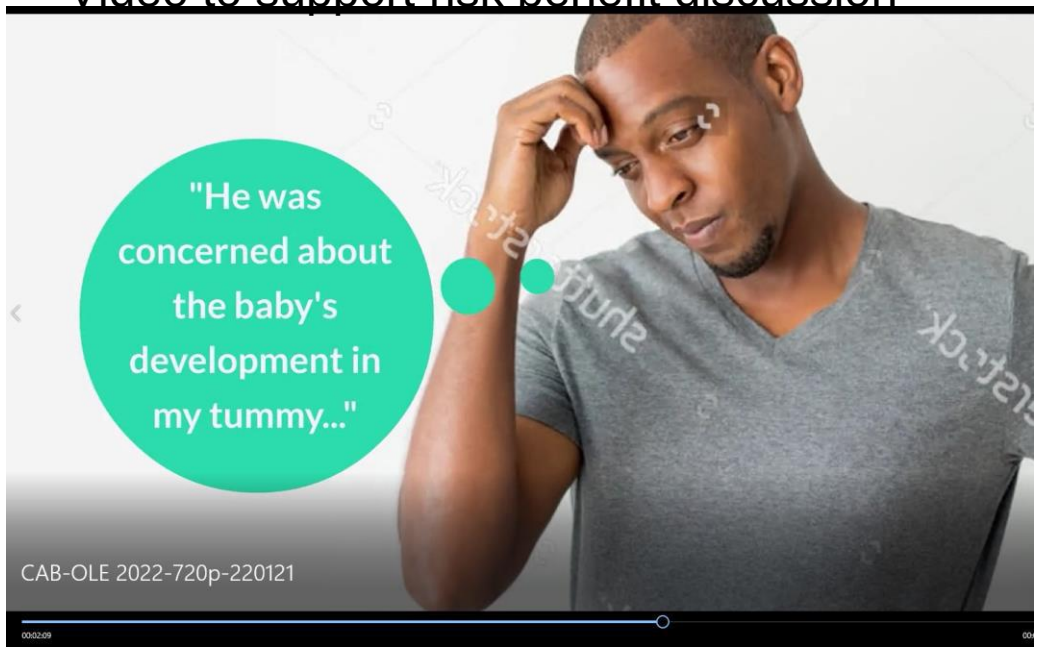
N=101 participants, mainly community stakeholders

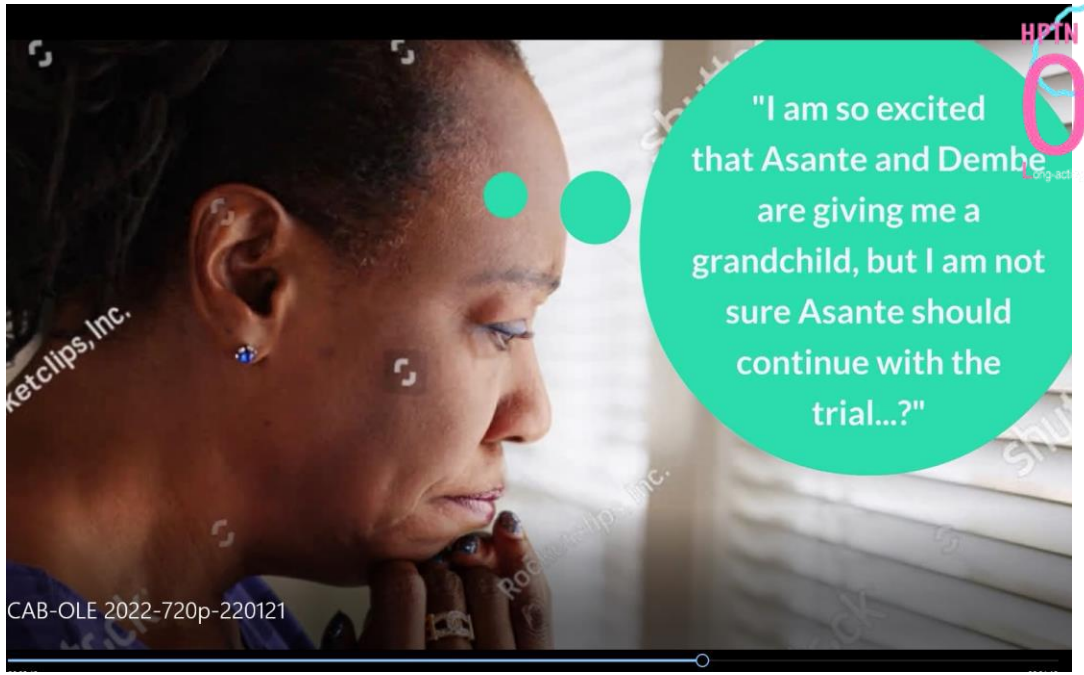
Emphasized safety concerns and need for information +++

