THE CHOICE AGENDA

More than Vessels: Pregnant People Deserve Inclusion in HIV Prevention Clinical and Implementation Research

December 14, 2022

14.12.22

More than Vessels: Pregnant People Deserve Inclusion in HIV Prevention Clinical and Implementation Research

Speakers:
Dr. Elaine Abrams
Raniyah Copeland
Dr. Lynda Stranix-Chibanda
Dr. Lisa Noguchi

Moderator:
Dr. Dvora Joseph Davey

THE CHOICE AGENDA

More Than Vessels: Pregnant People Deserve Inclusion in HIV Prevention Clinical and Implementation Research

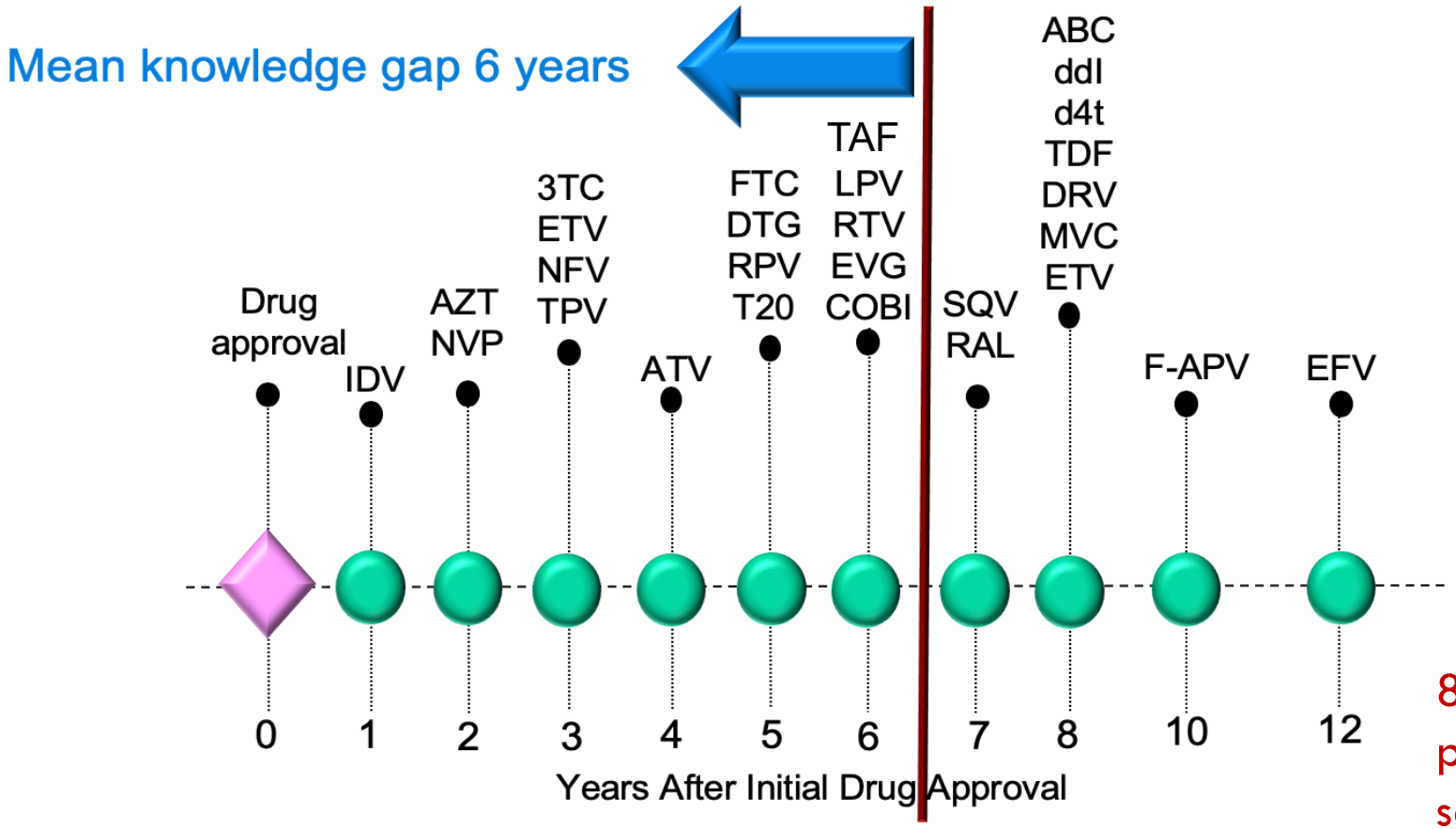
Elaine Abrams, MD
ICAP at Columbia University

Setting the scene on research and development related to HIV medicines for pregnant and breastfeeding women

Addressing the specific needs of a large proportion of people in need of ARVs

- **In 2021, there were an estimated 20.7 million women living with HIV , 1.3 million births to women living with HIV and 730,000 women over 15 years old newly acquired HIV infection in 2021.**
  - Women face substantial risk of HIV infection during pregnancy and breastfeeding in high burden countries with some studies suggesting relative increased risk of acquiring HIV infection during these periods.
  - Acute maternal infection during pregnancy and breastfeeding is associated with very high risk of HIV transmission to the baby.
- With expansion of 'treat all' and rollout of PrEP, **increasing numbers of women are conceiving while already on antiretrovirals** (ARVs).
- **Physiologic changes of pregnancy can affect drug absorption, distribution, biotransformation, and elimination**.
- **ARVs in pregnancy can be associated with adverse birth outcomes and/or toxicities particular to pregnant women and their babies**.
- Pregnant women are routinely **excluded from pre-licensure trials** and women of reproductive age must use contraception to participate in studies and if they become pregnant **study drug is stopped**

On average, 6-year delay from FDA drug approval to first published pharmacokinetics (PK) data in pregnancy, HIV drugs



Limited Data
Bictegravir
Cabotegravir
No published data
Doravirine
Ibalizumab
Lenacapavir

80% of women take a drug in pregnancy with minimal safety/efficacy data

Adapted from Colbers A et al. CID 2019

Pregnant women are excluded from pre-licensure drug trials resulting in delayed study of ARVs in pregnancy

Historical approach aims primarily to **protect the fetus/infant** from harm

Many <u>disincentives</u> for industry, funders & researchers to include pregnant / breastfeeding women in trials

Full nonclinical developmental and reproductive toxicology (DART) data often not available until **late** in drug development

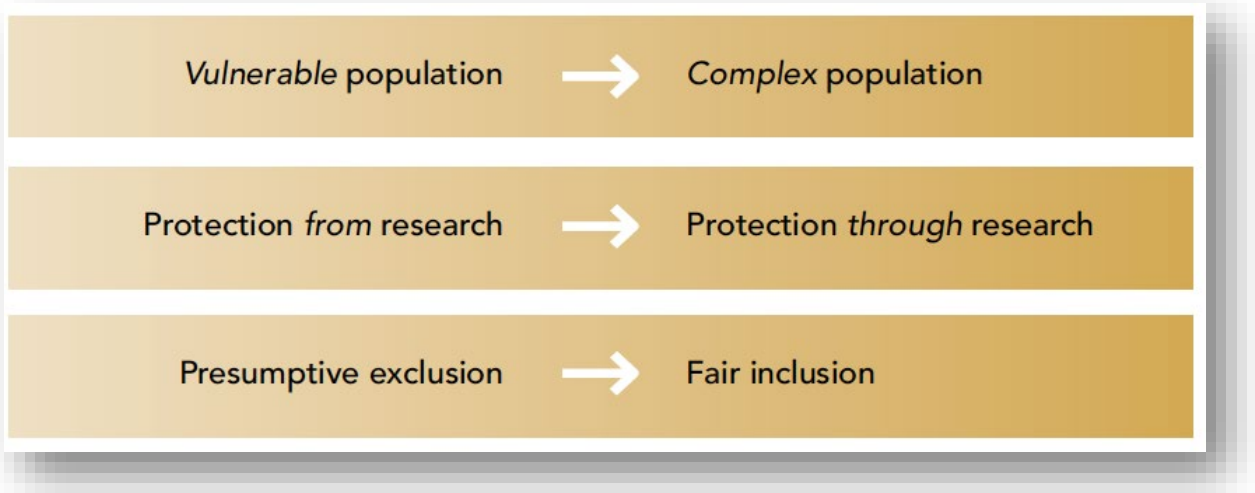
Most current pregnancy/lactation data arise from **post-marketing opportunistic studies** of women receiving antiretrovirals for clinical care

Minimal systematic **post-marketing surveillance** or observational studies that evaluate pregnancy and other outcomes following drug licensure and widespread use

A paradigm shift is underway

Over the past five years, multiple stakeholders have voiced their concerns around the exclusion of pregnant women from pre- and post-licensure drug trials and the associated harms and risks of these policies.

