

Annexes to the 2022 Rome Paediatric HIV and TB Action Plan

ANNEX 1

Rationale for inclusion of commitments related to HIV medicines during pregnancy and breastfeeding

More than 19 million women are living with HIV worldwide and the majority are of childbearing age. There is a public health imperative to ensure that these women access new and better drugs to improve HIV treatment and reduce transmission. Historically, pregnancy safety and pharmacokinetic (PK) data for new drugs are routinely delayed by as much as a decade after initial drug approval. Over the past five years, multiple stakeholders have voiced their concerns around the exclusion of pregnant women from pre- and post-registration drug trials and the associated harms and risks of these policies for the health of the mothers and their babies. In this context, WHO and the IMPAACT Network, in collaboration with a range of key stakeholders, convened a consultative process to identify and refine optimal approaches to studying new HIV-related agents during pregnancy and breastfeeding. Based on the consultative process, workshop members developed and adopted a framework and key principles for accelerating inclusion of pregnant and breastfeeding women in pre-registration clinical trials, with a goal to generate PK and preliminary safety data on all new HIV agents in pregnancy available at the time of drug approval (Fig.1).

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

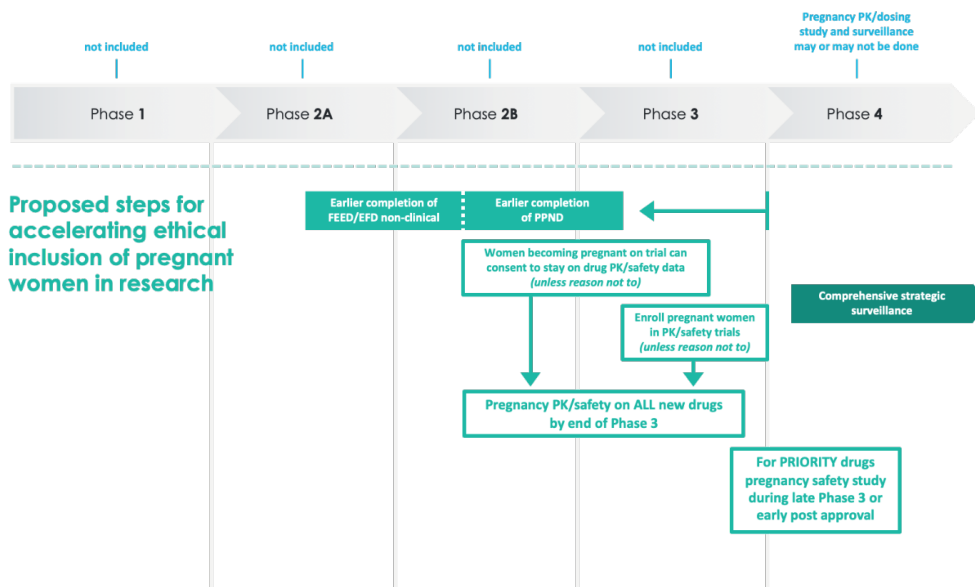


Figure 1. Framework for accelerated inclusion of pregnant women in pre-licensure clinical trials

(at: https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/call-to-action-to-accelerate-study-of-new-arv-for-pregnant-breastfeeding-women.pdf?sfvrsn=bb4febdc_14)

A Call to Action was launched on 1st December 2021 for stakeholders involved in studying antiretroviral agents for treatment and prevention of HIV to support greater inclusion of pregnant women and breastfeeding and contribute to a more equitable investigation of new HIV agents. With the momentum already generated, this dialogue is an opportunity to further move from theory to practice.

Research for informed choices: Accelerating the study of new drugs for HIV in pregnant and breastfeeding women



**World Health
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CIPHER
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A call to action

Equity demands that research is more inclusive of women

More than 19 million women are living with HIV worldwide and the majority are of childbearing potential. There is a public health imperative to ensure that these women can make informed choices about the drugs they take for HIV treatment or prevention. Information to support optimal antiretroviral drug choices in pregnancy has rarely been available for women or their health providers, largely due to historically protectionist and conservative approaches to clinical studies conducted in pregnant and breastfeeding women.

