Stakeholder perspectives on conducting PK studies in pregnant individuals

Public health and academic perspective

FDA-University of Maryland CERSI Pharmacokinetic Evaluation in Pregnancy Public Workshop- May 16, 2022

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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 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

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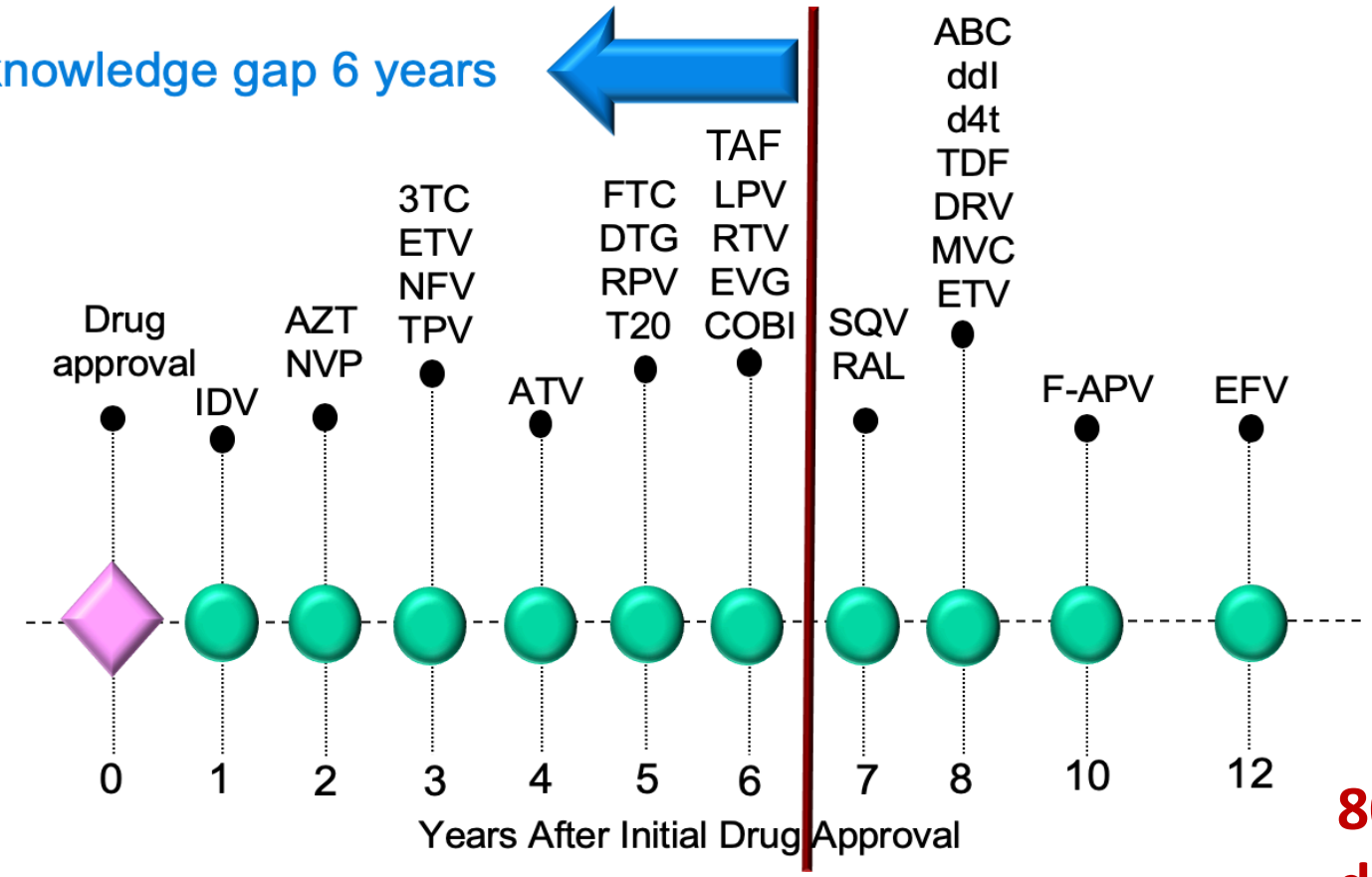
1 UNAIDS 2020; 2 Every Woman, Every Child 2015 ; 3 Start Free, Stay Free, AIDS Free 2021

