Antiretrovirals in pregnancy and breastfeeding: a research toolkit

Women's HIV Research Collaborative

15 April 2025

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HIV, Hepatitis and STIs

>> Launched at IAS, July 2024 <<

World Health Organization

Developed by the HIV, Hepatitis and STIs Pregnancy and Breastfeeding Therapeutics Working Group (HHS PTWG)

Please note: the terms 'women' and 'mothers' are used in the presentation and toolkit, but we intend these to be inclusive of all people who experience pregnancy, regardless of their gender identity.

Protecting the specific needs of mothers and babies is essential and cannot be left behind

- In 2023, an estimated 20.5 million women aged >15 years were living with HIV, and 520,000 women >15 years newly acquired HIV infection.
- In 2023, there were an estimated 1.3 million births to women living with HIV.
- Antiretroviral (ARV) drugs during pregnancy and breastfeeding prevent HIV vertical transmission, treat maternal health, prevent HIV acquisition
- However, ARVs can be associated with increased risk of adverse pregnancy outcomes

ARV regimen in pregnancy can affect multiple different outcomes

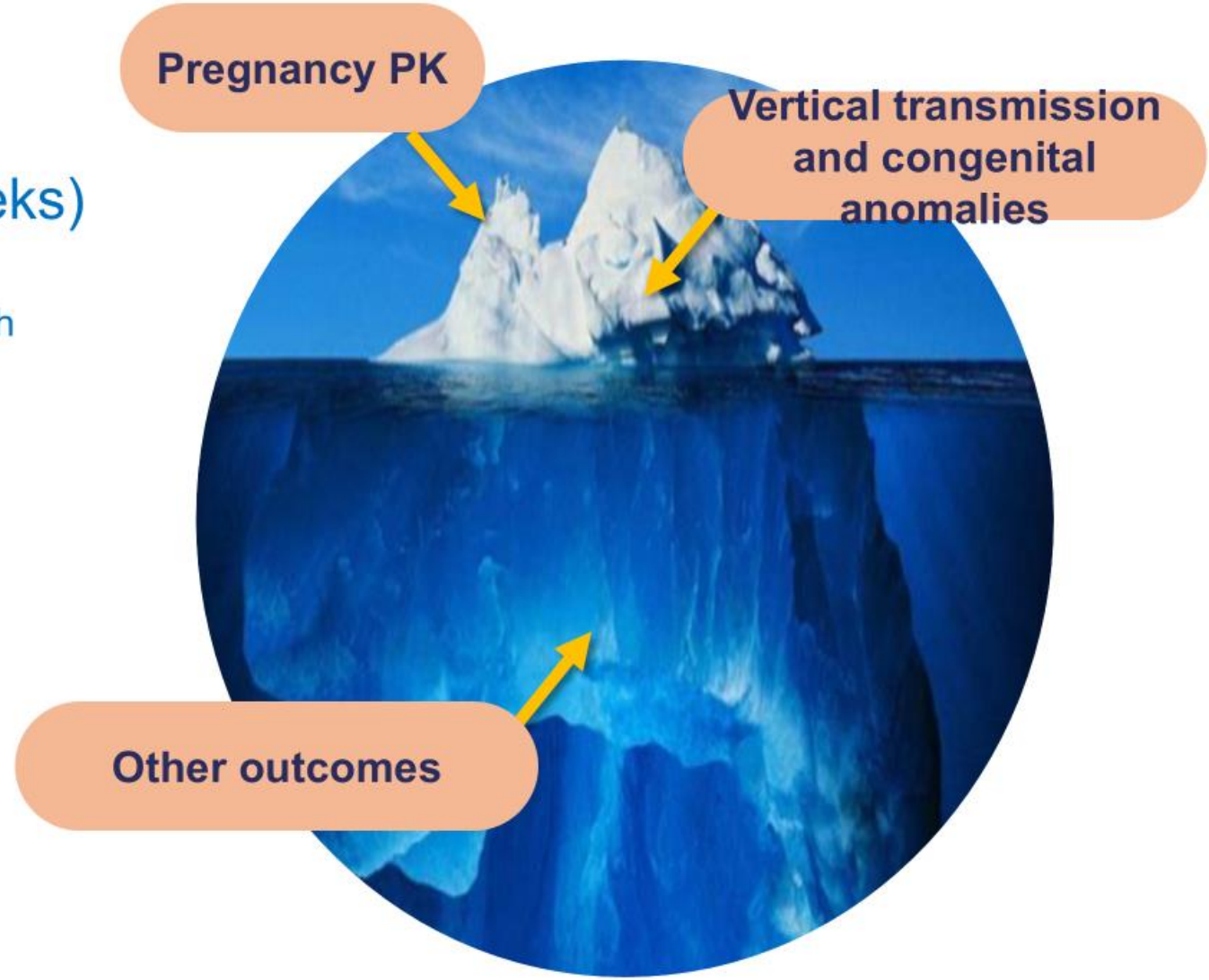
Other important outcomes:

Pregnancy outcomes

- Preterm delivery (**PTD**, birth <37 weeks)
- Low birthweight (**LBW**, <2500g)
- Small for gestational age (**SGA**, <10th percentile)
- Stillbirth
- Neonatal Death