- The Pregnancy + HIV/AIDS Seeking Equitable Study (PHASES) identified three major conceptual shifts that will facilitate the inclusion of pregnant women in research:

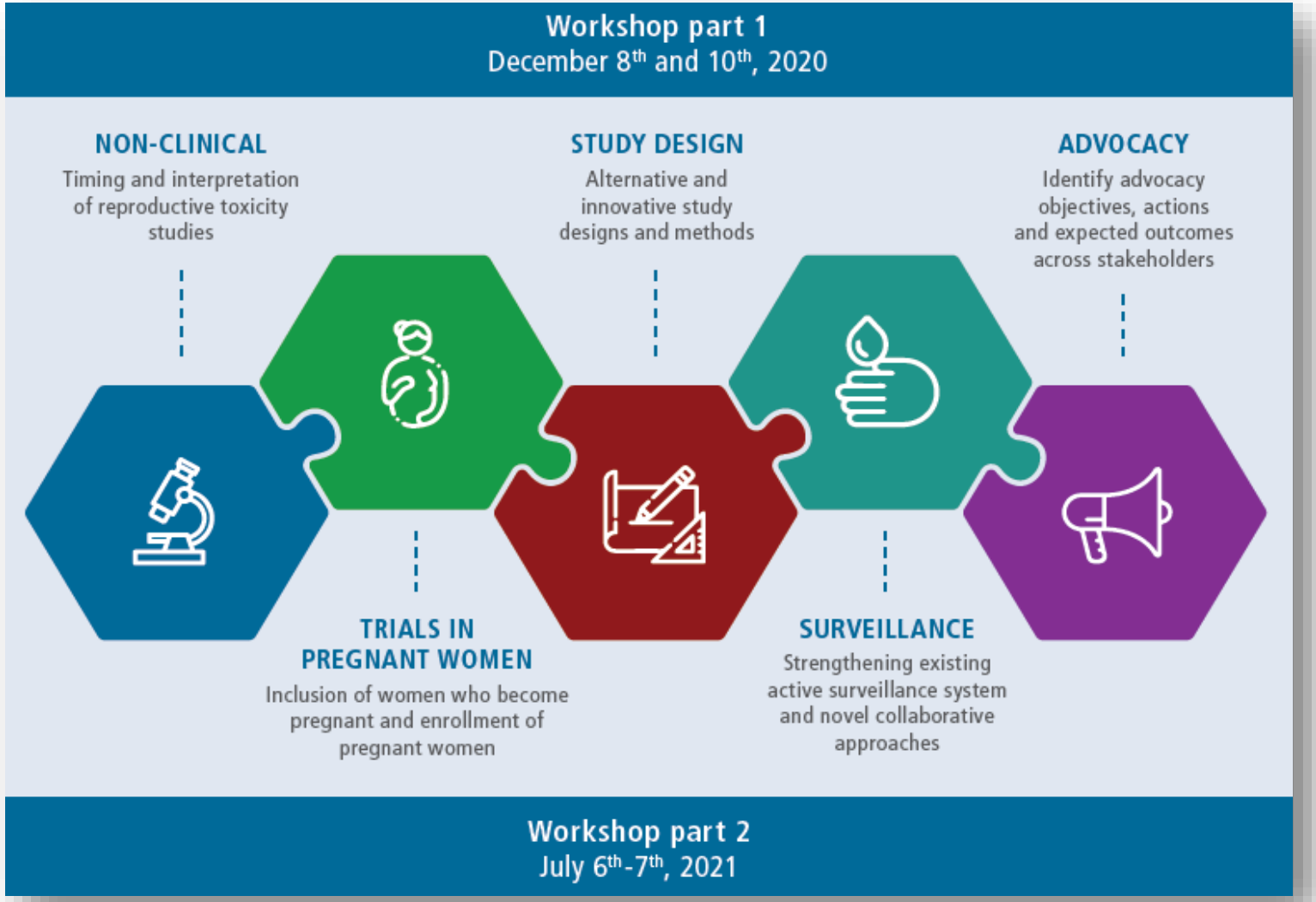


- *PHASES + AVAC have extended this work to advance HIV prevention research in pregnant and lactating populations: Think Tank Report and Action Plan*

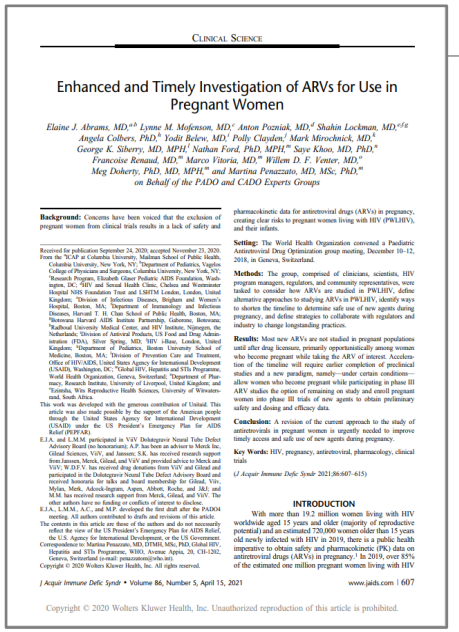
WHO & IMPAACT
Dec 2020 - July 2021

"Approaches to Enhance and Accelerate Study of New Drugs for HIV and Associated Infections in Pregnant Women"

Academic researchers, regulators, clinical experts, industry leaders, funders, civil society, ethicists, other key stakeholders



Charting a path to move from theory to action


CLINICAL SCIENCE

Enhanced and Timely Investigation of ARVs for Use in Pregnant Women

Elaine J. Abrams, MD,[a,b] Lynne M. Mofenson, MD,[c] Anton Pozniak, MD,[d] Shahin Lockman, MD,[e,f,g] Angela Colbers, PhD,[h] Yodit Belew, MD,[i] Polly Clayden,[j] Mark Mirochnick, MD,[k] George K. Siberry, MD, MPH,[l] Nathan Ford, PhD, MPH,[m] Saye Khoo, MD, PhD,[n] Francoise Renaud, MD,[m] Marco Vitoria, MD,[m] Willem D. F. Venter, MD,[o] Meg Doherty, PhD, MD, MPH,[m] and Martina Penazzato, MD, MSc, PhD,[m] on Behalf of the PADO and CADO Experts Groups

Background: Concerns have been voiced that the exclusion of pregnant women from clinical trials results in a lack of safety and pharmacokinetic data for antiretroviral drugs (ARVs) in pregnancy, creating clear risks to pregnant women living with HIV (PWLHIV), and their infants.

Setting: The World Health Organization convened a Paediatric Antiretroviral Drug Optimization group meeting, December 10–12, 2018, in Geneva, Switzerland.

Methods: The group, comprised of clinicians, scientists, HIV program managers, regulators, and community representatives, were tasked to consider how ARVs are studied in PWLHIV, define alternative approaches to studying ARVs in PWLHIV, identify ways to shorten the timeline to determine safe use of new agents during pregnancy, and define strategies to collaborate with regulators and industry to change longstanding practices.

Results: Most new ARVs are not studied in pregnant populations until after drug licensure, primarily opportunistically among women who become pregnant while taking the ARV of interest. Acceleration of the timeline will require earlier completion of preclinical studies and a new paradigm, namely—under certain conditions—allow women who become pregnant while participating in phase III ARV studies the option of remaining on study and enroll pregnant women into phase III trials of new agents to obtain preliminary safety and dosing and efficacy data.

Conclusion: A revision of the current approach to the study of antiretrovirals in pregnant women is urgently needed to improve timely access and safe use of new agents during pregnancy.

Key Words: HIV, pregnancy, antiretroviral, pharmacology, clinical trials

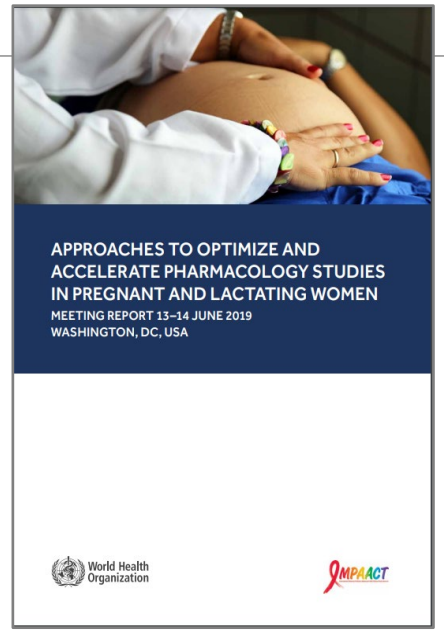
(*J Acquir Immune Defic Syndr* 2021;86:607–615)

INTRODUCTION

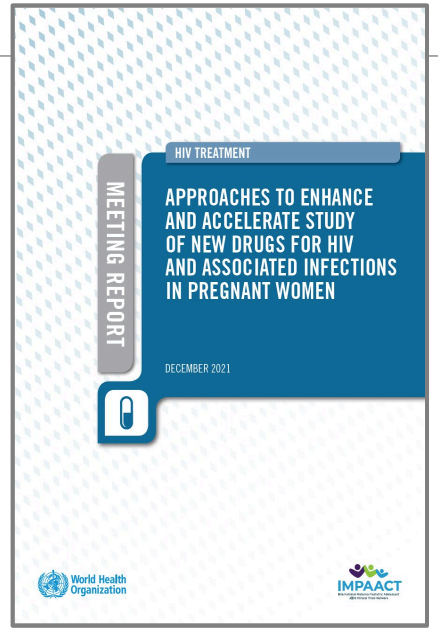
With more than 19.2 million women living with HIV worldwide aged 15 years and older (majority of reproductive potential) and an estimated 720,000 women older than 15 years old newly infected with HIV in 2019, there is a public health imperative to obtain safety and pharmacokinetic (PK) data on antiretroviral drugs (ARVs) in pregnancy.[1] In 2019, over 85% of the estimated one million pregnant women living with HIV