Pregnant and breastfeeding women are usually excluded from clinical trials of new agents pre- and post-licensure. Also, women of childbearing potential are typically under-represented in pre-licensure drug trials and are usually required to use dual contraception to participate. Furthermore, those who become pregnant while participating in a study must discontinue the study drug. Therefore, pregnancy safety and pharmacokinetic (PK) data for new drugs are routinely delayed by as much as a decade after initial drug approval if studies are performed at all. This results in substantial delays in women accessing new and better drugs. Additionally, despite the lack of data, these new drugs are prescribed for women of childbearing potential who become pregnant, as well as for pregnant women. This means that women have to make decisions about using new agents without adequate information about dosing or safety in pregnancy.

This lack of information from trials to guide the use of antiretrovirals in pregnant women shifts the burden of potential risk around drug safety from the clinical trial setting, where safety outcomes are carefully monitored, to the real-world clinical care setting, where safety outcomes are not systematically captured.

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.

For example, 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 inclusion of pregnant women in research. These shifts are: considering pregnant women as a complex population rather than a vulnerable population; moving from protecting from research to protecting through research; and promoting fair inclusion in, rather than presumptive exclusion from, clinical drug trials¹.

This paradigm shift requires a multi-stakeholder approach. Civil society and community-based organizations are increasingly demanding adequate information about the use of drugs in pregnancy. Some progress has been made in recent years to consolidate principles and forge consensus on the need to generate better data on HIV agents for pregnant women more rapidly. Building on ongoing efforts by regulators and the US PRGLAC Task Force², the World Health Organization (WHO)-convened Paediatric ARV Drug Optimization (PADO) and Conference on ARV Drug Optimization (CADO) groups have conducted expert consultations to discuss new principles for collecting more timely and complete data during pregnancy and breastfeeding³. The International AIDS Society’s Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) convened a series of stakeholder consultations on the preconception exposure of women to antiretrovirals and gathered the perspective of industry and regulators on challenges and opportunities to accelerate generation of evidence for pregnant and breastfeeding women.

Today, the COVID-19 pandemic continues to remind us of the importance of accelerating research during pregnancy. Many stakeholders rapidly implemented surveillance of COVID-19 vaccine pregnancy safety – an encouraging development. However, pregnant, and breastfeeding women were excluded from the vast majority of vaccine and therapeutic trials. This experience provides added momentum for this call to action.

The consultative process

Building on the efforts summarized above, WHO and the International Maternal Paediatric Adolescent AIDS Clinical Trials Network (IMPAACT) convened two consultative processes to identify and refine optimal approaches to studying the PK, safety and, as needed, efficacy of new HIV-related agents during pregnancy and breastfeeding. In June 2019, experts gathered to

¹ Ending the evidence gap for pregnant women around HIV & co-infections. The PHASES Working Group Pregnancy and HIV/AIDS: Seeking Equitable Study. July 2020.

² US Eunice Kennedy Shriver National Institute of Child Health and Human Development Task Force on Research Specific to Pregnant Women and Lactating Women <https://www.nichd.nih.gov/about/advisory/PRGLAC>

³ Abrams EJ, Mofenson LM, Pozniak A, Lockman S, Colbers A, Belew Y, Clayden P, Mirochnick M, Siberry GK, Ford N, Khoo S, Renaud F, Vitoria M, Venter WDF, Doherty M, Penazzato M; PADO and CADO Experts Groups. Enhanced and Timely Investigation of ARVs for Use in Pregnant Women. *J Acquir Immune Defic Syndr*. 2021 Apr 15;86(5):607- 615. doi: 10.1097/QAI.0000000000002597. PMID: 33298793.

review how best to investigate PK in pregnant and breastfeeding women and advised on the optimal timing and methods to undertake these studies⁴.

In December 2020, a virtual workshop was launched to further discuss approaches to accelerate investigation and evidence generation to inform safe use of new HIV agents in pregnant and breastfeeding women. Women living with HIV, academic researchers, clinical experts, regulators, industry, funders and other key stakeholders involved in studying HIV-related agents in pregnant and breastfeeding women participated in the process. The aims were to gain consensus on the optimal timing and design of studies of new agents for treating and preventing HIV and related conditions in pregnant women, identify strategies to accelerate the study of new agents in pregnancy, and formulate a strategic action plan for promoting the inclusion of pregnant women in research of new HIV agents. Following the December 2020 workshop, participants joined virtual workgroups to focus on five domains: non-clinical studies; trials in pregnant women; study design and methods; surveillance; and advocacy. The outcomes of these workgroup discussions were then shared with the workshop participants in a closing two-day session in July 2021.