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



Limited Data
Bictegravir
Cabotegravir

No published data
Doravirine
Ibalizumab
Islatravir
Lenacapavir

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

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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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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), "Ending the Evidence Gap for Pregnant Women around HIV & Co-infections", identified three major conceptual shifts that will facilitate the inclusion of pregnant women in research:
    1. considering pregnant women as a complex population rather than a vulnerable population
    2. moving from protecting from research to protecting through research
    3. promoting fair inclusion in, rather than presumptive exclusion from, clinical drug trials
- Paradigm shift requires a multi-stakeholder approach

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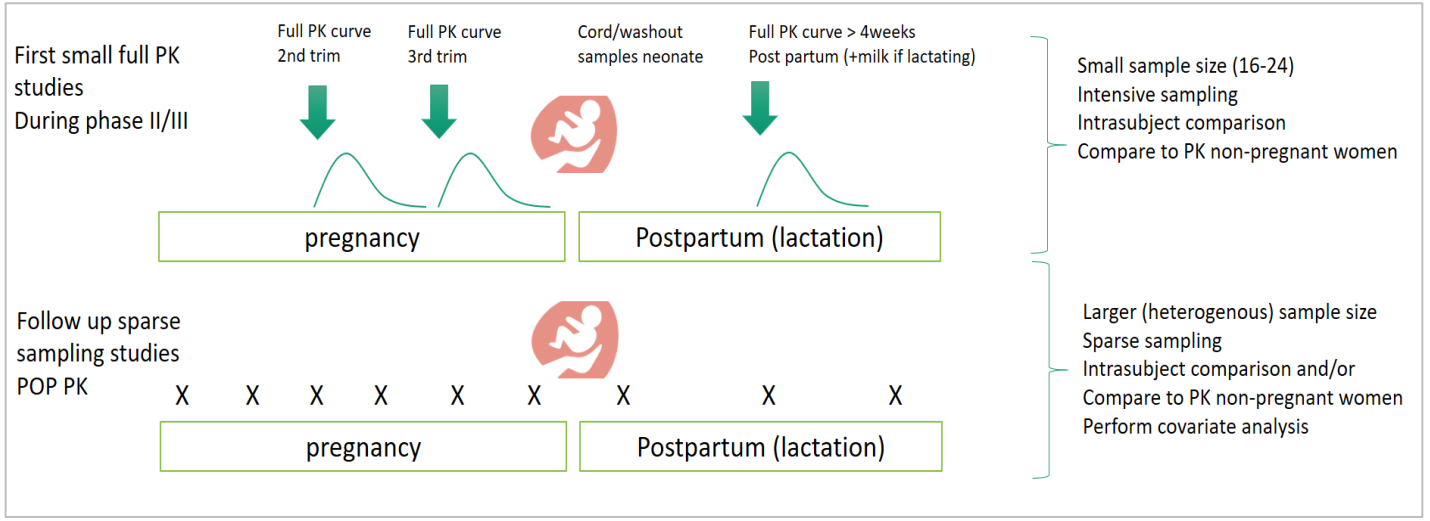
WHO & IMPAACT Dec 2019: advancing pharmacology studies in pregnant and breastfeeding women with HIV

Proposed approach to pharmacokinetic studies of ARVs during pregnancy and the postpartum period



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WHO & IMPAACT Dec 2020: “Approaches to Enhance and Accelerate Study of New Drugs for HIV and Associated Infections in Pregnant Women”

Organizing committee

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Alexandra Calmy (U of Geneva)
Shahin Lockman (Harvard U)
Angela Colbers (Radboud U)
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Polly Clayton (HIV i-BASE)
Imelda Mahaka (Pangaea Zimbabwe AIDS Trust)
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Academic researchers, regulators, clinical experts, industry leaders, funders, civil society, ethicists, other key stakeholders