J Acquir Immune Defic Syndr • Volume 86, Number 5, April 15, 2021 www.jaids.com | 607

https://pubmed.ncbi.nlm.nih.gov/33298793/



https://apps.who.int/iris/handle/10665/330454



https://www.who.int/publications/i/item/9789240040182

call-to-action-to-accelerate-study-of-new-arv-for-pregnant-breastfeeding-women.pdf (who.int)

https://onlinelibrary.wiley.com/toc/17582652/2022/25/S2

Studying new antiretrovirals in pregnancy: Key principles

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.**

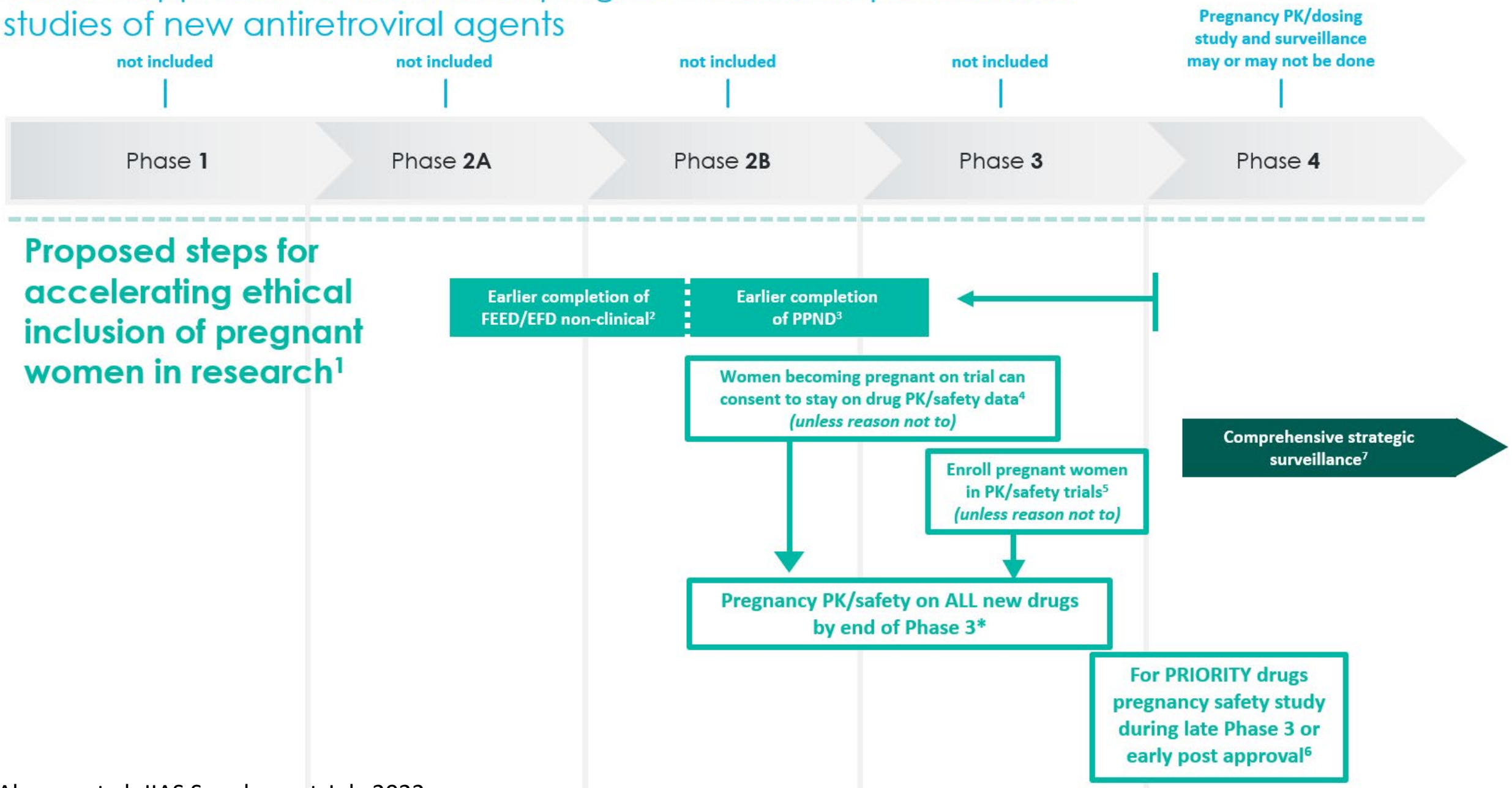
All new agents must be studied in pregnant woman for **pharmacokinetics/optimal dosing and short-term safety.**

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 post marketing surveillance/registries/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.

Current approach to inclusion of pregnant women in pre-licensure studies of new antiretroviral agents



Abrams et al. JIAS Supplement-July 2022

Framework to accelerate the study of new drugs for HIV in pregnancy: Key Principles

1. **Perform non-clinical developmental and reproductive toxicology (DART) studies earlier** during drug development for all new HIV agents
   - Fertility, early embryonic, and embryo-fetal development (FEED /EFD) studies completed during or no later than the end of Phase 2
   - Prenatal and postnatal development (PPND) studies completed during early or no later than the end of Phase 3
2. Women who become pregnant in pre-licensure trials **can consent to stay on** study drug
   - Once non-clinical FEED and EFD studies are completed with no negative signals and dosing is established in non-pregnant adults
   - To contribute pregnancy PK and safety data
3. Enroll pregnant women in specific studies to determine pregnancy PK and preliminary safety
   - **As soon as non-clinical PPND studies are completed** with no negative signals
   - For all new HIV agents.
4. Conduct **dedicated pregnancy safety studies** for all new HIV agents prioritized through WHO drug optimization work
   - as soon as dosing in pregnancy is confirmed
5. **Expand active surveillance** of drug safety in pregnancy
   - to enable systematic and rapid detection of adverse maternal, pregnancy and birth outcomes, especially rare events, such as birth defects.
6. **Involve women of childbearing age affected by HIV during all the steps of research study**

Now, more than ever we must take action together to transform the current paradigm and ensure that no women and mothers are left behind.

We must fast-forward to a future when women of reproductive age will no longer shoulder the burden of having fewer options to stay HIV-free or remain healthy and break the chain of HIV transmission.

We have an opportunity here and let's not miss it…

call-to-action-to-accelerate-study-of-new-arv-for-pregnant-breastfeeding-women.pdf (who.int)

MORE THAN VESSELS: PREGNANT PEOPLE DESERVE INCLUSION IN HIV PREVENTION CLINICAL AND IMPLEMENTATION RESEARCH

Raniyah M. Copeland, MPH
Founder & Principal
Equity & Impact Solutions

equity IMPACT solutions

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CENTERING EQUITY IN OUR APPROACH TO ENDING HIV

- New biomedical tools make ending HIV a theoretical possibility
- HIV offers a case study in challenges and opportunities of ending an epidemic
- Inclusive and equity-based research supports uptake of new tools for *all*

DEFINING EQUITY

HIV RESEARCH AND PREGNANT PEOPLE

- Research has a long history of explicitly and implicitly disregarding cis women and pregnant people
- Recent mobilization and advocacy has pointed towards new models to end the evidence gap for pregnant people
- But prioritization and resourcing continues to fall short of what's needed for immediate and wide-spread implementation of equitable practices and recommendations

Ending the evidence gap for pregnancy, HIV and co-infections: ethics guidance from the PHASES project

Building Capacity 	1. **Affirm the need for research with pregnant people:** Organizations with influence over the development, research, regulatory approval, guidance development, and use of HIV/co-infections drugs should affirm the imperative for responsible research with pregnant people to achieve a timely and equitable evidence base. 2. **Formulate a global network for advocacy and resources:** The global HIV/co-infections research and advocacy communities, supported by funders, should formalize a network dedicated to advancing needed research with pregnant people. This network should facilitate research with pregnant people by creating a portfolio of shared resources to empower researchers to pursue, and enable oversight committees to effectively evaluate, studies that meet the needs of people who are pregnant. 3. **Enhance training:** Those involved in the conduct, monitoring, oversight, and community consultation of research in the HIV/co-infections space should be provided training in the ethical and legal issues relevant to research with pregnant people.
Supporting inclusion 	4. **Design for inclusion:** Researchers designing trials in HIV/co-infections should commit to a goal of integrating pregnant people wherever possible and optimizing opportunities to gather pregnancy-specific data. 5. **Review for and facilitate inclusion:** Regulatory review sections, research ethics committees, and funders of HIV/co-infections research should require proposed clinical trials protocols to provide justification whenever pregnancy is indicated as a criterion for exclusion or removal from a trial, and should proactively support and incentivize inclusive designs. 6. **Ensure equitable research on pregnant persons' own health:** Agenda setters in HIV/co-infections research should commit to equitably promoting the study of pregnant persons' own health needs as a key pillar of effort and funding. Research into fetal safety outcomes should be matched by relevant maternal outcomes assessments to ensure that decisions about whether and which options to pursue during pregnancy are made with equitable consideration of the pregnant person's health.
Achieving priority research 	7. **Integrate pharmacokinetic (PK) studies:** Plans for pregnancy-specific PK pharmacokinetic studies should be integrated into new drug development plans and performed as early as possible, ideally before licensure, for all new preventives and treatments anticipated to be used during pregnancy. 8. **Enhance post-approval safety evaluations:** The HIV/co-infections research community should commit to a more robust and regularized structure of post-approval safety evaluations to ensure both adequate pharmacovigilance and pregnant people's timely access to important drugs. This includes expanding prospective registries, conducting timely prospective observational studies for drugs in widespread use during pregnancy, and conducting prospective cohort studies of unintended exposures to probe safety signals that stand in the way of pregnant people accessing important drugs. 9. **Address legacy evidence gaps:** Currently approved HIV/co-infections preventives and treatments should be reviewed for critical pregnancy-related evidence gaps that interfere with safe, evidence-based use in pregnancy, and research should be conducted to address those gaps.
Ensuring respect 	10. **Ensure access to life-saving experimental drugs:** Pregnant people should be guaranteed fair access to participate in trials and special access programs for experimental interventions that offer potential life-saving benefit in contexts where no or poor alternatives exist. 11. **Respect and support decisional authority:** When a pregnant person of legal standing is eligible to participate in research, their voluntary and informed consent should be sufficient to authorize participation. Accommodations should be made to facilitate a pregnant person's ability to engage the father, family, or other personal supports, and to promote understanding of the benefits and risks of research participation. 12. **Contextualize risk findings:** Those conducting HIV/co-infections research with pregnant people should anticipate possible adverse events and proactively develop communication strategies for adequately contextualizing them against baseline rates of such events. Communication of overall findings should take care to contextualize potential risks of an intervention against its potential benefits and the risk/benefit profiles of alternatives, and should include benefits to the pregnant person and those that would accrue secondarily to the child should the pregnant person's health be benefited.