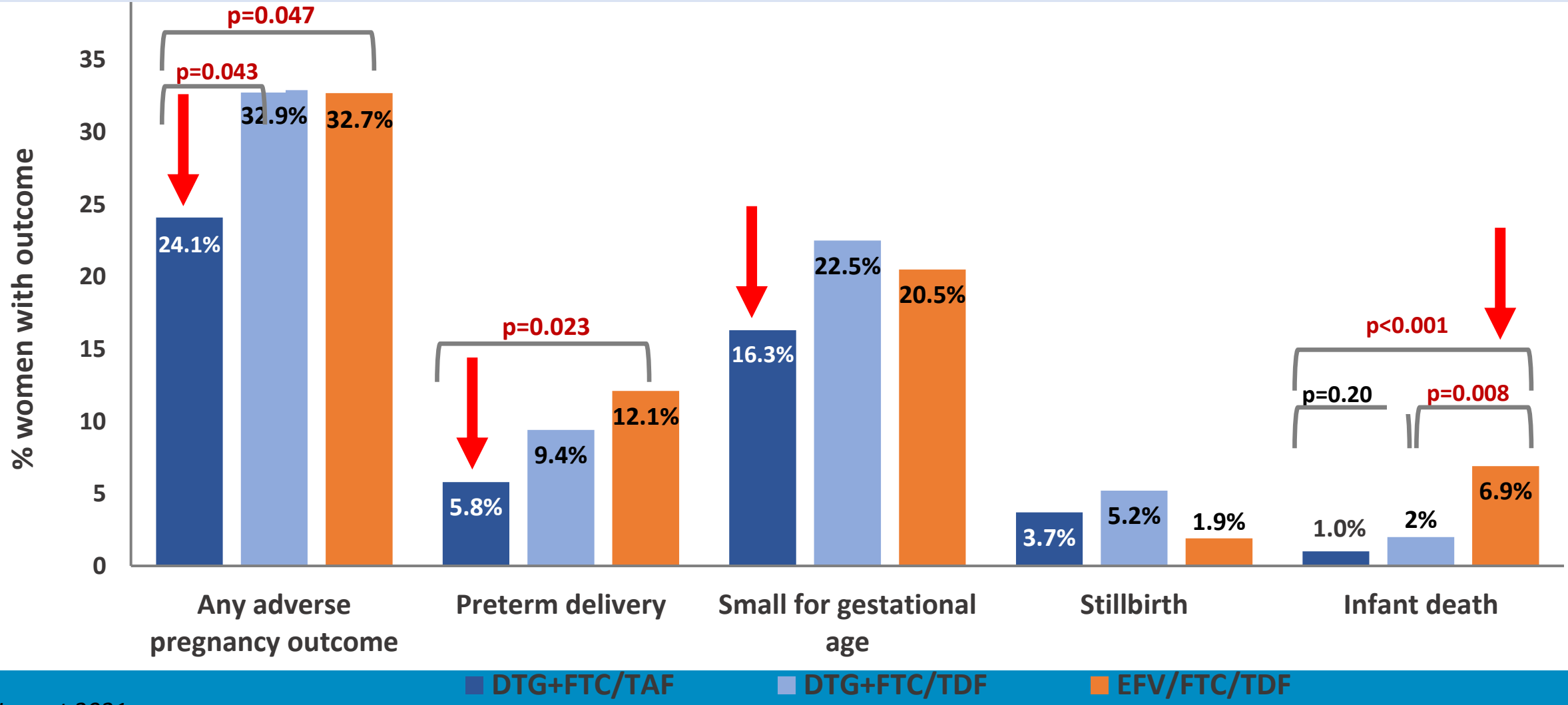
Mother's health outcomes

Child health, growth, neurodevelopmental outcomes



Example: ART regimen affects pregnancy and infant outcomes

Example: IMPAACT 2010 (VESTED) randomized trial



Lockman Lancet 2021;
Chinula Lancet HIV 2023

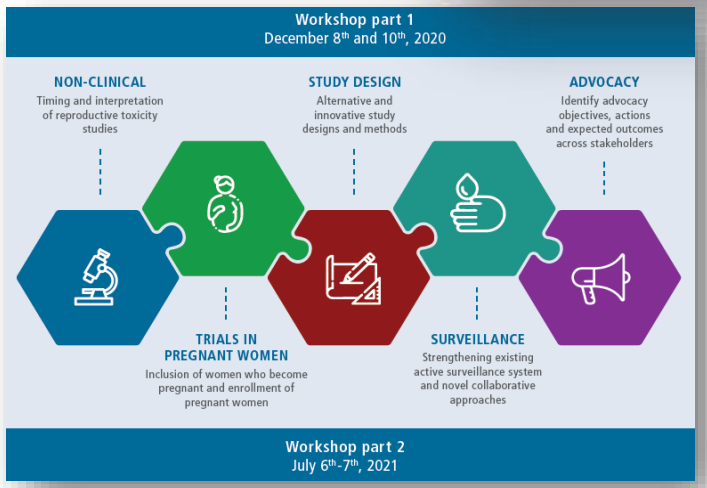
Generally poor track record for studying drugs in pregnancy

- **>90% of FDA-approved drugs had no data on safety/efficacy in pregnancy (up to 2010)**
- **Limited pregnancy/breastfeeding pharmacokinetic data for many ARVs,** typically long delay until initial data available, and insufficient high-quality safety data
- **Focus is often on potential harm to fetus of medications taken in pregnancy**
- In reality NOT taking treatment during pregnancy because of lack of data can harm mother and fetus
  - Avoidance or cessation of treatment, under-dosing, use of inferior treatment
- **Pregnant women generally excluded from research**
  - This does NOT remove risk, but simply shifts risk from setting with informed consent and intensive monitoring to routine clinical settings
- **Excluding pregnant women from pre- or post-registration clinical trials delays the introduction of safer ARVs for mother and baby**

Accelerating investigation in pregnancy and introduction of new and safer HIV medicines

- Over the past seven years, key stakeholders have articulated major conceptual shifts to support the inclusion of pregnant women in research, moving from "**protecting from research to protecting through research**"

- In 2020-2022, WHO and IMPAACT convened a series of **technical workshops** that included academic researchers, funders, regulators, clinical experts, industry leaders, civil society, ethicists.



"Approaches to Enhance and Accelerate Study of New Drugs for HIV and Associated Infections in Pregnant Women" (**WHO & IMPAACT, 2020-2021)**

Consensus on a new framework for investigation in pregnancy

GOAL: to have PK and preliminary safety data on all new HIV agents in pregnancy available at the time of drug approval.

- A new framework for a**ccelerating and studying new antiretrovirals in pregnancy** was produced, key principles adopted and disseminated through **a Call to Action.**
- The WHO subsequently convened a new **Working Group on Pregnancy and Breastfeeding Therapeutics for HIV, Hepatitis and STIs** to continue the technical dialogue.
- Move from theory to action