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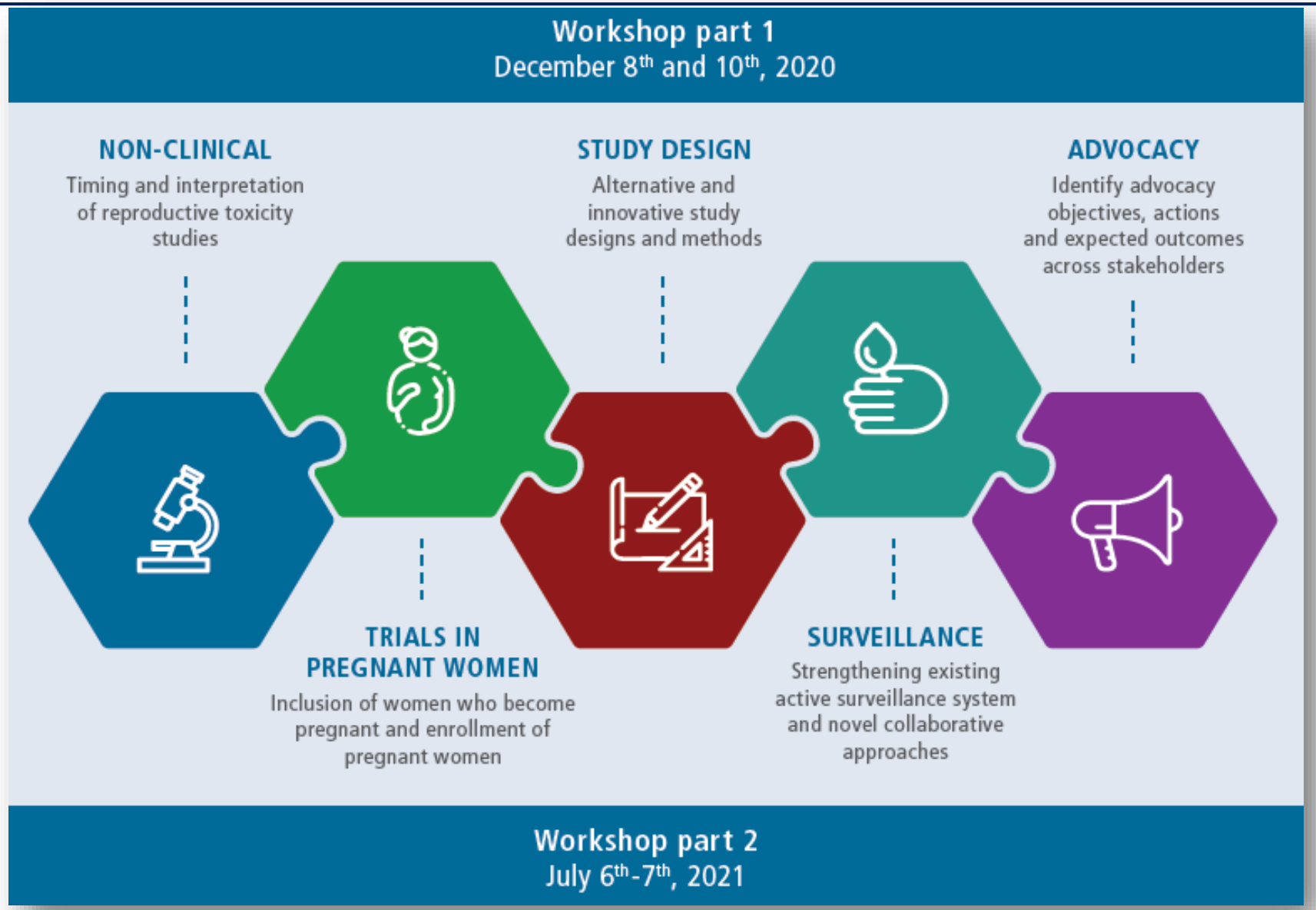

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Women should be supported to CHOOSE whether to take part in a trial

- 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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Key principles for studying new antiretrovirals in pregnancy

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

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

All new agents must to be studied in pregnant people 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 to during pregnancy once the ARV is licensed.

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

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A new framework to expedite the timelines for the study of new ARVs in pregnancy

Involve women of childbearing potential living with HIV from the identification of research questions through the study design, recruitment, conduct, and dissemination of results.
Perform non-clinical developmental and reproductive toxicology studies (DART) 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 the phase 2 registrational trials. • Pre- and postnatal development (PPND) studies should be completed during early phase 3 or no later than the end of phase 3 registrational trial
Women who become pregnant in registrational trials should be given the **option to make an informed choice to stay on study drug once early non-clinical FEED and EFD studies are completed**, with no negative signals and dosing is established in non-pregnant people.
Enroll pregnant women in specific studies to determine **PK and preliminary safety as soon as late non-clinical PPND studies are completed** with no negative signals for all new HIV agents.
Investigate adverse **maternal, pregnancy and birth outcomes through dedicated pregnancy safety studies for all new priority HIV agents** identified through CADO as soon as dosing is confirmed.
Expand systematic and rigorous active safety surveillance studies to enable systematic and rapid detection of adverse birth outcomes and rare events such as birth defects associated with exposure to antiretrovirals during pregnancy.