*Updated toward gender-inclusive language.

Journal of the International AIDS Society, Volume: 24, Issue: 12, First published: 15 December 2021, DOI: (10.1002/jia2.25846)

ALIGNING VALUES WITH ACTION

- How we empower women and pregnancy gives insight into how well we are achieving equity as a society

- Show us we're important with your resources and prioritization

THE CHOICE AGENDA

HIV prevention research – a new forum for advocacy on the latest

HIV Prevention Clinical Research and Pregnant and Lactating People

More Than Vessels: Pregnant People Deserve Inclusion in HIV Prevention Clinical and Implementation Research

Dr Lynda Stranix-Chibanda

Date: December 14, 2022

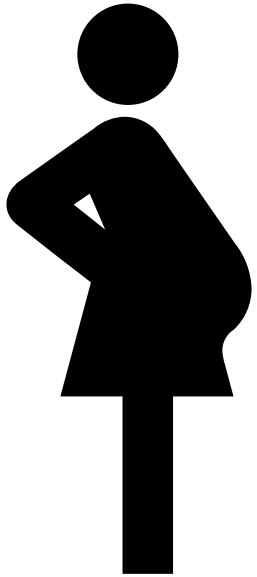
University of Zimbabwe - Clinical Trials Research Centre

Saving Lives Through Innovative Research Strategies

UNIVERSITY OF ZIMBABWE

Faculty of Medicine and Health Sciences

Advancing HIV prevention research in PLP



- Oral TDF/XTC
- DPV ring
- CAB LA injection
- LEN injection

Oral TDF/XTC data from **treatment** in PLP

- Benefits of **ART** far outweigh any risk to PLP/child
- PLP at higher risk of acquiring HIV
  - Higher chance of vertical transmission (acute infection → high viral load)
  - <30% infants with HIV in SSA born to people who tested negative in ANC (UNAIDS 2021)
- Offer PrEP to PLP at risk of HIV and continue to document
  - Safety: pregnancy outcomes, bone and renal health, infant growth and development
  - PK: drug levels 1/3 lower in pregnancy


AIDS

Articles & Issues ▾ For Authors ▾ Journal Info ▾

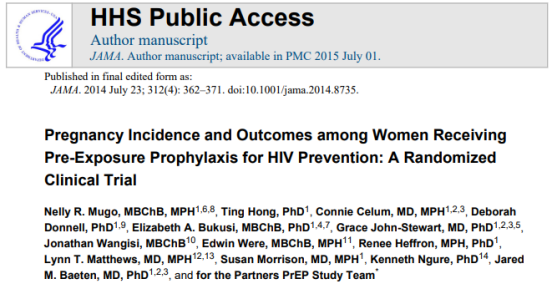
CLINICAL SCIENCE

Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding

Mofenson, Lynne M.; Baggaley, Rachel C.; Mameletzis, Ioannis

Author information

AIDS: January 14, 2017 - Volume 31 - Issue 2 - p 215-232


HHS Public Access

Author manuscript

JAMA. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:

JAMA. 2014 July 23; 312(4): 362–371. doi:10.1001/jama.2014.8735.

Pregnancy Incidence and Outcomes among Women Receiving Pre-Exposure Prophylaxis for HIV Prevention: A Randomized Clinical Trial

Nelly R. Mugo, MBChB, MPH[1,6,8], Ting Hong, PhD[1], Connie Celum, MD, MPH[1,2,3], Deborah Donnell, PhD[1,9], Elizabeth A. Bukusi, MBChB, PhD[1,4,7], Grace John-Stewart, MD, PhD[1,2,3,5], Jonathan Wangisi, MBChB[10], Edwin Were, MBChB, MPH[11], Renee Heffron, MPH, PhD[1], Lynn T. Matthews, MD, MPH[12,13], Susan Morrison, MD, MPH[1], Kenneth Ngure, PhD[14], Jared M. Baeten, MD, PhD[1,2,3], and for the Partners PrEP Study Team*

Mugo; *JAMA* 2014


JAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY Open Access

Review | Open Access |

Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading?

Dvora L Joseph Davey, Jillian Pintye, Jared M Baeten, Grace Aldrovandi, Rachel Baggaley, Linda-Gail Bekker, Connie Celum, Benjamin H Chi, Thomas J Coates ... See all authors

First published: 08 January 2020 | https://doi.org/10.1002/jia2.25426 | Citations: 27

Joseph Davey; *JIAS* 2020


THE LANCET HIV

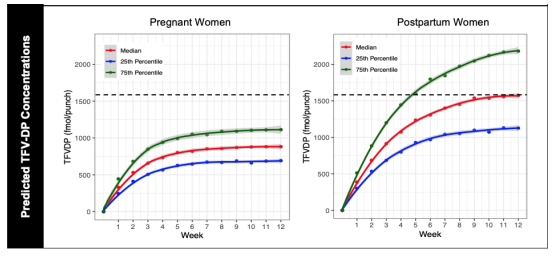
Volume 9, Issue 3, March 2022, Pages e214-e222

Viewpoint

Where are the pregnant and breastfeeding women in new pre-exposure prophylaxis trials? The imperative to overcome the evidence gap

Dvora L Joseph Davey PhD, Prof Linda-Gail Bekker PhD, Prof Elizabeth A Bukusi PhD, Prof Benjamin H Chi MD, Prof Sinead Delany-Moretlwe PhD, Prof Ameena Goga PhD, Prof Anne Drapkin Lyerly MD, Prof Nyaradzo M Mgodi PhD, Prof Nelly Mugo MBChB, Prof Landon Myer PhD, Lisa M Noguchi PhD, Lynda Stranix-Chibanda MD, Catherine Slack PhD, Jillian Pintye PhD

Joseph Davey; *The Lancet HIV* 2022



IMPAACT 2009; Stranix-Chibanda *CID 2021*

DPV ring studies underway in PLP

- Opportunistic data from ~250 new pregnancies during phase 3 and OLE trials
  - Stopped using DPV ring as soon as pregnancy was identified
  - Found to be safe during conception and early pregnancy
- Dedicated trial for pregnant people, enrolled in phases throughout pregnancy and lactation
  - Started with latest stages of pregnancy,
  - Then earlier and earlier stages,
  - DSMB safety review between phases

Published in final edited form as:
J Acquir Immune Defic Syndr. 2018 December 15; 79(5): 566–572. doi:10.1097/QAI.0000000000001861.

Pregnancy and infant outcomes among women using the dapivirine vaginal ring in early pregnancy

Bonus Makanani[#1], **Jennifer E. Balkus**[#2,3,4], **Yuqing Jiao**[4], **Lisa M. Noguchi**[5], **Thesla Palanee-Phillips**[6], **Yamikani Mbilizi**[1], **Jothi Moodley**[7], **Kenneth Kintu**[8], **Krishnaveni Reddy**[6], **Samuel Kabwigu**[8], **Nitesha Jeenariain**[7], **Ishana Harkoo**[9], **Nyaradzo Mgodi**[10], **Jeanna Piper**[11], **Helen Rees**[6], **Rachel Scheckter**[12], **Richard Beigi**[13], and **Jared M. Baeten**[2,3,14]

NEWS RELEASES

Monday, February 10, 2020

NIH-Funded Clinical Trial to Test PrEP, Dapivirine Ring for Safety in Pregnant Women

Study Also to Examine Whether Pregnant Women Accept, Use These HIV Prevention Tools.

https://www.thebodypro.com/article/study-test-safety-prep-dapivirine-ring-pregnancy

CAB LA data from treatment in PLP

- Small number of pregnancy outcomes in women exposed to CAB at conception ~n=25
  - CAB tail phase kinetics within similar range to non-pregnant women

HIV MEDICINE | BHIVA British HIV Association

ORIGINAL ARTICLE | Open Access

Pregnancy outcomes and pharmacokinetics in pregnant women living with HIV exposed to long-acting cabotegravir and rilpivirine in clinical trials

Parul Patel, Susan L. Ford, Mark Baker, Claudia Meyer, Louise Garside, Ronald D'Amico, Rodica Van Solingen-Ristea, Herta Crauwels, Joseph W. Polli, Ciara Seal ... See all authors

