A Call to Action
on World AIDS Day

Research for Informed Choices:

Accelerating the Study of New Drugs for HIV in Pregnancy

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

World Health Organization

Agenda & Housekeeping

- Introduction by *Martina Penazzato* on behalf of IMPAACT/WHO
- Core principles of the framework by *Elaine Abrams*
- Review of the **Call to Action** by *Organizing Committee*
- Hearing directly from our stakeholders
- Closing

Please post any questions in the **Q&A**
for comments and reactions
feel free to use the chat box

Organizing Committee

Elaine Abrams
(Columbia University)

Alexandra Calmy
(University of Geneva)

Polly Clayden
(HIV i-Base)

Angela Colbers
(Radboud University)

Shahin Lockman
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Imelda Mahaka
(PANGEA)

Martina Penazzato
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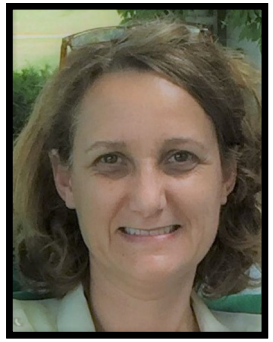


Francoise Renaud
(WHO)

Marissa Vicari
(IAS/CIPHER)

Jennifer Zech
(ICAP at Columbia University)

Turning Theory into practice

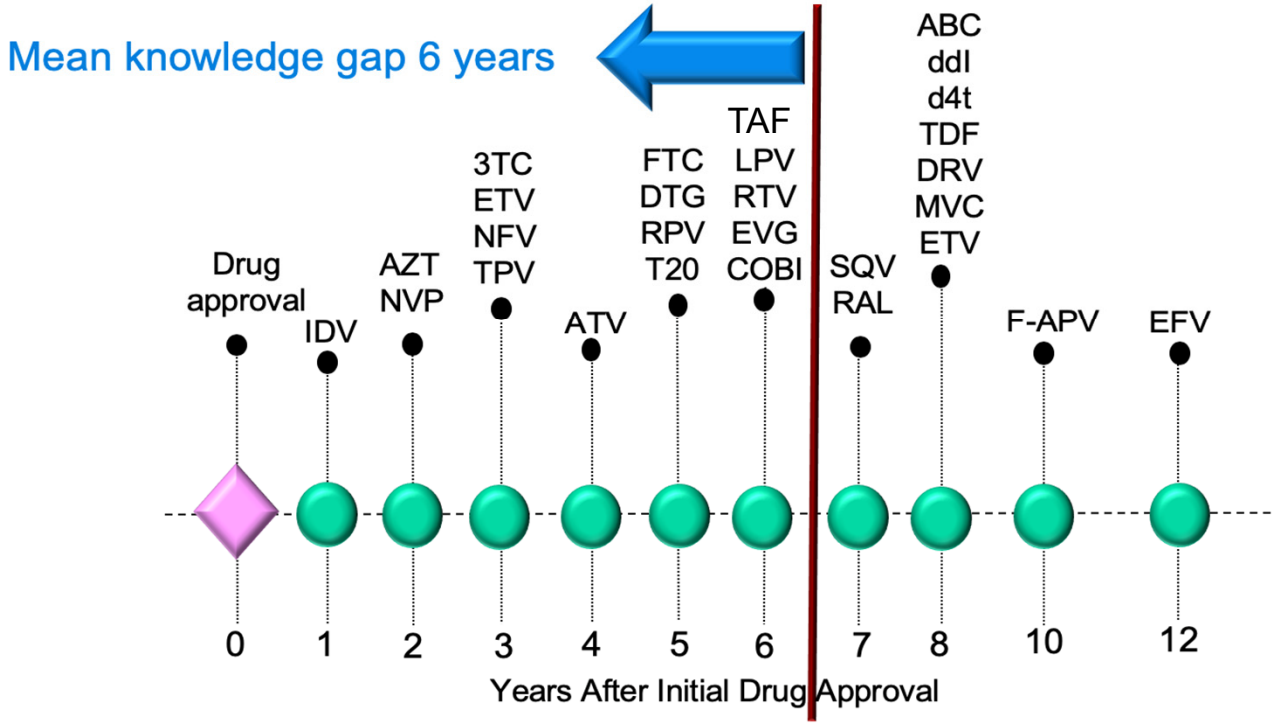
With a concerted effort to ensure that women are not left behind