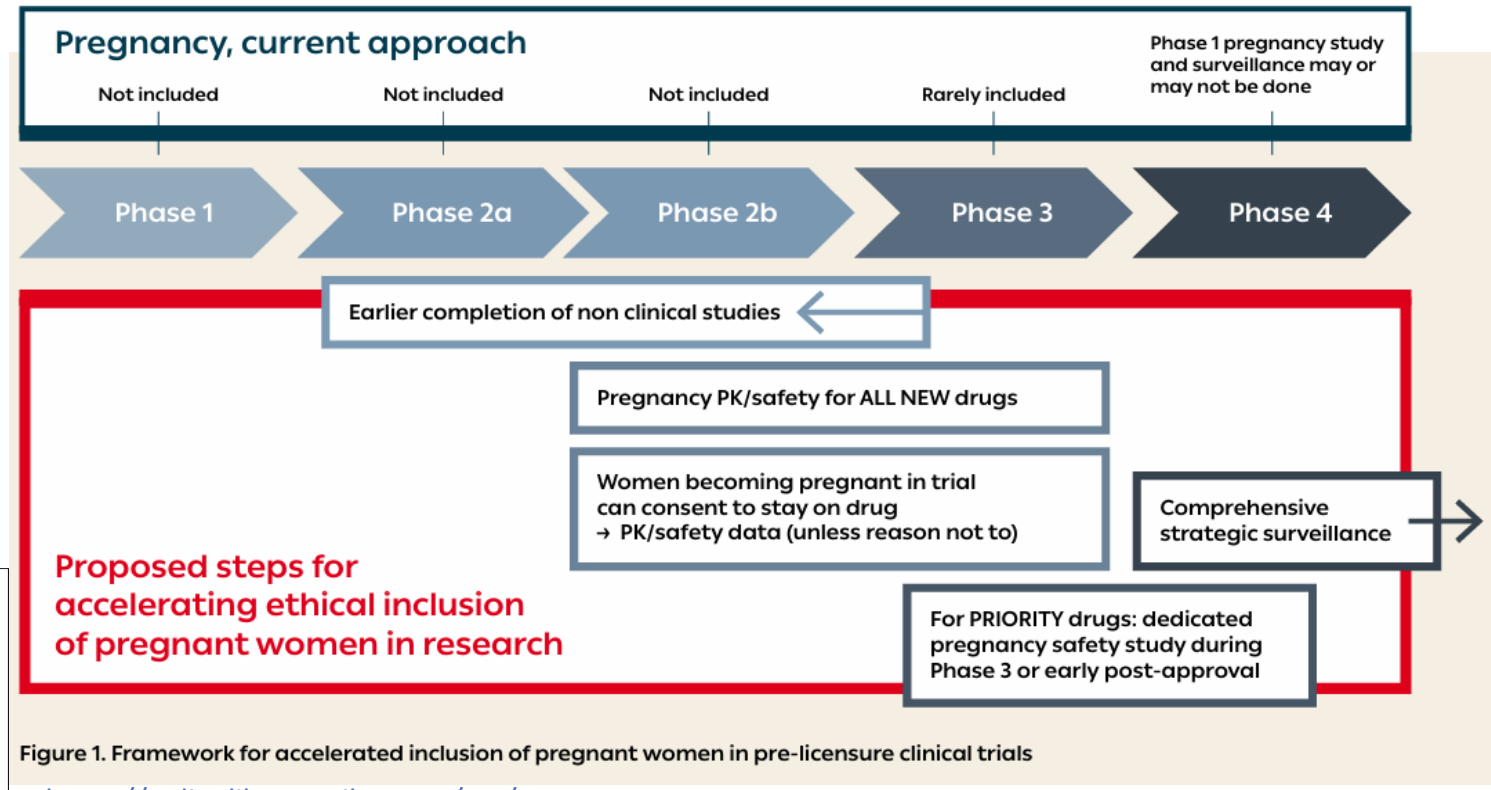


Figure 1. Framework for accelerated inclusion of pregnant women in pre-licensure clinical trials

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

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

The WHO convened a working group on Pregnancy and Lactation Therapeutics for HIV, Hepatitis, and STIs

Continue the **technical dialogue and implementation of strategic actions** to support implementation and acceleration of R&D and surveillance for new HIV agents in pregnancy

Develop **resources to optimize clinical research** in pregnancy **- toolkit** (endpoints and materials made available)

Technical advice to **WHO guidelines and ARV optimization** processes – **ART and PrEP in pregnancy** (DTG, TAF, **CAB LA**, LEN, others)

Implement a **new Collaborative framework of surveillance** for the safety of HIV drugs in PLW – **ART and PrEP**

Contribute to **High-Level Dialogues** to galvanize commitment and promote accountability – Roma 6 Global Action Plan

Leverage multiple fora to **disseminate the key principles** and engage with the constituencies – regulatory work ICH, WHA resolution

Facilitate **engagement of community** of women living with HIV, HEP or STIs - from planning to communication

Antiretrovirals in pregnancy research toolkit

Goal: to support and accelerate generation of pregnancy and lactation data for HIV, viral hepatitis and STI medicines for treatment and prevention

- Open-access, “living” repository
- Practical materials from 23 studies of pregnant/lactating women
- Guidance on harmonizing pregnancy outcome/ endpoint data
- Links to videos, guidance, networks, learning hubs
- Contributions by more than 30 PTWG members