First published: 21 November 2022 | https://doi.org/10.1111/hiv.13439

- Ongoing monitoring in Antiretroviral Pregnancy Registry

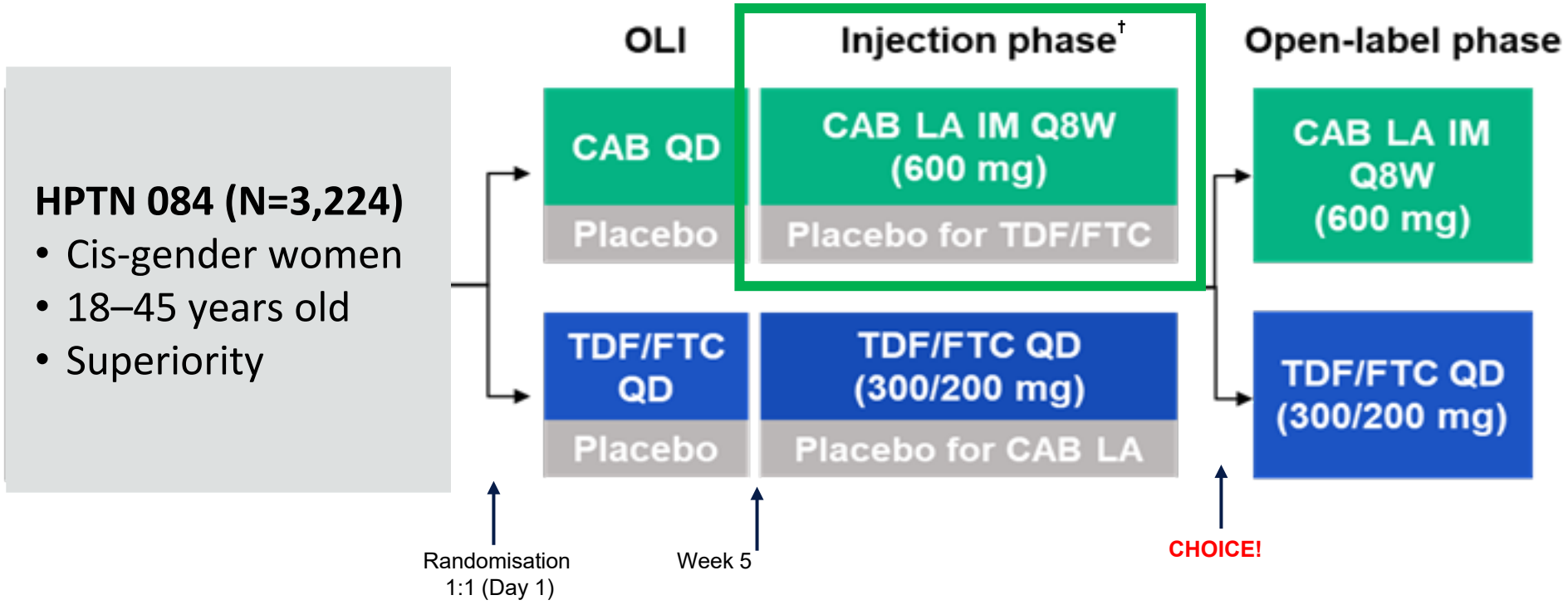
THE ANTIRETROVIRAL PREGNANCY REGISTRY
INTERIM REPORT
1 JANUARY 1989 THROUGH 31 JANUARY 2022

http://www.apregistry.com/

CAB LA data from PrEP in PLP

Opportunistic data from 63 new pregnancies exposed to **CAB LA at conception** in HPTN 084

- Stopped injections as soon as pregnancy was detected and switched to oral TDF/FTC PrEP



https://www.084life.org/

Delany-Moretlwe, IAS 2022

Evaluation of CAB-LA Safety and PK in Pregnant Women in the Blinded Phase of HPTN 084

00700

Author **Sinead Delany-Moretlwe**[1], James P. Hughes[2], Xu Guo[3], Brett Hanscom[3], Craig W. Hendrix[4], Jennifer Farrior[5], Ribka Berhanu[1], Alex Rinehart[6], Susan Ford[6], James Rooney[7], Adeola Adeyeye[8], Raphael Landovitz[9], Myron Cohen[10], Mina C. Hosseinipour[10],Mark A. Marzinke[4] on behalf of HPTN 084 study group Institutions 1 Wits RHI, University of the Witwatersrand Johannesburg, South Africa, 2 University of Washington, Seattle, WA, United States, 3 Fred Hutchinson Cancer Research Center, Seattle, WA, United States, 4 The Johns Hopkins University School of Medicine, Baltimore, MD, United States, 5 FHI 360, Durham, NC, United States, 6 ViiV Healthcare, Research Triangle Park, NC, United States, 7 Gilead Sciences, Inc, Foster City, CA, United States, 8 National Institute of Allergy and Infectious Diseases, Bethesda, MD, United States, 9 University of California Los Angeles, Los Angeles, CA, United States, 10 University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Delany-Moretlwe, IAS 2022

Similar pregnancy outcomes from CAB LA vs TDF/FTC

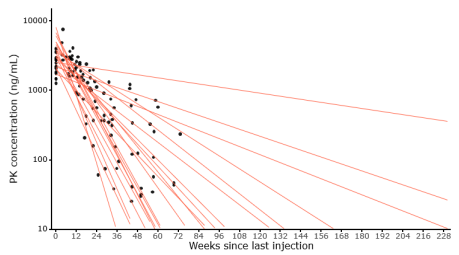
	Total n=132	CAB n=63	TDF/ FTC n=69
Ongoing	57	23	34
Known pregnancy outcomes*			
Live births	61	31	30
Pregnancy loss			
>=37 weeks	0	0	0
20-36 weeks	3	1	2
<20 weeks**	13	9	4
Congenital anomalies	0	0	0

**includes multiple births*
***includes ectopic pregnancy, elective and spontaneous abortion*

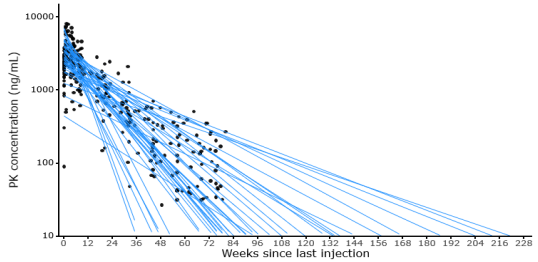
CAB LA generally well tolerated in pregnancy

	CAB		TDF/FTC		
	Events/py (n=39 py)	Incidence (95% CI)	Events/py (n=29 py)	Incidence (95% CI) (per 100 py)	P-value
Any Grade 2+ AE	44	113	49	166	0.06

CAB LA drug concentrations similar in pregnant vs non-pregnant state



HPTN 084: Pregnant Cases (n=18)

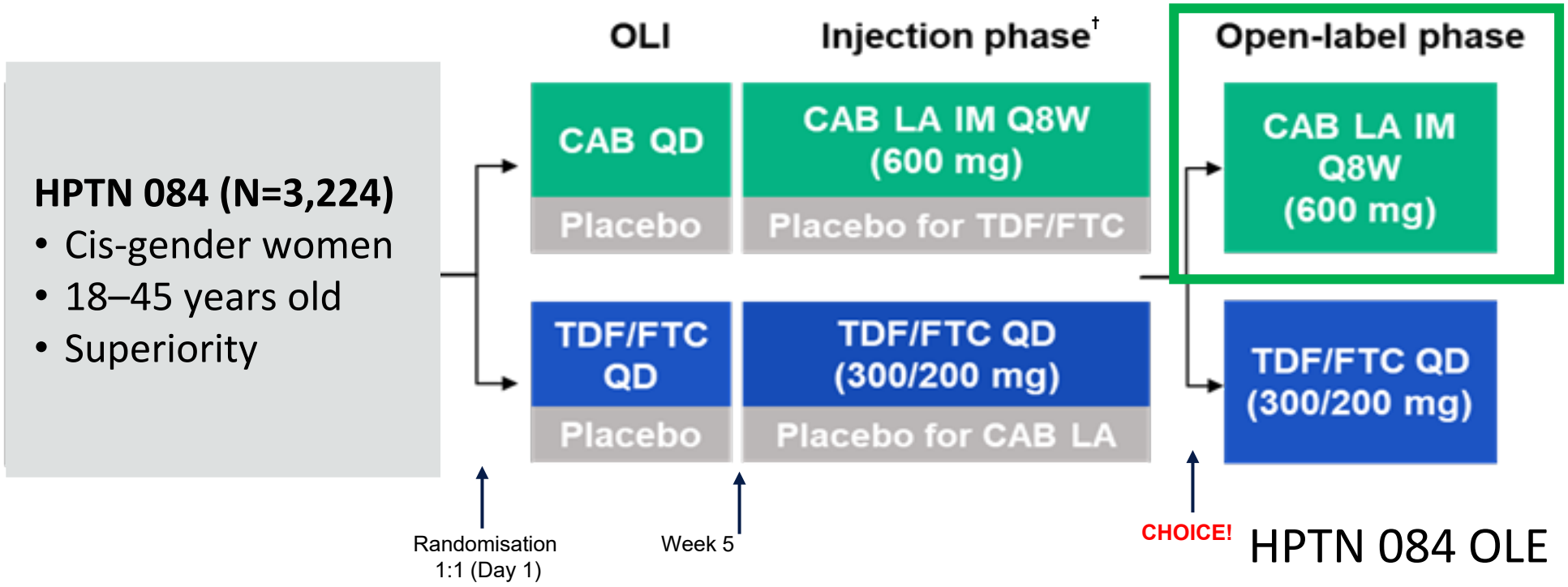


HPTN 077: Non-Pregnant Cases (n=39)

CAB LA data from PrEP in PLP

Opportunistic data from new pregnancies exposed to **CAB LA throughout** pregnancy and lactation in HPTN 084 OLE

- No contraception requirement
- Can consent to stay on CAB LA in pregnancy
- Sub-study to observe safety and PK PLP/infants



HPTN 084 OLE
Data available 2023-24

https://www.084life.org/

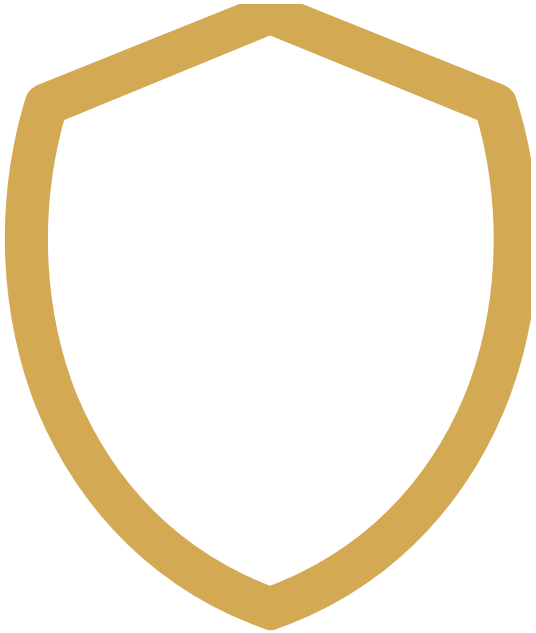
LENACAPAVIR (LEN)