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

- In 2020, there were an estimated 19.9 million women living with HIV and 600,000 women over 15 years old were newly acquired HIV infection in 2020[1]
- 225 million women have an unmet need for family planning annually.[2]
- **There were an estimated 1.3 million births to women living with HIV in 2020[3]**
- With expansion of 'treat all' and rollout of PrEP, **increasing numbers of women are conceiving while already on antiretrovirals** (ARVs).[1]
- **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**.
- Delayed introduction of new ARVs for pregnant and breastfeeding women limits regimen harmonization across populations and, in turn, impedes ART and PrEP scale up efforts

1 UNAIDS 2021; 2 Every Woman, Every Child 2015 ; 3 Start Free, Stay Free, AIDS Free 2021

Time from FDA drug approval to first published pharmacokinetics data in pregnancy, HIV drugs



Limited Data
Bictegravir (n=2)
Cabotegravir (n=3)

No published data
Doravirine
Ibalizumab
Islatravir
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 registrational 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 / lactating 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 **postmarketing 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

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Polly Clayton (HIV i-BASE)
Imelda Mahaka (Pangaea Zimbabwe AIDS Trust)
Jennifer Zech (ICAP at Columbia)

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

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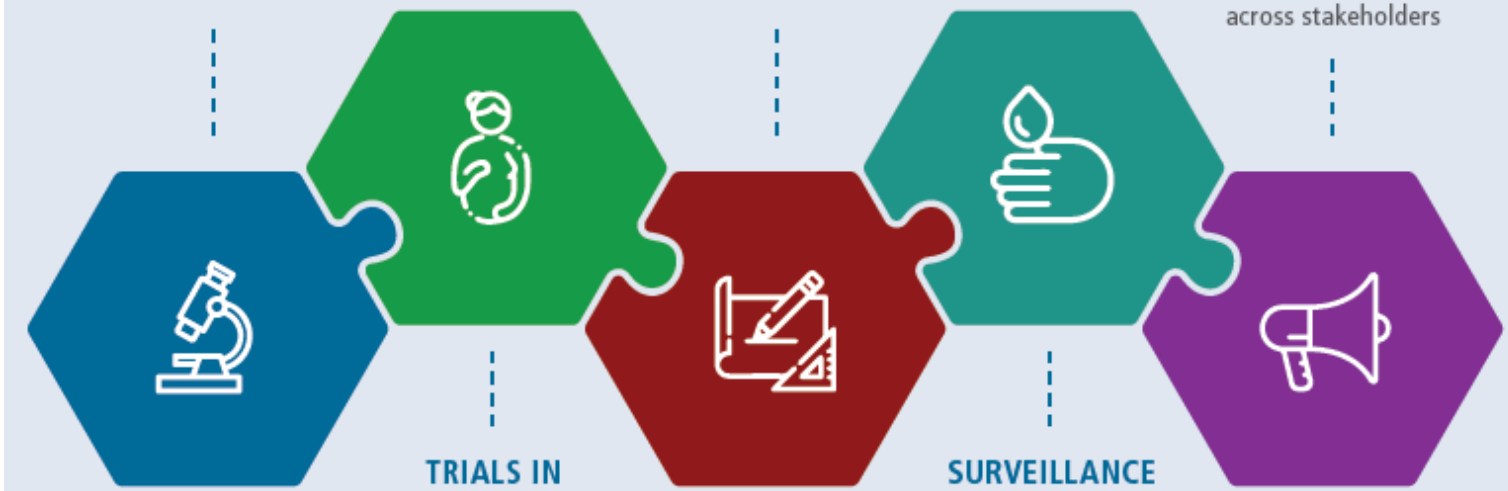
Workshop part 1
December 8th and 10th, 2020



NON-CLINICAL
Timing and interpretation of reproductive toxicity studies

TRIALS IN PREGNANT WOMEN
Inclusion of women who become pregnant and enrollment of pregnant women

STUDY DESIGN
Alternative and innovative study designs and methods

SURVEILLANCE
Strengthening existing active surveillance system and novel collaborative approaches

ADVOCACY
Identify advocacy objectives, actions and expected outcomes across stakeholders