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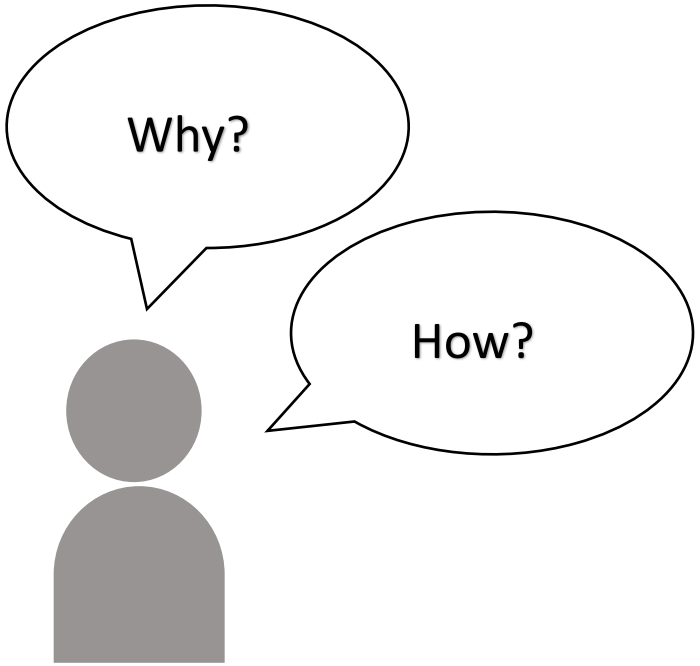
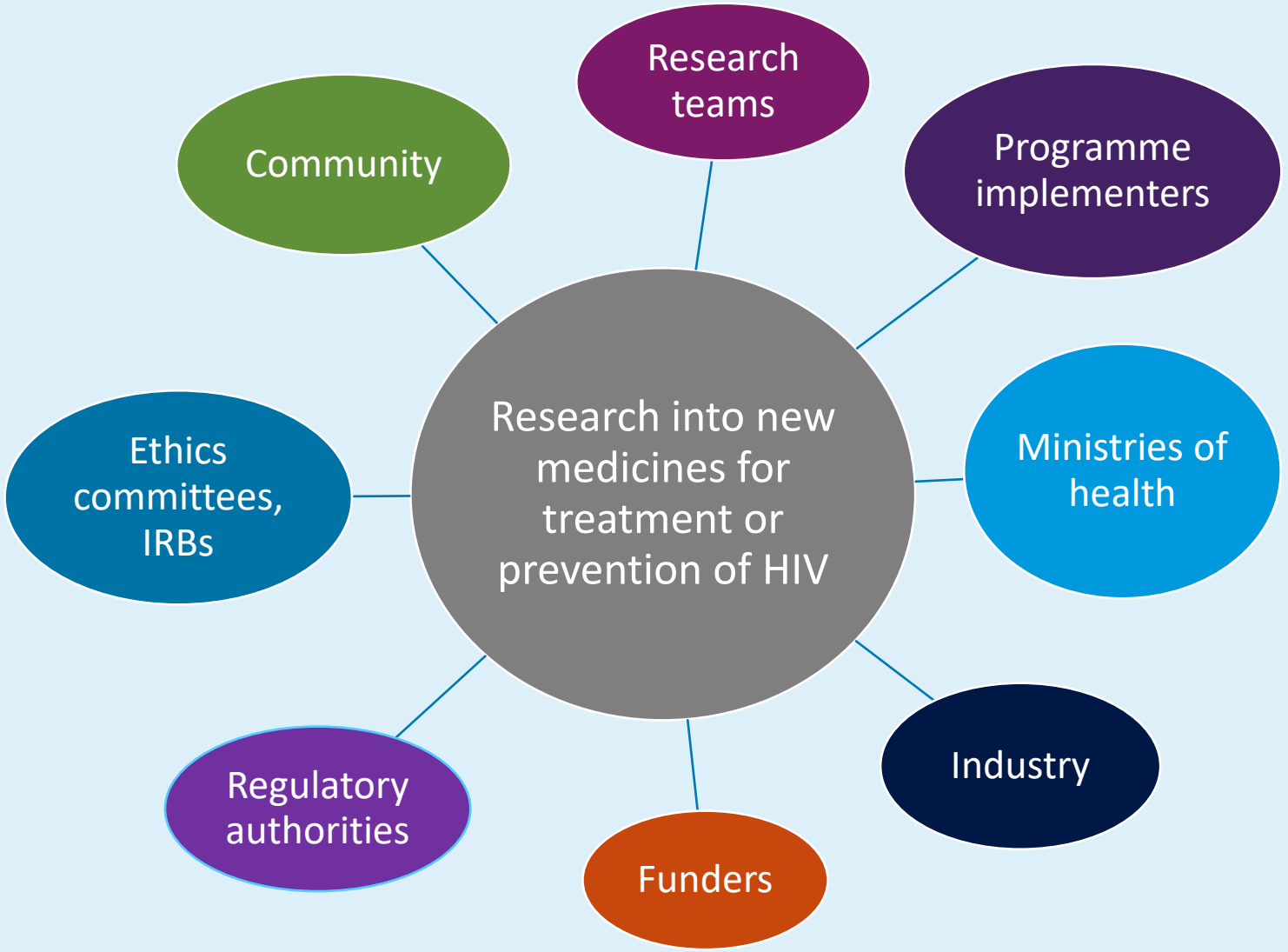
Target audience





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- **Ethical considerations**
- **Community engagement and communication**
- **Pharmacokinetics and dosing**
- **Clinical trials and observational studies**
- **Surveillance studies and registries**
- **Outcome measures**
- **Key background references**

Ethical considerations

Resources in this section

- → Ethical guidelines for research in pregnancy
- → Affirming statements, guidance and reports
- → Tools for research design and evaluation
- → Advocacy and training resources

Conceptual shifts that support inclusion

The increasing consensus on the ethical imperative to conduct research with pregnant people reflects a trio of conceptual shifts in how we think about research with this population. These include a shift from understanding pregnant people as a vulnerable population to understanding them as a complex population; from the idea that pregnant persons and fetuses should be protected from research to the recognition that they are best protected through research; and from the general practice of summarily excluding pregnant persons from research, without justification (presumed exclusion) to a model in which they have equitable access to both the direct benefits of research and the benefits of a robust evidence base that would result from their fair inclusion in the biomedical research agenda. Further discussion of each conceptual shift can be found below.

Until recently, pregnant persons were categorized alongside children, prisoners, and individuals with intellectual disabilities as a vulnerable population. Yet unlike these populations there is nothing about pregnancy per se that constrains a person's ability to provide valid consent or makes them particularly susceptible to exploitation. This designation is therefore inaccurate, and had a chilling effect on research in pregnancy. Ethical and regulatory guidance no longer uses the term vulnerable to describe pregnant people; some instead designate them as a complex population to capture the scientific and ethical complexities that research in pregnancy can bring up.

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Author: Anne Drapkin Lyerly

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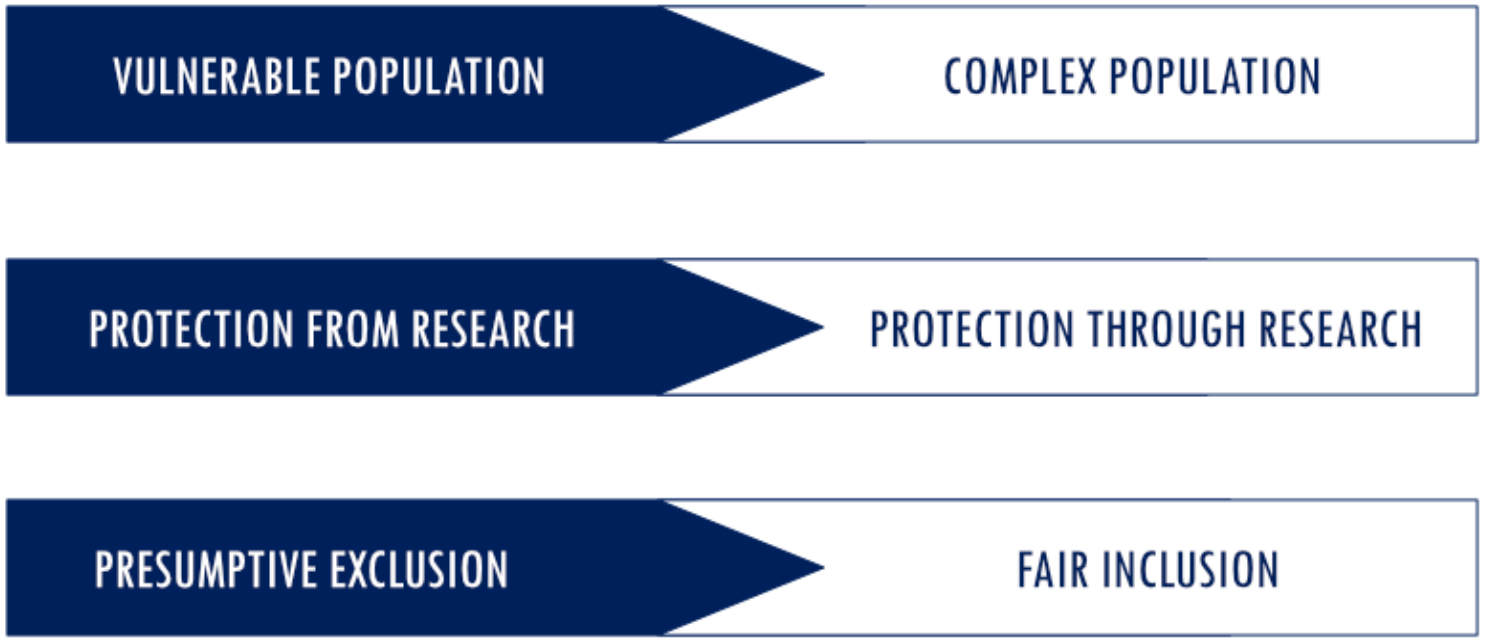
- **Data harmonization**
- **Key background references**