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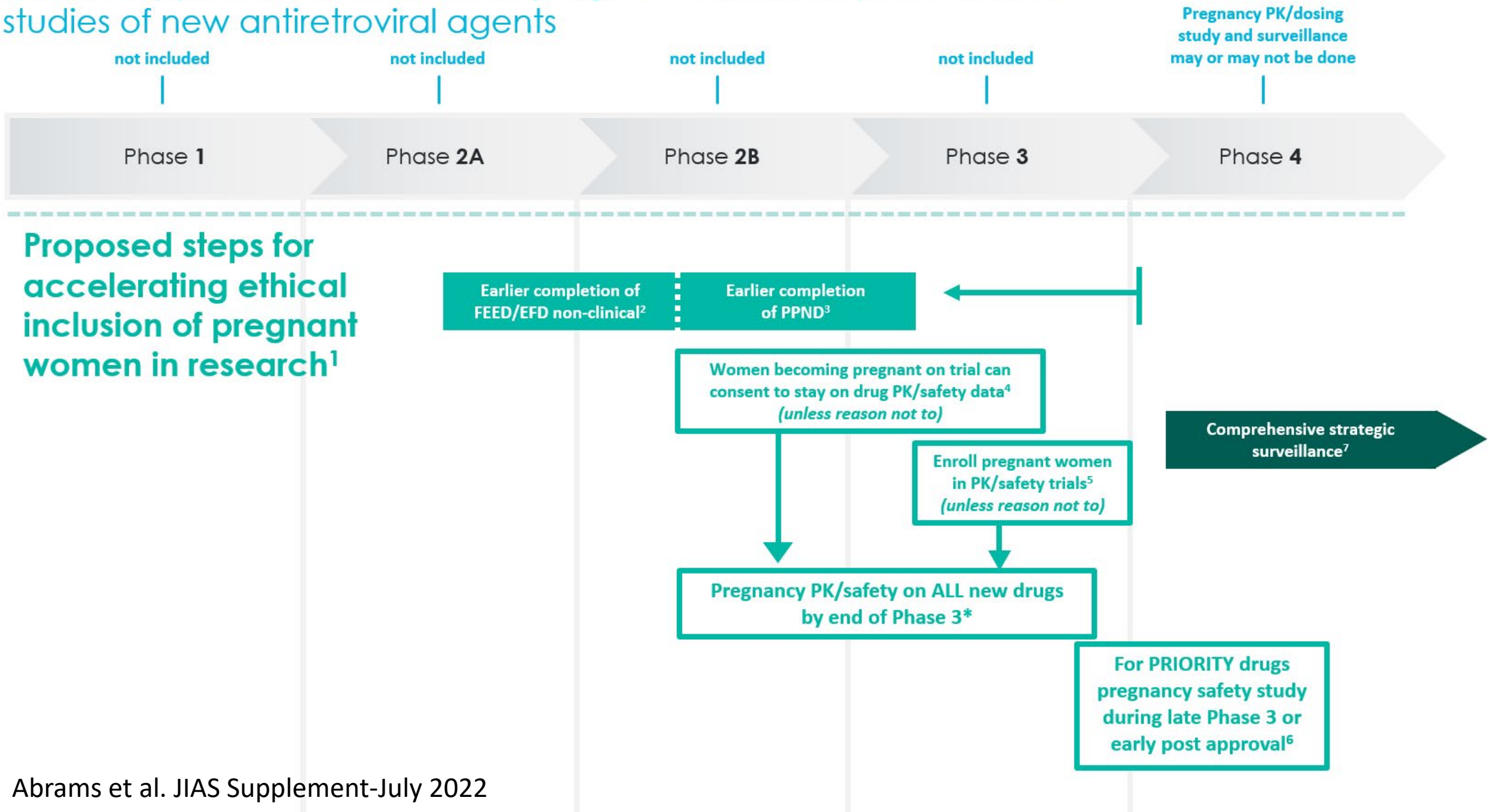