Consensus on a new framework

Based on the consultative process, workshop members developed and adopted a framework for accelerating inclusion of pregnant and breastfeeding women in pre-licensure clinical trials, with a goal to have PK and preliminary safety data on all new HIV agents in pregnancy available at the time of drug approval.

The framework includes the following key principles:

- 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-foetal 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.

⁴ Eke AC, Olagunju A, Momper J, Penazzato M, Abrams EJ, Best BM, Capparelli EV, Bekker A, Belew Y, Kiser JJ, Struble K, Taylor G, Waitt C, Mirochnick M, Cressey TR, Colbers A; participants of the WHO-IMPACT workshop on “Approaches to Optimize and Accelerate Pharmacokinetic Studies in Pregnant and Lactating Women”. *Optimizing Pharmacology Studies in Pregnant and Lactating Women Using Lessons From HIV: A Consensus Statement*. *Clin Pharmacol Ther*. 2021 Jul;110(1):36-48. doi: 10.1002/cpt.2048. Epub 2020 Oct 15. PMID: 32930408; PMCID: PMC8167886

- Enrol 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 CADO⁵ 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.

While the above principles refer to specific agents for treatment or prevention of HIV, the group emphasized how these can also be applied to HIV associated infections and potentially adapted for other conditions that impact the health of women of reproductive age.