- Lenacapavir: LA injectable administered every 6 months
  - Pursuing simultaneous treatment and prevention studies
- PURPOSE 1 (underway, results due >2024)
- PURPOSE 3 (planned)
- Young women in USA and SA
- Compared to daily oral FTC/TDF or FTC/TAF
- May re-consent to continue during pregnancy
  - Opportunistic PK/safety data collected

NCT04994509; www.avac.org/trial/purpose-1.

https://www.avac.org/trial/purpose-3-hptn-102

Equitable **protection** from drug-related risks



- Mission of research – gather evidence to decrease risks in clinical settings
- Pregnant persons and offspring need and deserve such protection
- Exclusion from research doesn't eliminate risks – it exports them to the clinical setting, where they **expand**

Equitable **access** to medications

- Pregnant people deserve timely access to new medications
- Lack of data leads to reticence to prescribe or take medicines; cautions against use in public health guidance
- Leaves pregnant people and offspring exposed to risks of disease

Equitable **respect** for pregnant people's health

- Tendency for fetal or child outcomes overshadow attention to maternal outcomes
- Decisions about research (and treatment) should reflect due consideration for the pregnant person's health
- Failure to do so treats them as a "vessel or vector" rather than a person in their own right

PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY

THE CHOICE AGENDA

HIV prevention research – a new forum for advocacy on the latest

Momentum is building for advancing HIV prevention research in PLP, but many gaps remain

More Than Vessels: Pregnant People Deserve Inclusion in HIV Prevention Clinical and Implementation Research

Dr Lynda Stranix-Chibanda

lstranix@uz-ctrc.org

UZ-CTRC

University of Zimbabwe - Clinical Trials Research Centre

Saving Lives Through Innovative Research Strategies

UNIVERSITY OF ZIMBABWE

Faculty of Medicine and Health Sciences

Thank you

HIV prevention implementation research and the ethical inclusion of pregnant and lactating people: the CATALYST study

Catalyzing access to new prevention products to stop HIV

LISA NOGUCHI, PHD, CNM, FACNM
JHPIEGO
DECEMBER 14, 2022

PEPFAR

USAID
FROM THE AMERICAN PEOPLE

MOSAIC
Maximizing Options to Advance Informed Choice for HIV Prevention

Overview

- Review why ethical inclusion of pregnant and lactating people is important in implementation research
- Discuss common challenges
- Briefly outline the CATALYST approach

For CATALYST, the term "women" is inclusive of individuals assigned female at birth of any gender identity and trans women.

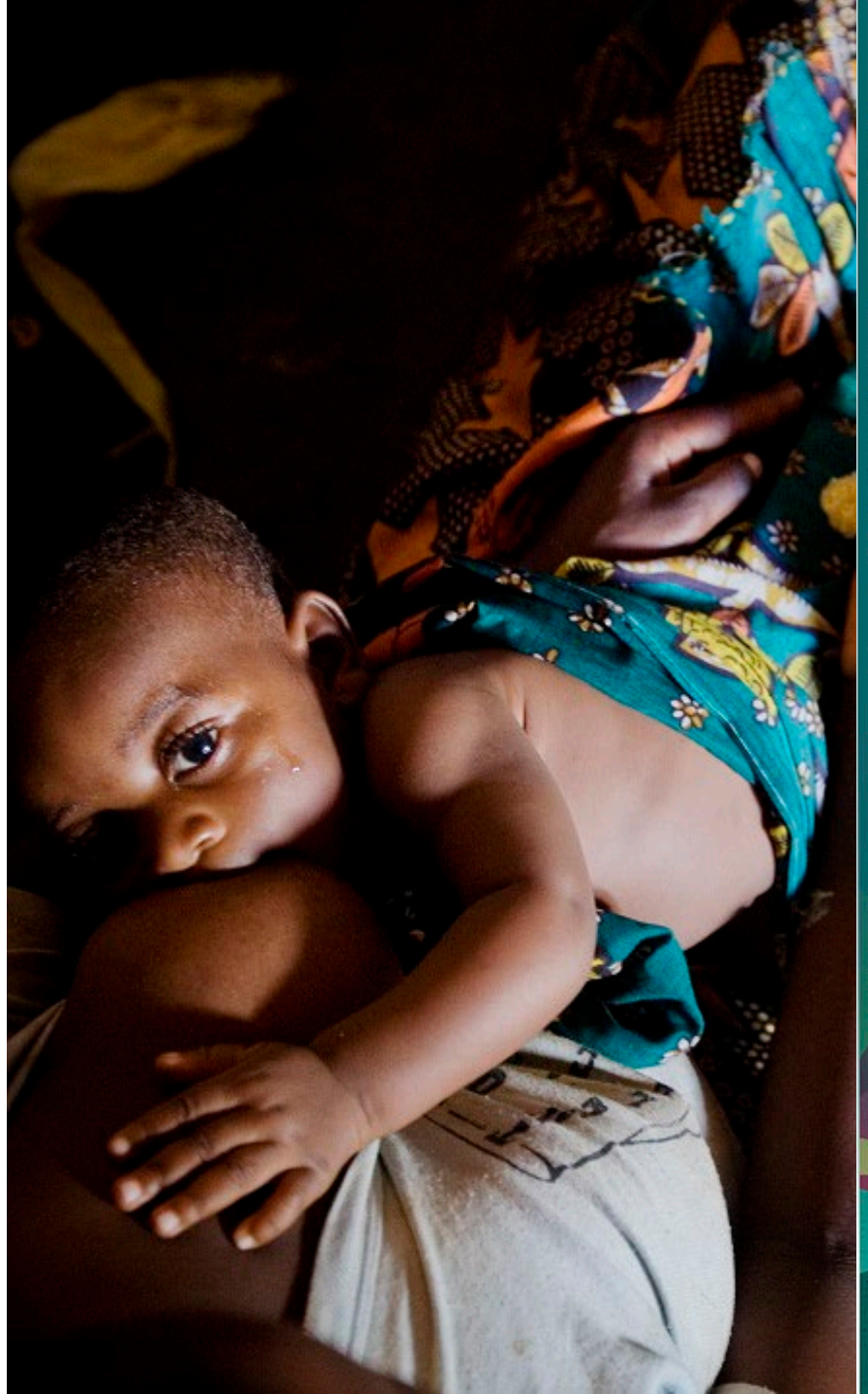
How do we take proven interventions to the "real world"?

- We learn fantastic things in clinical research, such as proving that certain interventions to prevent HIV are efficacious
- How might those efficacious interventions work outside of research in different contexts?
- The "real world" is messy!
- Implementation research is embedded in reality
  - Helps to clarify contextual factors – and how to deliver interventions in diverse settings
- More/better implementation research could help people access benefits of proven interventions faster!

Just because a recipe is successful on TV doesn't mean that you or I will be successful to cook it in our own homes!

Ethical inclusion of pregnant and breastfeeding people

- In real contexts, pregnancy and breastfeeding are more common than in clinical trials
- We KNOW the chance of acquiring HIV is higher during pregnancy and the postnatal period vs. other times
- We KNOW pregnancies will occur during product use (no FP mandate!)
- We KNOW countries need to be able to include pregnant and postpartum people in PrEP programming – but how do we optimize approaches?



What are some of the challenges faced?

- Participants and participant management
  - Eligibility criteria much less restrictive – no “perfect participants”
  - Seen for study visits less frequently compared to clinical research
  - Tracking can be very challenging, compensated less or typically not at all for participation
- Study outcomes
  - May be defined differently in different countries
  - Not always captured in public sector health service delivery settings
- Study settings: real clinics have real challenges
  - Understaffing, labor strikes, unfair wages or no wages at all
  - Different culture of documentation compared to clinical research
  - Participants leave town and/or access healthcare in different locations

What's an example?

- Understanding when in pregnancy someone is exposed to a particular drug is important for understanding its impact
- Determining gestational age (how far along someone is in their pregnancy) is not always straightforward
  - Date of first day of last menstrual period may be unknown
  - Access to ultrasound may be limited to none
  - Entry to antenatal care may be too late to measure or estimate gestational age with optimal precision
  - Provider skills vary in terms of calculation of gestational age, measurement of the pregnant uterus, interpretation of ultrasound, and triangulation of different results
  - Antenatal care record may be imprecise or just incomplete

Here's another example…

Favorite is 19 years old. After she was treated for syphilis, she decided to join your study. She used the dapivirine ring and then fell pregnant, as she was not using family planning. After you counsel her, she understands that the evidence so far looks like the ring is safe during pregnancy, but she opts to switch to oral PrEP. She then misses her next follow up appointment. When you try to track her down, you hear from her sister that Favorite has gone to their mother's village to have the baby. A few months later, she comes back to the study clinic for a PrEP refill and you ask about her delivery. She can't recall the name of the health center. Sadly, her baby passed inside the womb, but she is not sure if it was before or after she arrived at the health center in labor, because there wasn't a nurse available to check the baby's heartbeat.

Here's another example…

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CATALYST STUDY LEADERSHIP

Protocol Chair: Kristine Torjesen, FHI 360

Protocol Co-Chair: Elizabeth Irungu, Jhpiego Kenya

Lesotho Principal Investigator: Tafadzwa Chakare, Jhpiego Lesotho

Kenya Principal Investigator: Robinson Karuga, LVCT Health

South Africa Principal Investigator: Nicolette Naidoo, Wits RHI

Uganda Principal Investigator: Carolyne Akello, FHI 360 Uganda

Zimbabwe Principal Investigator: Emily Gwavava, PZAT

The CATALYST study is funded by PEPFAR through USAID as part of the MOSAIC project

TIMELINE

October: FHI 360 IRB submission

Coming Soon: Local IRB submissions in each CATALYST country

STUDY GOAL

The overall study goal is to characterize and assess the implementation of an enhanced service delivery package providing informed choice of PrEP products among women at PEPFAR delivery sites in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe.