Workshop part 2
July 6th-7th, 2021

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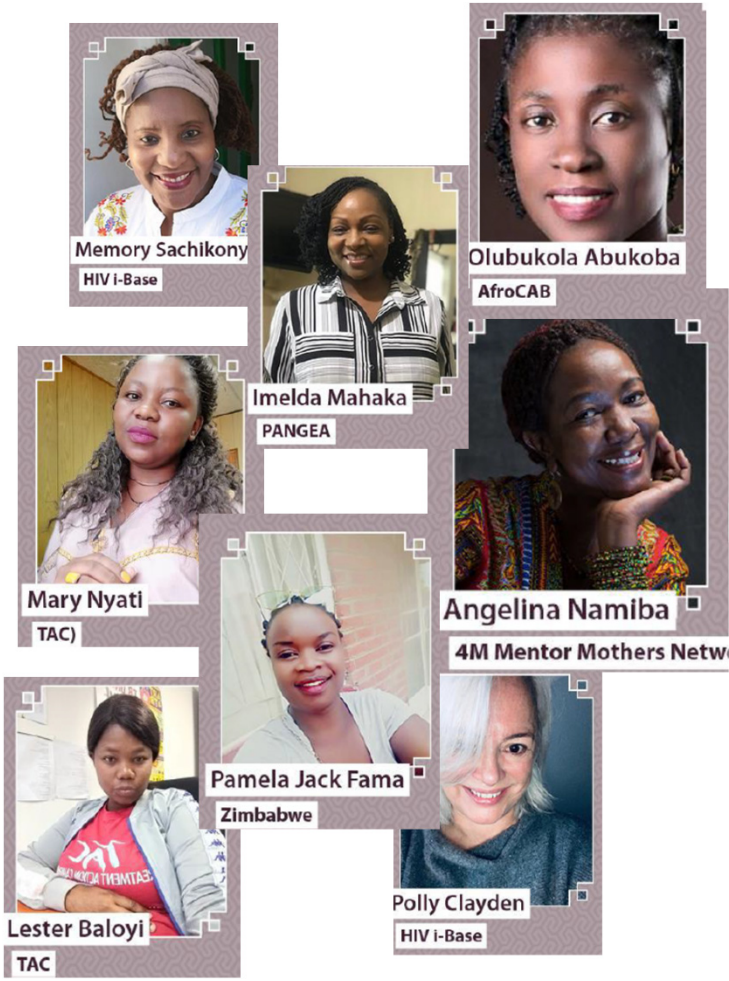
Women should be supported to CHOOSE whether to take part in a trial

- Women want and need a good evidence base for treatment in pregnancy
- Unfair/coercive to require contraception in order to take part in a trial
- Women can benefit directly from taking part in trials
- Essential to provide information in a clear and transparent manner
- Women should be involved in every stage of clinical trial planning and conduct



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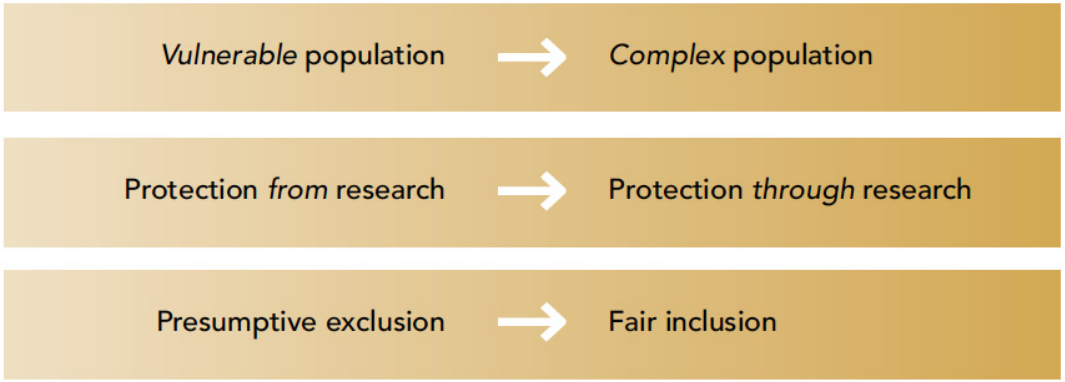
A paradigm shift is underway

- 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:

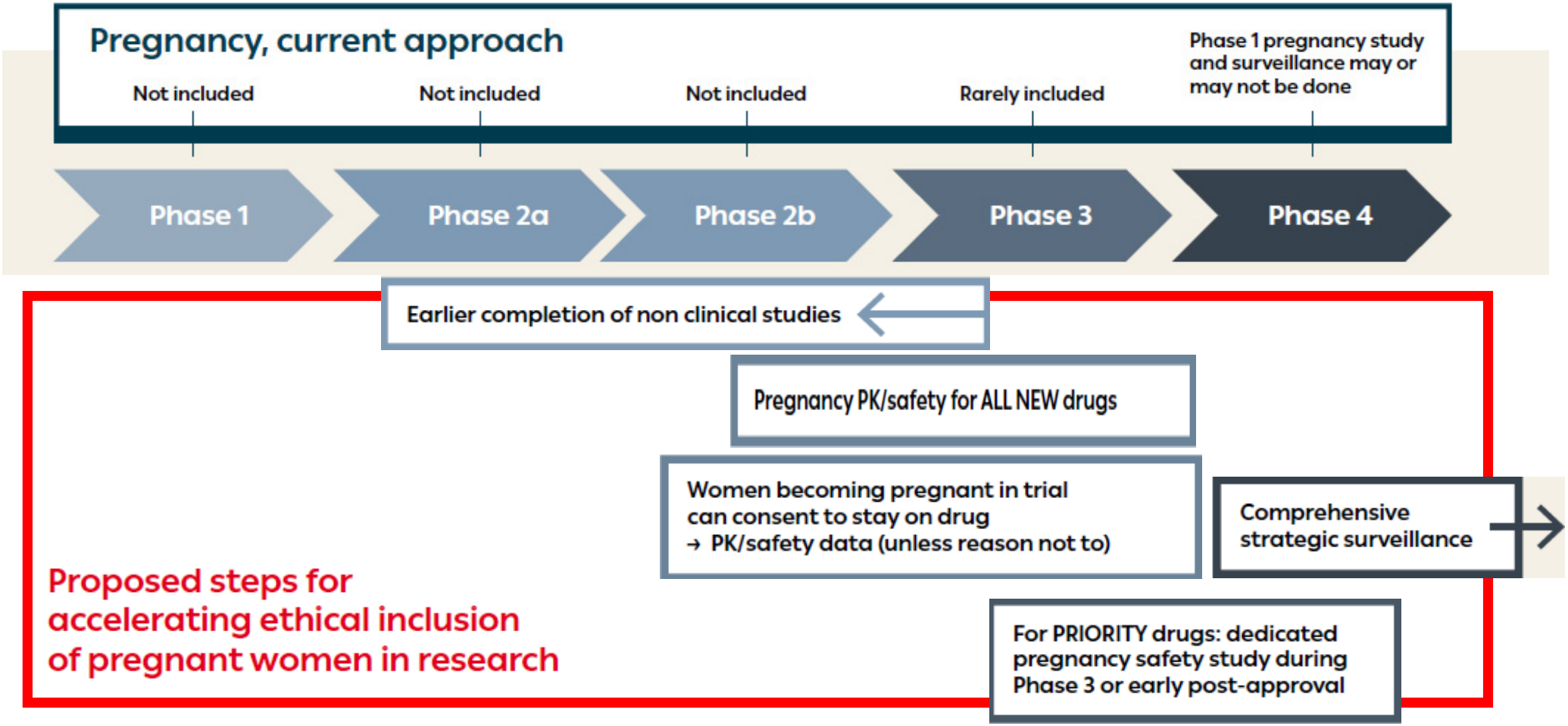


- **Paradigm shift requires a multi-stakeholder approach**

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

- **Involve women of childbearing potential affected by HIV** from the identification of research questions through the study design, recruitment, conduct and dissemination of results.
- **Perform non-clinical developmental and reproductive toxicology (DART) studies earlier** during drug development for all new HIV agents:
  - Fertility and early embryonic development (FEED) and embryo-fetal development (EFD) studies should be **completed during** or no later than the end of **Phase 2 registrational trials**.
  - Prenatal and postnatal development (PPND) studies should be completed **during early Phase 3** or no later than the end of Phase 3 registrational trials.
- **Women who become pregnant in pre-licensure trials should be given the option** to make an informed choice **to stay on study drug** and contribute pregnancy PK and safety data once non-clinical FEED and EFD studies are completed, with no negative signals and dosing is established in non-pregnant adults.
- **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**.
- **Investigate adverse pregnancy and birth outcomes** through dedicated pregnancy safety studies for all new **priority HIV agents** identified through CADO as soon as dosing in pregnancy is confirmed.
- **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.