Conceptual shift



The PHASES Working Group, call to action, 2020

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Resources

Ethical guidelines for research in pregnancy

Entities that advise or govern the conduct of research have issued guidance on the conduct of research in pregnancy. These include nongovernmental organizations (e.g., the Council for International Organizations of Medical Science (CIOMS)) and governmental entities. While these guidance documents permit and sometimes explicitly support a wide range of research to be conducted in pregnancy, there is some debate about how they should be interpreted or applied. Some key documents are linked below, with selected commentaries.

Note that this is an incomplete (and in process) list, and those conducting research in countries not represented here will need to consider local guidance, as available.

WHO and the Council for International Organizations of Medical Sciences (CIOMS)

Starting in the late 1970s, CIOMS in cooperation with WHO has issued guidelines to provide "internationally vetted ethical principles and detailed commentary on how universal ethical principles should be applied, with particular attention to low-resource settings." The document was revised most recently in 2016 and includes a Guideline on *Pregnant and Lactating Women as Research Participants* (Guideline 19, p. 71). The Guideline states that, "Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted" and addresses several areas of controversy:

- International Ethical Guidelines for Health-related Research Involving Humans. Council for International Organizations of Medical Sciences (CIOMS) and WHO, 2016.
  - Commentary:
    - How the CIOMS guidelines contribute to fair inclusion of pregnant women in research. van der Graaf R, Zande IS, and Delden JJM. Bioethics, 2019 Mar;33(3):367-373
    - Ideal and Nonideal Theories: The Challenges of Decision-Making in an Imperfect World. Luna F. Philosophy and Medi 2021;139: 17-40.

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Community engagement and communication

→ Resources in this section

Since the beginning of the HIV epidemic, community engagement and activism have played a critical role in shaping clinical research and drug development. This engagement has been acknowledged as a vital component of successful outcomes by key health agencies, including WHO.

There are several challenges and barriers to studying agents for HIV treatment and prevention in women of childbearing potential and pregnant women. They are typically not only thinking about their own health, but also the health of their child, and balancing the risks and benefits even in the face of uncertainty. Therefore, engaging the community of women living with HIV is critical to accelerating research in this population.

Stakeholder consultations across treatment and prevention trials broadly agree on several recommendations:

- Pregnant women and women who become pregnant have the right to make their own choice about participating in research.
- Clear and understandable information must be shared for informed decision making.
- Pregnant women should be included in research in a timely manner.
- Contraception should not be a prerequisite to study participation and women who become pregnant should be able to stay on study drug.
- Pregnant women should be engaged across the lifecycle of trials.

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Authors: Polly Clayden, Sinead Delany-Moretlwe

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Informed choices for pregnant women! New approaches and good practices for studying antiretrovirals in pregnancy. IAS 2021, 18–21 July. Virtual satellite session SA49. Community panel (from 11.28 to 36.27 minutes)

In this community panel at IAS 2021, we hear the voices of women involved in grassroots treatment literacy and advocacy, trial participants and mothers living with HIV. The messages that pregnant women should be enrolled in clinical trials, where appropriate, and that they should be supported to make their own decisions about participating, as well as the many advantages to the research, are very clear.

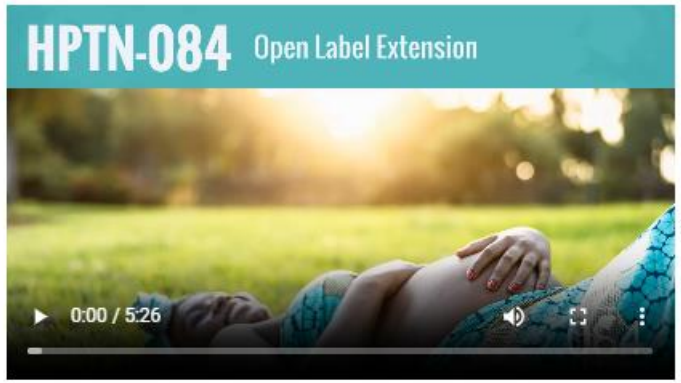
Accelerating investigation of novel therapeutics in pregnancy: from theory to action. AIDS 2022, Satellite session.

See presentation on 'Effective and meaningful support of participants in research'.

In this session we hear from a community representative talking about strategies to include pregnant people in trials.

Examples of tools that can be used to enhance communication and community literacy

HPTN 084 LIFE video for pregnant participants



This is an example of a video developed for pregnant participants that was primarily used to address potential questions participants might have but could also be shared on Whatsapp or other social media with partners, family or other stakeholders to provide information on the reasons for inclusion of pregnant women in the trial as well as proactively addressing questions that might arise.

DELIVER and Be-PROTECTED video

This is an example of a video developed for participants and stakeholders to provide information about the trials enrolling pregnant and lactating people. The video provides explanations in an accessible visual format.