Specific objectives focus on characterizing implementation; implementation facilitators and barriers; patterns of PrEP use and use effectiveness; sociodemographic and contraceptive use correlates; and clinically relevant indicators among users, including rates of HIV infection and drug resistance.

PrEP Products

All PrEP products (oral PrEP, PrEP ring, CAB PrEP) used in the study will be **post-regulatory approval**, hence the study will be conducted in two stages with currently approved **oral PrEP and PrEP ring offered in Stage I, and the addition of CAB PrEP in Stage II** only after it is approved by the regulatory authority in each country.

CATALYST will implement an enhanced service delivery package that supports product choice

Guiding principles for pregnant and breastfeeding populations (PBFP) in CATALYST

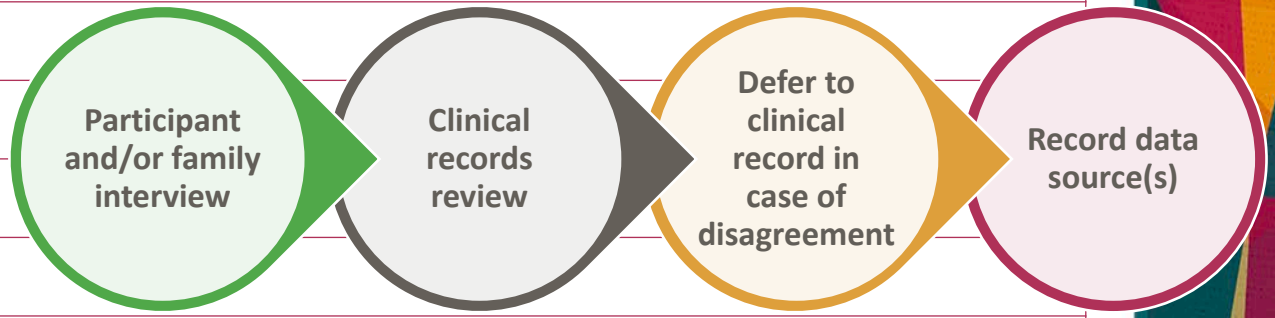
1. **Ethical inclusion of PBFP** (no specific exclusion criterion for PBFP)
   We may not see many PBFP seeking enrollment, but **they will appear** during follow-up
2. **Make the protocol safe for PBFP**, but don't design a *clinical safety study*
3. **Ensure high-quality informed consent and counseling**
4. **Adapt CATALYST procedures to emerging safety data from other studies**
   Key safety analyses for PBFP will continue in HPTN 084 OLE, MTN-042 (DELIVER), etc.
5. **Work with the local standard of care**, e.g., antenatal care settings, for clinical management (build positive, informed relationships)
6. **Collect pregnancy outcomes**, but collaborate/pool data for analysis
7. **Link to a registry**, if feasible, to follow outcomes beyond scope of CATALYST

What do participants need to understand? What goes in counseling messages for PBFP?

- Pregnancy-related counseling (result of urine test)
- Importance of ANC for those who continue pregnancy, local options for management and care of pregnancy
- Increased risk of HIV acquisition associated with pregnancy and postpartum periods
- Options for HIV prevention during pregnancy, breastfeeding
- What is known and not known about the benefits and potential risks of study product(s) for PBFP
- Any product-specific considerations for use during pregnancy, breastfeeding

What pregnancy outcomes will be included in CATALYST?

Outcome
Term live birth
Preterm birth
Stillbirth
Spontaneous abortion
Neonatal death
Congenital anomaly
Gestational age at pregnancy outcome
Sex
Weight



Protocol Safety Review Team

Reviews all SAEs and pregnancy cases and outcomes

Review occurs rapidly, prior to onward reporting to ethics committees and product developers, as relevant

ACKNOWLEDGMENTS

CATALYST PBFP Working Group

MOSAIC is made possible by the generous support of the American people through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Agency for International Development (USAID) cooperative agreement 7200AA21CA00011. The contents of this presentation are the responsibility of MOSAIC and do not necessarily reflect the views of PEPFAR, USAID, or the U.S. Government.

Photo Credit: MOSAIC Consortium

@MOSAICproj

www.prepwatch.org/mosaic/

www.mosaicproject.blog

EXTRA SLIDES

Who and how many in the study cohort?

- **Eligibility criteria**
  - Test HIV-negative on same day as enrollment (using standard testing algorithms)
  - Self-identify within at least one population of interest
    - AGYW, FSW, PBFP, AFAB of any gender identity, male at birth who identify as women
    - Age restrictions might vary by country, but when possible will include ≥15 years
  - Interested in learning about HIV prevention
  - Willing to provide informed consent and be contacted for follow-up
- **Sequential sampling**
- **Divided into two stages**
  - Stage I: Oral PrEP and Ring PrEP available
  - Stage II: Oral PrEP, Ring PrEP, and CAB available

CAB on site? Approximately 6 months post NMRA approval.

- Recognizing unknowns, approximately **11,265** individuals could be enrolled

What do we need to get from study data?

- A decent estimate of gestational age for pregnant participants
- Understanding of when all participants are moving in and out of pregnant and breastfeeding states
- Type, timing, duration of study product used at individual level
- Pregnancy outcomes for all pregnancies, as feasible
- During informed consent process, women will be asked if the study team has permission to abstract data from antenatal clinic (ANC) and relevant delivery site facility records

Once we sort who is pregnant, what are key additional procedures?

Provide client-centered counseling	Understand PBFP Status	Optimize chance to collect PO	Collect PO
Product and choice counseling and procedures (follow specific guidance for pregnancy)	Complete/update key data on pregnancy and breastfeeding status	Complete/update anticipated/current location for antenatal care and delivery	Collect pregnancy outcome when available
A	B	C	D

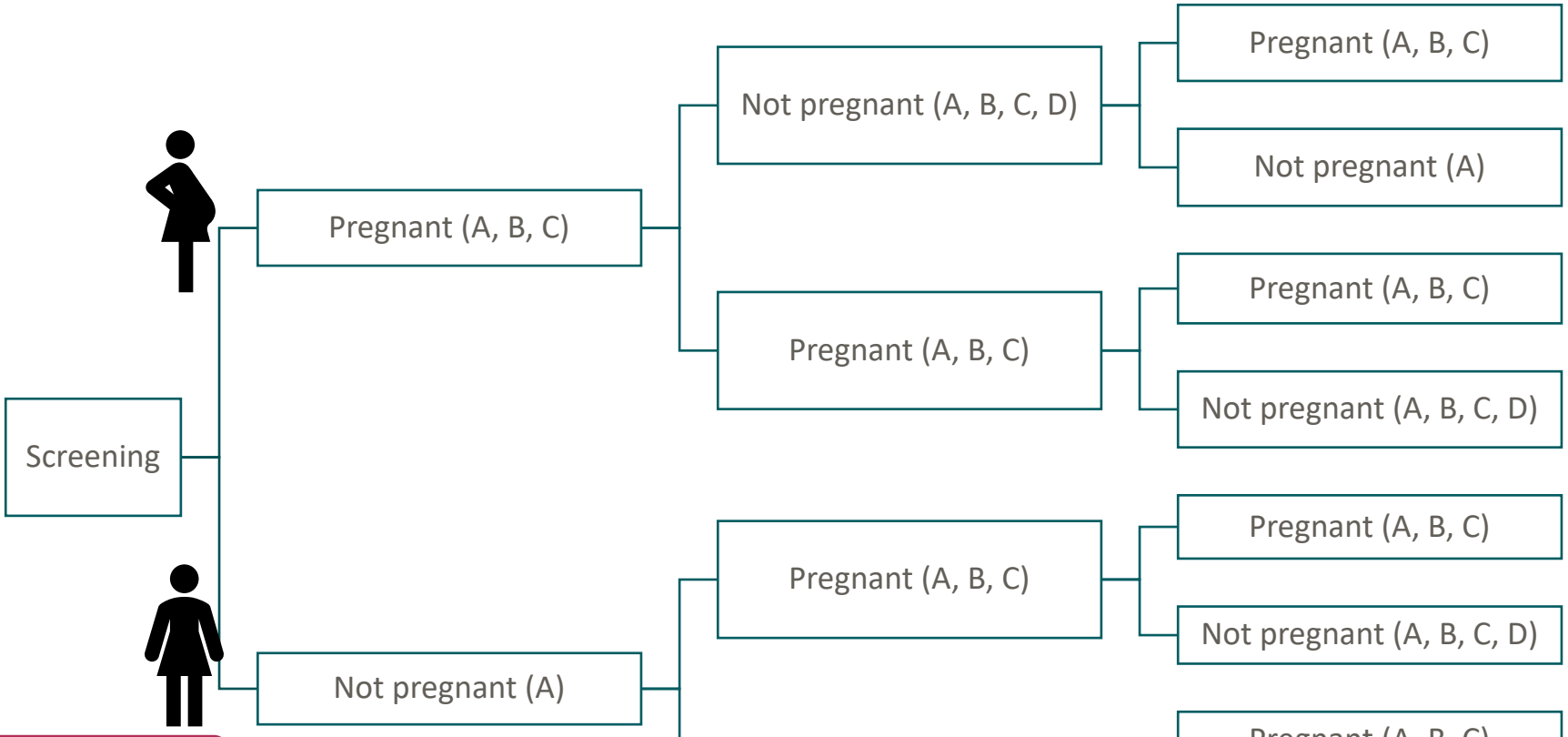
LNMP, if known
Current pregnancy status, breastfeeding status
Estimated gestational age
Any referral for clinical management

Additional options to augment ascertainment of birth defect outcomes

- Global Birth Defects Description and Coding (GBDDC) App
  - For areas where local expertise in congenital anomaly diagnosis is scarce
  - Aims to improve description and coding of major externally visible congenital anomalies for surveillance and research
- Full description of how app was designed can be found at Global birth defects app: An innovative tool for describing and coding congenital anomalies at birth in low resource settings - Dolk - - Birth Defects Research - Wiley Online Library
- Collaboration with local members of African Neonatal Association

Counseling re CAB PrEP

- Providers will counsel PBFP about risks and benefits of using PrEP, including CAB, during pregnancy and/or breastfeeding
- Where NMRA-label does not specifically comment on whether CAB PrEP can be used in pregnancy and/or breastfeeding
  - PBFP will be offered CAB PrEP *if user and provider agree that* benefits outweigh potential risk to fetus or breastfeeding infant



- **A** •Product and choice counseling/procedures
- **B** •Complete/update PBFP CRF at every contact
- **C** •Collect anticipated/current location for ANC and delivery
- **D** •Collect pregnancy outcome when available

Participants will vary in how they walk through follow-up period, in terms of pregnancy status.