Framework for accelerated inclusion of pregnant women in registrational clinical trials



To move from theory to practice we need urgent action

..but

No one can do this alone

..therefore

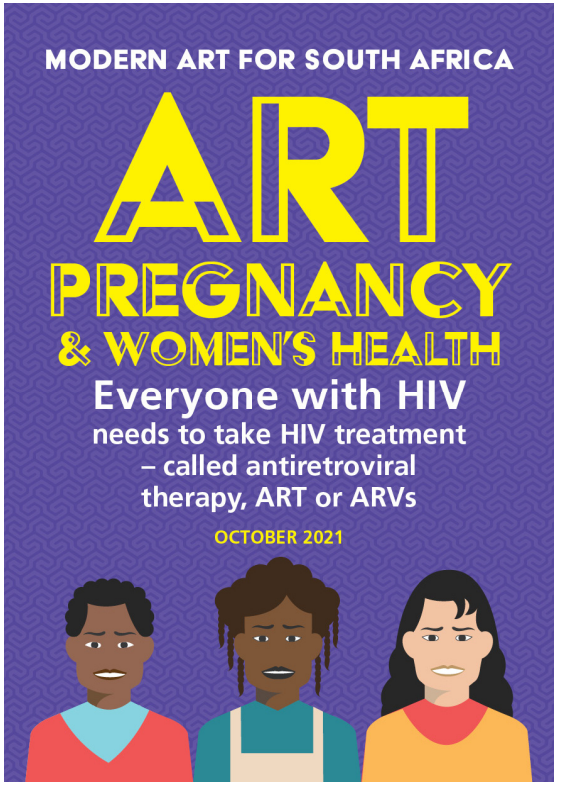
We need a concerted effort to ensure that women are not left behind

Stakeholders

- Civil society and community-based organizations
- Regulators
- Researchers
- Industry
- Funders
- Institutional Review Boards and Ethics Committees
- Publishers
- WHO

Civil society and community-based organizations

- Engage as **partners** in each stage of the HIV treatment and prevention research and surveillance process, including identification of the research questions, protocol development, study implementation, and results interpretation and dissemination.
- Take the lead in building **community literacy, peer education and advocacy** on the inclusion of pregnant women in pre-licensure trials and active surveillance programmes for HIV agents.
- Partner with researchers to develop **tools to aid in communication** about the need for clinical trials and surveillance in pregnancy and the interpretation and application of their findings when they are available.



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Regulators

- Develop **guidance** on the **acceptable minimal data** to include in the **product information** notice in order to enable pregnancy-specific studies.
- Revise expected **timing** of non-clinical **developmental and reproductive toxicity** studies so that they are **completed earlier** (as defined in the framework).
- **Encourage and support** allowing women who **become pregnant** in clinical trials to choose to **stay on the study drug** and contribute pregnancy PK and safety data (after dosing is established in PK studies in non-pregnant women and if no major concern is raised by non-clinical FEED/EFD studies).
- Identify ways to **encourage enrolment** of **pregnant women in Phase 3** pre-licensure of non-pregnant adults and in post-approval Phase 4 trials for priority agents for HIV treatment and prevention.

Regulators

- **Strongly recommend** that **PK in pregnancy** be available at the time of **licensure** of **all new agents** for HIV prevention and treatment.
- **Promote** the conduct of dedicated **pregnancy safety trials** for **priority** HIV agents (either during Phase 3 trials in non-pregnant women or early post-registration).
- **Promote and support** use of standardized and harmonized methods for **active surveillance of safety** of HIV agents in pregnancy.
- **Encourage** systematic reporting of **pregnancy safety data** from a network of sites or collected in active surveillance programmes to a **global pregnancy registry**.
- **Foster alignment between regulatory agencies** on the above-described key principles and their implementation.