Materials from 2 networks

World Health Organization

Authors: Polly Clayden, Sinead Delany-Moretlwe

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Pharmacokinetics and dosing

→ Resources in this section

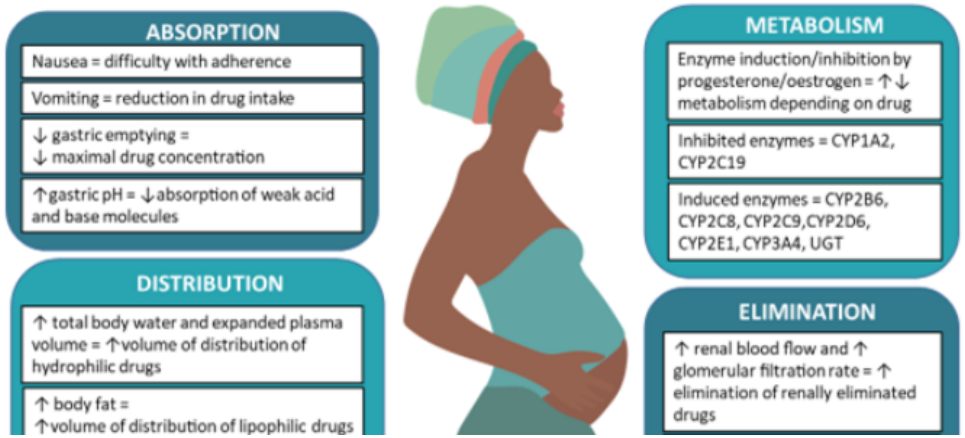
Pregnant women have historically been excluded from clinical trials to prevent eventual drug-related adverse effects on the women and her pregnancy. However, the lack of data in pregnancy is problematic as it may prevent the use of newer more effective treatment due to the lack of data on safety, pharmacokinetics and the related optimal dosing in this population.

Pharmacokinetics is defined as "what the body does with a drug".

Pharmacokinetics studies the absorption, distribution, metabolism/biotransformation and excretion (ADME) of medicines.

The aim is to generate effective but non-toxic exposure to a medicine in the body. This means that the plasma concentrations of a drug should not be too low, which may lead to reduced efficacy, or too high, which may lead to toxicity.

Figure: changes in absorption, distribution, metabolism/biotransformation and excretion during pregnancy



Authors: Angela Colbers, Catia Marzolini, Catriona Waitt, Wendy van der Wekken

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Resources

30 June 2018

Toolkit for research and development of paediatric antiretroviral drugs and formulations

Module 3 of this toolkit focuses on research in pregnant and breastfeeding women. Key considerations are given about the timing of pharmacokinetic studies in pregnancy and lactation and which data are key to collect.

Report and papers generated after the "Approaches to Optimize and Accelerate Pharmacokinetic Studies in Pregnant and Lactating Women" workshop in 2019, organised by WHO and IMPAACT

This workshop brought together the different stakeholders with the aim to generate consensus on how to optimize and accelerate pharmacokinetic studies in pregnant and lactating women. This workshop was focussed around antiretrovirals for treatment of HIV, but the main outcomes can be applied more generally to treatment of infectious diseases or chronic diseases that need to be treated during pregnancy.

Optimizing Pharmacology Studies in Pregnant and Lactating Women Using Lessons From HIV: A Consensus Statement

Innovative Approaches for Pharmacology Studies in Pregnant and Lactating Women: A Viewpoint and Lessons from HIV

Studies and programmes

IMPAACT 2026

IMPAACT 2026 is a Phase IV, prospective, pharmacokinetic (PK) study of selected antiretroviral (ARV) and anti-tuberculosis (TB) drugs during pregnancy and postpartum. The study is designed to evaluate the following: the PK of ARV medicines used in clinical care during pregnancy and postpartum; the PK of ARVs when used in combination with first-line TB medicines in clinical care during pregnancy and postpartum; the PK of second-line TB medicines when used in clinical care during pregnancy and postpartum; the kinetics of placental and breastmilk transfer of long-acting injectable ARVs after maternal dosing during pregnancy; and the kinetics of breastmilk transfer of other select ARVs from mother to child during breastfeeding.

- Study website
- Protocol
- Manual of procedures
- Informed consent form (see protocol, pages 144-221)

Materials from 2 studies

World Health Organization

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Clinical trials and observational studies

→ materials & resources

This section provides an overview of the key considerations for the conduct of pregnancy safety studies and a list of materials and resources used in clinical trials and observational studies involving pregnant and breastfeeding people.

Introduction

This section focuses on studies of pregnancy safety (and sometimes efficacy) in larger numbers of women than are traditionally included in pregnancy pharmacokinetics (PK)-only studies, which generally provide preliminary and short-term safety data on small numbers of pregnant women. These studies may be clinical trials that enroll pregnant women (e.g. for drugs that may be used by large numbers of women who are or may become pregnant); clinical trials that enroll people who are not pregnant but that gather relevant pregnancy data in women who become pregnant on-study; and observational studies that enroll pregnant women (or women who become pregnant during follow-up). Examples of materials (protocols, informed consent forms, case report forms, and manuals of procedures) from each of these types of studies are provided in this section.

Ideally, for new drugs that are expected to be used by pregnant women, pregnancy PK, dosing and short-term safety data from at least a small number of women should be generated prior to drug licensure unless non-clinical or early clinical data suggest reproductive toxicity (see the PK section for more detail on pregnancy PK studies). In many cases, these data can be generated by gathering pregnancy PK data in consenting women who become pregnant during pre-licensure trials. For drugs that will be used by adolescent and adult women in

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Authors: Shahin Lockman, Claire Townsend, Sinead Delaney-Moretlwe

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Materials and resources

Clinical trials enrolling pregnant and/or breastfeeding women

HIV TREATMENT

IMPAACT 2010 / VESTED

IMPAACT 2010 was a phase 3 open-label trial that studied the virologic efficacy and safety of three ART regimens started in pregnancy after the first trimester.

IMPAACT 2010 trial materials are included because this trial enrolled women during pregnancy (between 14- and 28-weeks' gestation) and randomized participants to start one of three study drug regimens, and because the trial was designed and powered to evaluate both virologic efficacy and safety endpoints (birth/pregnancy outcomes, and maternal and child adverse events and other relevant clinical outcomes).