Abrams et al. JIAS Supplement-July 2022

New Collaborative Conceptual Framework for Surveillance of Safety of ARVs in Pregnancy

SAFETY DATA SOURCES

Pregnancy registries

- Scope and definitions
- ARV Pregnancy Registry (exposure registry)
- Congenital anomaly registries
- WHO global databases (e.g. vigibase)
- Funding agencies and sponsors

Cohort and surveillance studies

- Scope and definitions
- Birth defect surveillance programs
- European Pregnancy and Paediatric Infections Cohort Collaboration, The Tsepamo study (Botswana)
- Other initiatives (e.g., eSwatini, Kenya, South Africa)
- Technical partners and support agencies

Clinical studies

- Scope and definitions
- Ongoing studies and surveillance services for clinical studies
- Innovative studies
- Research agencies and sponsors

eHealth Databases

- Scope and definitions
- Medical records, medical claim databases
- Population based records e.g. EUROCAT
- Key partners

PLATFORM
Convening role
Consolidation
Communication

KEY ENABLERS

Data, harmonization and digitalization

- Scope, definitions, standards, data quality indicators
- Linkages
- Protocols, tools and materials
- Key partners

Regulations, guidance and research

- Drug Regulatory Authorities (FDA, EMA, NDRAS)
- WHO-led drug optimization work
- Systematic review and network meta-analysis
- Other reviews of evidence
- Surveillance, monitoring and research agenda
- Key partners and enabling grants

Public health approach for WHO ARV guidelines & Advisory Safety Committee of Medical Products

- Informing national and global policies on ARV safety in pregnancy for HIV prevention and treatment
- Maternal outcomes
- Pregnancy outcomes
- Birth outcomes
- Infant/child outcomes
- PreP outcomes

Renaud et al. JIAS Supplement-July 2022

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

Proposed steps for accelerating ethical inclusion of pregnant women in research[1]

Earlier completion of FEED/EFD non-clinical[2]

Earlier completion of PPND[3]

IMPACT 2026s/PANNA

Women becoming pregnant on trial can consent to stay on drug PK/safety data[4] *(unless reason not to)*

LENACAPAVIR

Enroll pregnant women in PK/safety trials[5] *(unless reason not to)*

Comprehensive strategic surveillance[7]

Tsepamo

Pregnancy PK/safety on ALL new drugs by end of Phase 3*

HPTN 084 extension

For PRIORITY drugs pregnancy safety study during late Phase 3 or early post approval[6]

VESTED IMPAACT 2010

Are there success stories to learn from?

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

- **Rolling protocols established to assess PK** and confirm dosing in pregnant and lactating women in post-marketing phase
- **Active surveillance** established that can prospectively follow multiple regimens and formulations and compare one to another in the postmarking phase
- **Removal of contraceptive requirement** and possibility of remaining on study drug (post-approval)
- Well conducted **dedicated safety study** assessing maternal, birth and infant outcomes
- **Removal of contraceptive requirement** and collection of PK data should participants become pregnant and choose to stay on the study drug (pre-approval).

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LENACAPAVIR

Tsepamo

HPTN 084 extension

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TO MOVE FORM THEORY TO PRACTICE we need urgent actions…BUT No one can do this alone…therefore We need a concerted effort to ensure that women are not left behind

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

Launched on Dec 1st, 2021

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

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.

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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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Next Steps

- Utilize existing **political platforms** to galvanize commitment and promote accountability.
- **Journal Supplement** in JIAS for wide dissemination to the scientific community.
- Continue the technical dialogue and implementation of strategic actions through **WHO-convened working group.**
- Leverage multiple fora to disseminate the key principles and **engage with the constituencies** that can contribute and take action.

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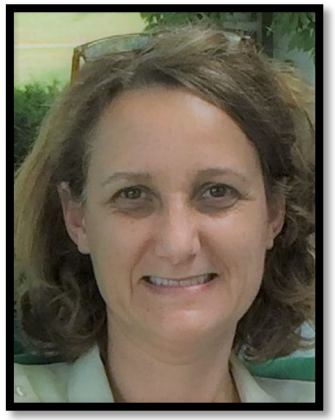

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Thank you

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