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Researchers

- Promote and implement **study designs and novel research approaches** that **accelerate availability of high-quality evidence** on the PK and safety of new HIV agents in pregnancy.
- Develop in vitro and in silico methods to **better predict reproductive toxicity and drug exposure** in pregnancy and placental and milk transfer of new agents for HIV treatment and prevention.
- **Remove contraception restrictions** in HIV treatment and prevention pre-licensure trials once early non-clinical toxicity data are available, without major concerns, and dosing in non-pregnant women is established.
- Ensure that a **detailed community engagement plan is developed** for all research and surveillance for HIV treatment and prevention.
- **Develop a collaborative research infrastructure** to strengthen **systematic population data collection, registries and master protocols** to promote alignment and harmonization across studies.

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Industry

- **Conduct non-clinical reproductive toxicity studies earlier in drug development:** FEED and EFD studies should be completed during or no later than the end of Phase 2 registrational trials for all new ARVs; and PPND studies should be completed during early Phase 3 or no later than the end of Phase 3 registrational trials for priority agents.
- **Require inclusion of pregnancy investigation plans** aligned with the above-described principles for pre-licensure trials early during drug development for all HIV agents unless a justifiable scientific rationale exists.
- **Remove requirements for contraception** in HIV treatment and prevention prelicensure trials **once non-clinical toxicity data** (from FEED/EFD studies) are available, with **no negative signals**, and once **dosing** in non-pregnant women is **established**.

Industry

- **Allow and enable women who become pregnant in clinical trials to choose to stay on the study drug and contribute pregnancy PK and safety data** (**after** effective dosing is established for non-pregnant women **and if** no major concern is raised by non-clinical FEED/EFD studies).
- Determine **PK and dosing during pregnancy on all agents** for HIV treatment and prevention **before drug registration if** no major concern is raised by non-clinical studies.
- Support **dedicated pregnancy safety trials for priority agents** before or shortly after drug registration.
- Support **active surveillance of the safety of new HIV agents** used in pregnancy as these new agents are approved and introduced, with a focus on high prevalence countries.

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Funders

- Fund **studies investigating pregnancy PK** for all new HIV agents before drug registration.
- Fund **clinical trials** of adequate size to assess the **safety in pregnancy of high priority new agents** with expected broad use for treatment and prevention of HIV.
- Support a **global platform to strengthen active surveillance** of safety of HIV agents in pregnancy, building harmonization and linkages between surveillance networks, with a focus on the most-affected countries and populations.

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Institutional Review Boards and Ethics Committees

- Ensure that Institutional Review Board and Ethics Committee members can **access relevant expertise** for the **interpretation and application of results** of non-clinical developmental and reproductive toxicity studies.
- **Systematically require** and **assess the scientific rationale** when pregnant women are **excluded** from a study proposal and/or protocol.

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Publishers

- Strongly encourage **reporting of gender, pregnancy and breastfeeding status** for all HIV treatment and prevention studies that include women of childbearing potential, particularly randomized clinical trials.
- Strongly encourage provision of a **justifiable scientific rationale if women are not permitted to consent to stay on the study drug if they become pregnant or if pregnant women are excluded from enrolment** in Phase 3 pre-licensure and Phase 4 post-approval studies of new HIV agents.

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- Build on existing accountability frameworks, such as The Global R&D Observatory, to monitor R&D efforts to **enable earlier generation of evidence** to support use of new antiretrovirals in pregnant and breastfeeding women.
- Convene and facilitate a **standing expert group** to enable timely prioritization of new HIV agents and provide guidance on research priorities and surveillance for use of HIV agents in pregnant and breastfeeding women.
- **Continue to host active technical dialogue** to ensure development and updating of appropriate tools and policies to support implementation of accelerated approaches in research and innovations in surveillance to **generate high-quality evidence for new HIV agents in pregnancy**.

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Now let's hear directly from our stakeholders…

Video link

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Next Steps

- Utilize existing political platforms as galvanize commitment and promote accountability
- Journal supplement in JIAS for wide dissemination to the scientific community
- Continue the technical dialogue and implementation of strategic action through a WHO-convened working group

Thank you!

- Speakers
- Meeting participants
- All stakeholders involved

All of you who will help us succeed!

[Call to Action Announcement]

[Call to Action]

[Meeting Report]

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