- Study website
- Protocol
- Manual of procedures
- Informed consent forms (see Appendix III of the protocol, pages 142-163)
- Case report forms - general (PDF, 610 KB)
- Case report form - generic pregnancy (PDF, 30 KB)
- Case report form - pregnancy and obstetric (PDF, 330 KB)

Materials from 14 studies

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Authors: Shahin Lockman, Claire Townsend, Sinead Delaney-Moretlwe

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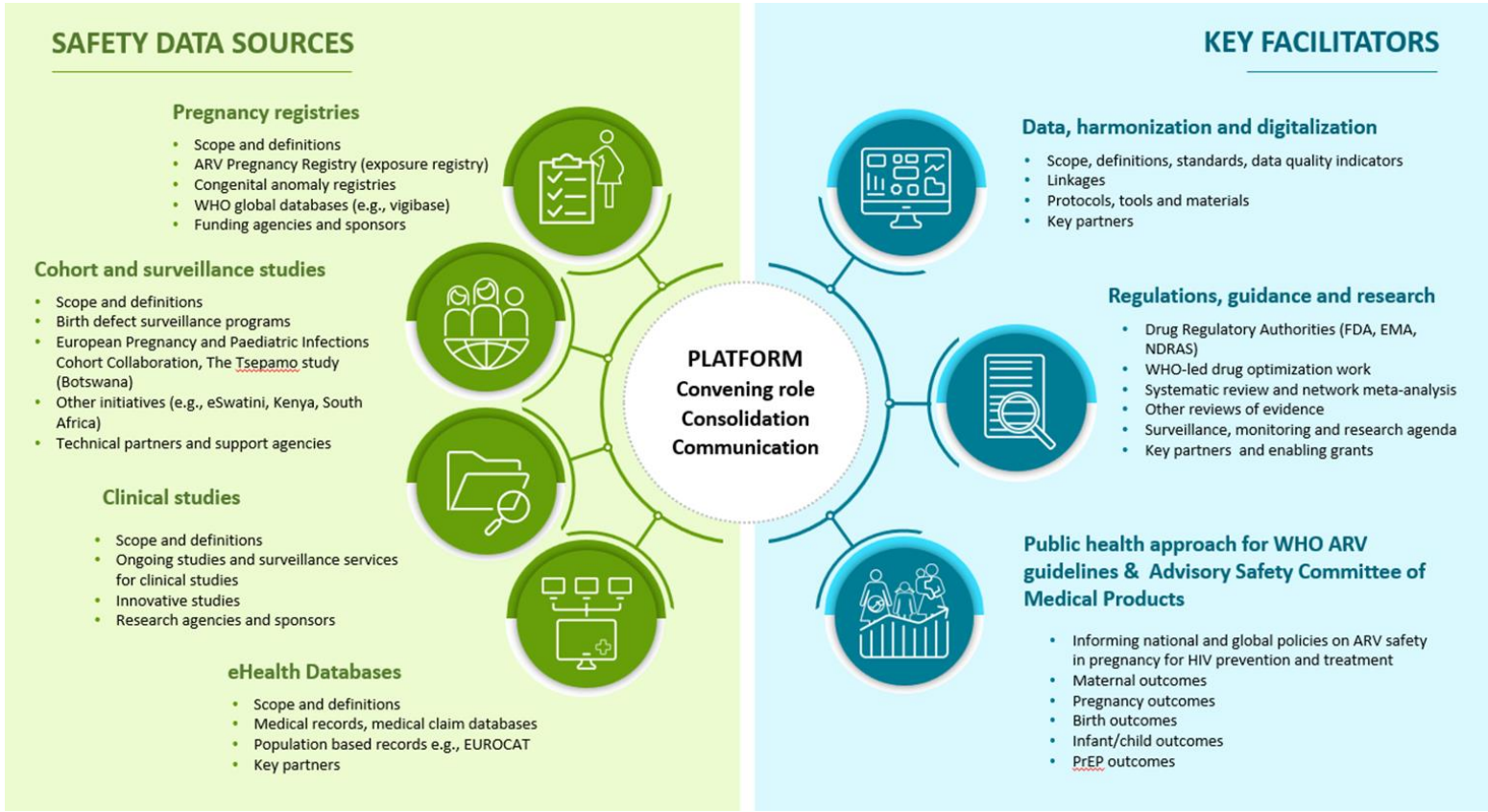
Surveillance of medicines in pregnancy and breastfeeding

→ study materials



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Study materials

Links to study materials from key pregnancy and birth surveillance studies and registries are provided below.

Tsepamo Birth Outcomes Surveillance Study

Surveillance study of birth outcomes among infants born to HIV-infected and HIV-uninfected women in Botswana, with a focus on specific antiretroviral regimens taken from conception or during pregnancy.

- Study protocol (MS Word, 540 KB)
- Case report form (PDF, 270 KB)
- Overview of operations slide set (PPTX, 2.9 MB)
- Training presentation slide set (PPTX, 3.8 MB)
- Consent form - photographs (MS Word, 50 KB)
- Training presentation on newborn surface examination slide set (PPTX, 3.8 MB)

Hospital-based birth defects surveillance in Kampala, Uganda

Birth defect surveillance system at sentinel hospital sites in Kampala, Uganda, that includes all informative births to women with and without HIV. The study also encompasses a nested case-control of infants with and without birth defects to determine the association between early use of co-trimoxazole and antiretrovirals and birth defects.

- Study protocol (MS Word, 1.3 MB)

Materials from 7 studies

Author: Lynne Mofenson

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Core endpoints

Birth outcomes	Maternal outcomes	Neonatal/infant outcomes
Stillbirth (≥28 weeks)	Mortality during pregnancy, labour/delivery, and in facility	Neonatal death (in facility)
Preterm birth <37 weeks		
Very preterm birth <32 weeks		
Birthweight		
Small for gestational age (SGA) (<10th %ile)		
Congenital anomalies reported at birth		
Miscarriage (any <28 wks; early <20 wks)		

Expanded endpoints

Birth outcomes	Maternal outcomes	Neonatal/infant outcomes
Stillbirth (≥28 weeks)	Mortality during pregnancy, labour/delivery, and in facility	Neonatal death (in facility)
Preterm birth <37 weeks	Pregnancy and labour/delivery complications	Infant mortality (first year)
Very preterm birth <32 weeks	Eclampsia/pre-eclampsia	Growth (first year)
Birthweight	Weight gain in pregnancy	
Small for gestational age (SGA) (<10th %ile)	Caesarean section (emergency vs. elective)	
Congenital anomalies with neonatal surface exam		
Miscarriage (any <28 wks; early <20 wks)		