What is beyond the scope of CATALYST?

- Pregnancy and infant outcomes that occur after CATALYST study implementation has ended
- Cabotegravir level at time of pregnancy diagnosis (for participants who had injection in past 12 months)
- Detailed inquiry into pregnancy complications
- Infant outcomes at 1, 6, and 12 months
  - Growth, neurodevelopmental, survival (beyond neonatal period)
- INSTI resistance among infants with HIV infection
- Enrollment of comparator groups beyond target study population

PLOS ONE

RESEARCH ARTICLE

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

Jennifer E. Balkus[1,2]*, Moni Neradilek[2], Lee Fairlie[3], Bonus Makanani[4], Nyaradzo Mgodi[5], Felix Mhlanga[5], Clemensia Nakabiito[6], Ashley Mayo[7], Tanya Harrell[2], Jeanna Piper[8], Katherine E. Bunge[9], on behalf of the MTN-042B Study Team[¶]

1 Department of Epidemiology, University of Washington, Seattle, Washington, United States of America, **2** Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America, **3** Faculty of Health Sciences, Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Gauteng, South Africa, **4** College of Medicine-Johns Hopkins Research Project, Blantyre, Malawi, **5** University of Zimbabwe College of Health Sciences Clinical Trials Research Centre, Harare, Zimbabwe, **6** Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda, **7** FHI 360, Durham, North Carolina, United Stated of America, **8** US National Institutes of Health, Bethesda, Maryland, United States of America, **9** Department of Obstetrics and Gynecology, University of Pittsburgh, Pittsburgh, Pennsylvania, United Stated of America

When should registries be initiated?

- Time of initial marketing
- When a new indication is approved
- When patterns of use show product used by those of reproductive age/potential
- …or earlier!
  - Be ready to assess margins of safety
  - Detect safety signals

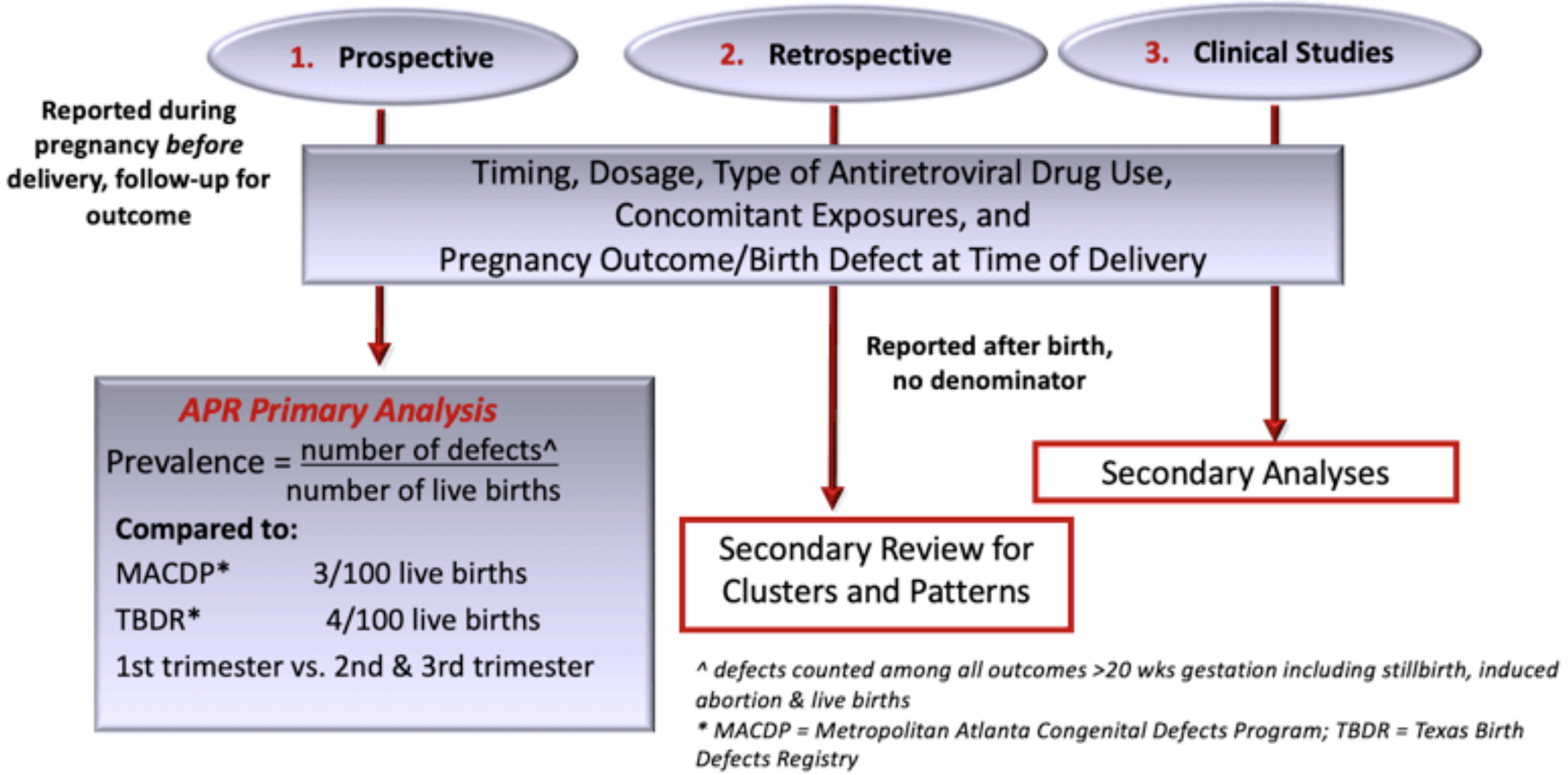
Antiretroviral Pregnancy Registry (APR)

THE ANTIRETROVIRAL PREGNANCY REGISTRY

- Voluntary prospective, exposure-registration, observational study
  - Designed to collect/evaluate outcomes of pregnancy exposures to ARVs
- Aims to provide early signal of any major teratogenic effect associated with prenatal exposure to products in the Registry
- Minimal initial information collected (age, LMP, exposure, dosage, timing of exposure)
- At time of delivery, healthcare provider prompted to provide follow-up data on pregnancy outcome
  - Collects many variables not typically accessible in lower resource settings
- Advisory Committee reviews data and establishes consensus on results of data, makes recommendations

http://www.apregistry.com/forms/registration.pdf

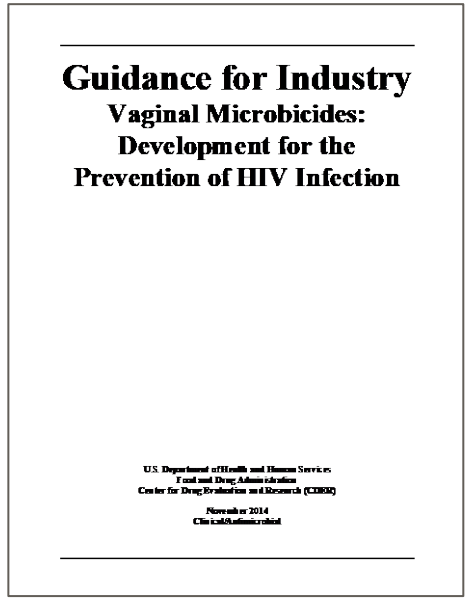
Antiretroviral Pregnancy Registry Analysis



Albano et al. CROI 2021.

MTN-016: EMBRACE

- EMBRACE: Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure (2008-2020)
- Prospective observational cohort study
  - Fell pregnant during trials, or planned exposures in safety studies
- 460 women and 413 infants enrolled across 17 sites


Guidance for Industry
Vaginal Microbicides: Development for the Prevention of HIV Infection

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2014
Clinical/Medical/Revised

"Women who become pregnant during the trial should be followed in a pregnancy exposure registry such as the Microbicide Trials Network Registry MTN-016."
– 2014 Guidance for Industry

UBOMI BUHLE (Understanding Birth Outcomes from Mothers and Infants, Building Healthcare by Linking Exposures)

- Pregnancy exposure registry in South Africa
  - Data from individual pregnancy exposure registries
- Prospective inclusion of those attending antenatal care at 15 sentinel clinics across Gauteng, KZN, and Western Cape
  - Follow-up to time of delivery
- Capacity building on maternal and infant care and data capture
- Exposures, comorbidities, obstetric history, maternal, pregnancy, and birth outcomes
  - Neonatal surface examination (liveborn plus stillbirths) from records
- Global Birth Defects Description and Coding App

Common registry could help to address common challenges in implementation studies

- Gestational age assessment, esp. where ultrasound is uncommon
- Continuity of care in health system and contact with participants
- Medical records completion, accuracy, access in public sector
  - Related to overburdened, understaffed, underpaid (or unpaid) workforce
  - Culture of documentation not consistent with typical standards for registry
  - Paper-based systems still prevail in many settings
- Variables that require complex lab capacity or specimen transport
- Choice of comparator group(s)
- Some highly desired evidence locally (e.g., impact on future fertility) is particularly challenging to generate and not typical registry focus