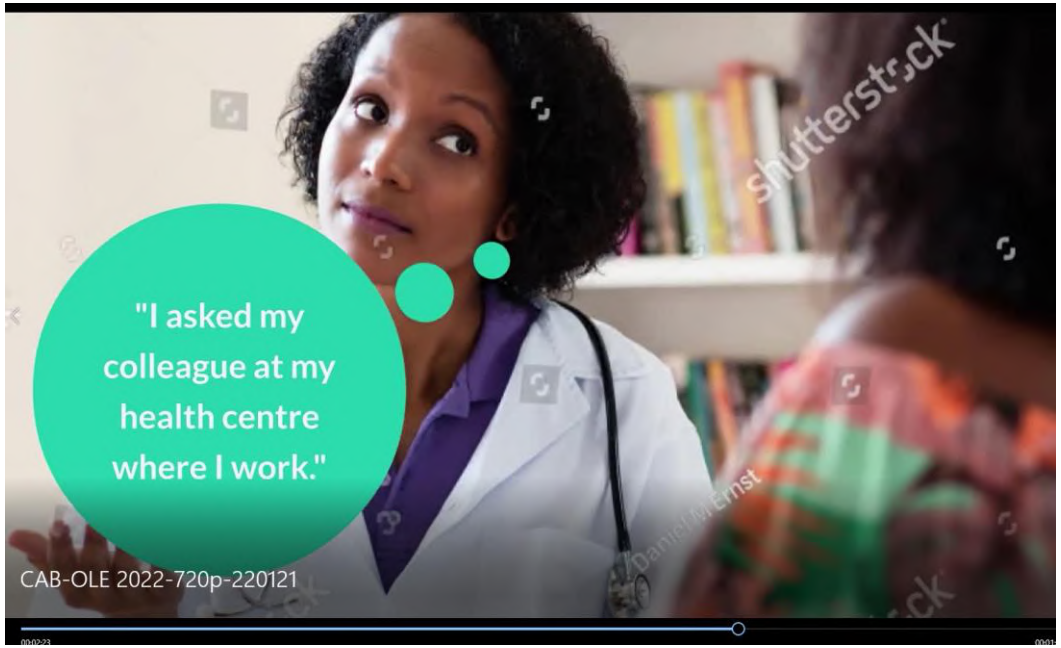
Pregnant women part of social network with many stakeholders in a safe pregnancy outcome

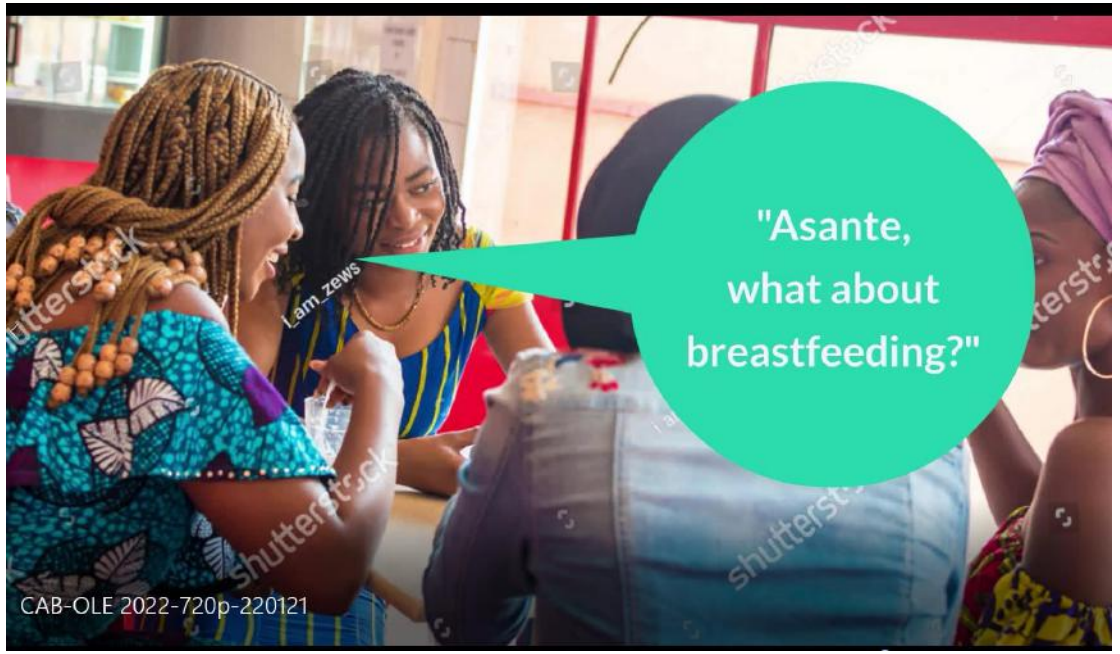
White, JIAS in press

Video to support risk benefit discussion









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Acknowledgments

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- National Institutes of Mental Health

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- 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!

UM1AI068619-17 (HPTN Leadership and Operations Center), UM1AI068617-17 (HPTN Statistical and Data Management Center), and UM1AI068613-17 (HPTN Laboratory Center).