Comprehensive endpoints

Birth outcomes	Maternal outcomes	Neonatal/infant outcomes
Stillbirth (≥28 weeks)	Mortality during pregnancy, labour/delivery, and in facility	Neonatal death (in facility)
Preterm birth <37 weeks	Pregnancy and labour/delivery complications	Infant mortality (first year)
Very preterm birth <32 weeks	Eclampsia/pre-eclampsia	Growth (first year)
Birthweight	Weight gain in pregnancy	Congenital anomalies (through 6 months of age)
Small for gestational age (<10th %ile)	Caesarean section (emergency vs. elective)	Hospitalization (first year)
Congenital anomalies with neonatal surface exam and fetal U/S	Gestational diabetes	Lab toxicity testing)
Miscarriage (any <28 wks; early <20 wks)	Liver, neuropsychiatric, renal, bone toxicity (depending on drug)	Neurodevelopment

Endpoints: definitions

Proposed standardized definitions for pregnancy, birth and infant outcomes:

- Stillbirth
- Miscarriage
- Preterm birth
- Birthweight
- Small for gestational age
- Congenital anomalies
- Maternal mortality
- Neonatal and infant mortality

Example: Stillbirth

"Born without sign of life at ≥28 weeks estimated gestational age

If estimated gestational age not available: born without sign of life, and ≥1000g birthweight and/or ≥35cm body length"

Definitions harmonized with WHO core pregnancy indicators

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Endpoints: Pregnancy outcome "background" prevalence ranges in general population

Outcome	Range (%)
Miscarriage, <20 weeks' gestation	15%-30%
Stillbirth (ranging from ≥20 weeks to ≥28 weeks' gestation)	0.3%-2.5%
Preterm <37 weeks (in live births)	6%-22%
Low birthweight <2,500g (in live births)	10%-14%
Small for gestational age (SGA) (in live births)	16%-30%
Neonatal death (through 28 days)	1.7%-3.2%
Infant mortality (through 1 year)	2.6%-3.1%
Congenital anomalies	1%-4.3%
Congenital anomalies in studies that include only major structural abnormalities of prenatal origin that affect health, survival, physical or cognitive functioning	0.4%-0.7 %
Neural tube defects	8-50 per 10,000
Maternal mortality (during pregnancy or within 42 days of delivery)	<1%-5%

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Endpoints: Pregnancy outcome "background" prevalence ranges in women living with HIV

Outcome	Range (%)
Miscarriage, <20 weeks' gestation	20%-37%
Stillbirth (ranging from ≥20 weeks to ≥28 weeks' gestation)	1%-4%
Preterm <37 weeks (in live births)	10%-26%
Low birthweight <2,500g (in live births)	12%-24%
Small for gestational age (SGA) (in live births)	10%-25%
Neonatal death (through 28 days)	1-4%
Infant mortality (through 1 year)	1-7%
Congenital anomalies	2-6%
Congenital anomalies in studies that include only major structural abnormalities of prenatal origin that affect health, survival, physical or cognitive functioning	0.4%-0.6%
Neural tube defects	8-50 per 10,000
Maternal mortality (during pregnancy or within 42 days of delivery)	2%-6%

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Examples of sample size estimates for pregnancy studies/ surveillance

By sample size

Outcome Type	Power*	N1	N2	N	P1	P2	R1	Alpha
NTD	0.8	250	250	500	0.031	0.00012	256.59	0.05
NTD	0.9	250	250	500	0.041	0.00012	339.03	0.05
NTD	0.975	250	250	500	0.058	0.00012	485.41	0.05
Stillbirth	0.8	250	250	500	0.072	0.02	3.61	0.05
Stillbirth	0.9	250	250	500	0.084	0.02	4.18	0.05
Stillbirth	0.975	250	250	500	0.103	0.02	5.15	0.05
Neonatal Death	0.8	250	250	500	0.077	0.023	3.36	0.05
Neonatal Death	0.9	250	250	500	0.089	0.023	3.87	0.05
Neonatal Death	0.975	250	250	500	0.109	0.023	4.72	0.05
Infant Mortality	0.8	250	250	500	0.086	0.028	3.05	0.05
Infant Mortality	0.9	250	250	500	0.098	0.028	3.49	0.05
Infant Mortality	0.975	250	250	500	0.118	0.028	4.21	0.05
Congenital Anomalies/Maternal Mortality	0.8	250	250	500	0.089	0.03	2.96	0.05
Congenital Anomalies/Maternal Mortality	0.9	250	250	500	0.101	0.03	3.37	0.05
Congenital Anomalies/Maternal Mortality	0.975	250	250	500	0.121	0.03	4.04	0.05
Low Birthweight/PTB	0.8	250	250	500	0.213	0.12	1.77	0.05
Low Birthweight/PTB	0.9	250	250	500	0.229	0.12	1.91	0.05
Low Birthweight/PTB	0.975	250	250	500	0.255	0.12	2.12	0.05
Miscarriage	0.8	250	250	500	0.308	0.2	1.54	0.05
Miscarriage	0.9	250	250	500	0.326	0.2	1.63	0.05
Miscarriage	0.975	250	250	500	0.355	0.2	1.77	0.05

By ratio

Target						Ratio	
Power	N1	N2	N	P1	P2	R1	Alpha
0.8	4388	4388	8776	0.075	0.06	1.25	0.05
0.9	5874	5874	11748	0.075	0.06	1.25	0.05
0.975	8590	8590	17180	0.075	0.06	1.25	0.05
0.8	2033	2033	4066	0.15	0.12	1.25	0.05
0.9	2722	2722	5444	0.15	0.12	1.25	0.05
0.975	3980	3980	7960	0.15	0.12	1.25	0.05
0.8	963	963	1926	0.275	0.22	1.25	0.05
0.9	1289	1289	2578	0.275	0.22	1.25	0.05
0.975	1885	1885	3770	0.275	0.22	1.25	0.05
0.8	1207	1207	2414	0.09	0.06	1.5	0.05
0.9	1615	1615	3230	0.09	0.06	1.5	0.05
0.975	2362	2362	4724	0.09	0.06	1.5	0.05
0.8	553	553	1106	0.18	0.12	1.5	0.05
0.9	740	740	1480	0.18	0.12	1.5	0.05
0.975	1081	1081	2162	0.18	0.12	1.5	0.05
0.8	255	255	510	0.33	0.22	1.5	0.05
0.9	342	342	684	0.33	0.22	1.5	0.05
0.975	499	499	998	0.33	0.22	1.5	0.05

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Pregnancy toolkit: next steps

- Disseminate – please share!
- Keep up-to-date, develop new sections (e.g. lessons learned, case studies)
- Collate additional key resources, particularly from STI and hepatitis fields

Thank you!

Please contact us with any questions, comments or feedback at:

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https://www.who.int/tools/antiretrovirals-in-pregnancy-research-toolkit

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Acknowledgements

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