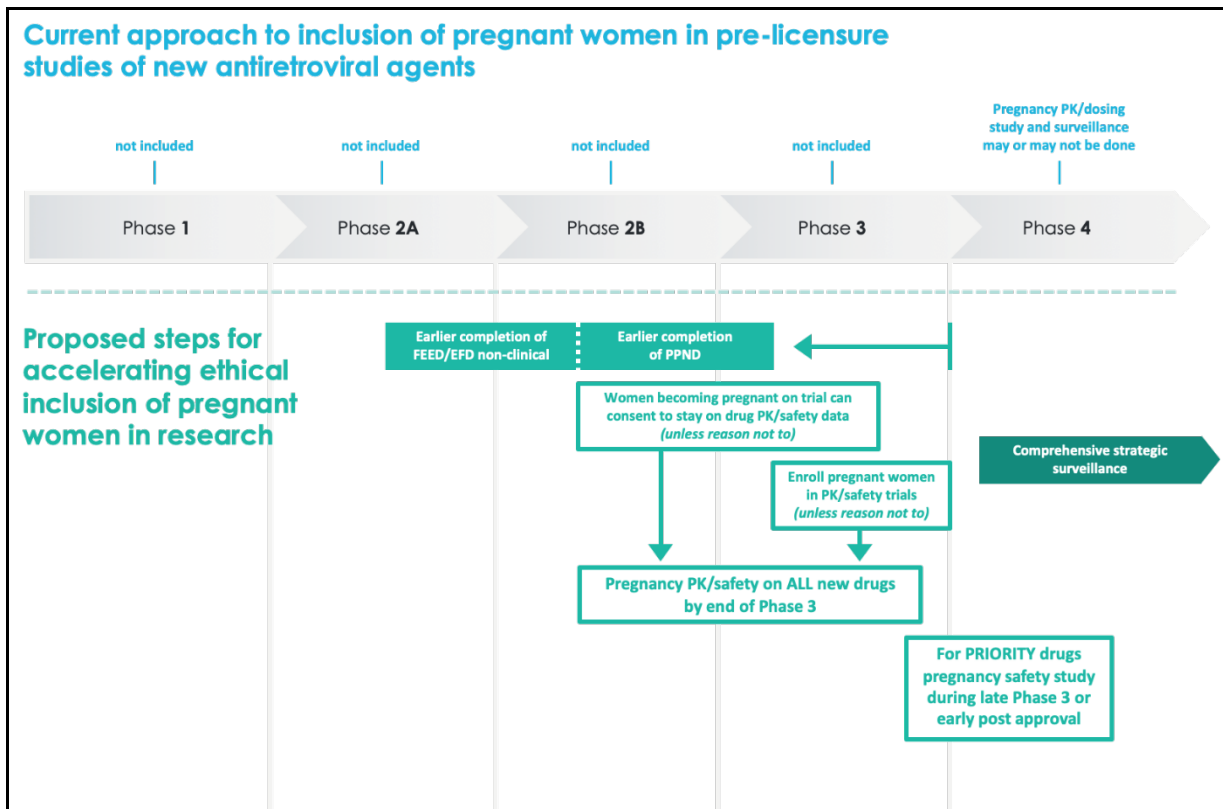


Figure 1. Framework for accelerated inclusion of pregnant women in pre-licensure clinical trials (at: https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/call-to-action-to-accelerate-study-of-new-arv-for-pregnant-breastfeeding-women.pdf?sfvrsn=bb4febd_c_14)

⁵ Conference on ARV Drug Optimization (CADO) <https://www.who.int/groups/antiretroviral-drug-optimization>

Call to action

Stakeholders involved in studying antiretroviral agents for treatment and prevention of HIV should support greater inclusion of pregnant women and breastfeeding and contribute to a more equitable investigation of new HIV agents in the following ways:

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.

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 pre-licensure 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.
- 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.

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, Figure 1).
- 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 and of non-pregnant adults in post-approval Phase 4 trials for priority agents for HIV treatment and prevention.
- 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.

Institutional Review Board 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.

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.

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.

World Health Organization (WHO)

- Build on existing accountability frameworks, such as The Global R&D Observatory⁶, 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.

⁶ <https://www.who.int/observatories/global-observatory-on-health-research-and-development>

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.

Outcomes and next steps

WHO and the IMPAACT network will work towards ensuring wide dissemination of the outcomes of the workshop to the broader scientific community and a wide range of stakeholders, including funders, research networks, affected communities, relevant innovator companies and regulatory agencies. Workshop participants will continue to engage on following up and supporting the implementation of the strategic actions identified and guided by the framework. Existing platforms will be leveraged to ensure appropriate monitoring and tracking of strategic actions and high-level commitments by the full set of stakeholders involved.

ANNEX 2

RATIONALE FOR INCLUDING COMMITMENTS RELATED TO TB CARE DURING PREGNANCY AND BREASTFEEDING & ASKS

Pregnant and postpartum women are a key vulnerable population who have a high risk of developing TB disease and having poor TB treatment outcomes, regardless of HIV status. Infants born to women with TB also have a higher risk of developing TB, with higher morbidity and mortality compared to those born to women without TB, regardless of maternal HIV status.

Historically, pregnant women have been systematically excluded from trials on the prevention and treatment of TB because of the potential teratogenic risks of new medications and the perceived complexity of studying pregnant women in trials. This approach has resulted in a lack of access to much-needed TB treatment and prevention regimens and agents, resulting in potential harm for women and their infants. Furthermore, most newer TB medications and regimens for prevention and treatment are used off-label in pregnant women, without any appropriate dosing or safety data in pregnancy, putting mothers and infants at risk.

Routine national TB surveillance systems currently do not capture data or report to WHO data on pregnancy status for TB preventive therapy (TPT) or for TB treatment, resulting in limited data on TB treatment outcomes in women and their infants.

Actions for considerations

Therapeutic research

1. For all priority existing licensed or routinely used TB drugs, the pharmacokinetics and safety of should be studied in pregnant women across therapeutic indications (TB prevention, TB disease, drug-susceptible and drug-resistant TB).

The research community, funders, industry and regulators should urgently address these research gaps in ongoing and future work for all priority first-line and licensed 2nd line drugs.

2. For new drugs, non-clinical developmental and reproductive toxicology studies should be conducted earlier during drug development for all new TB drugs/regimens
 - a. 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.
 - b. Prenatal and postnatal development (PPND) studies should be completed during early Phase 3 or no later than the end of Phase 3 registrational trials

Industry and regulators should urgently commit to addressing this gap.

3. For new TB regimens for prevention and treatment, pregnant women should be included earlier in therapeutic trials. The inclusion of pregnant women should be considered early in the design and implementation of TB trials, with a careful risk-benefit assessment for the timely inclusion and methods to do so. Pregnant women should be enrolled in specific studies to determine pregnancy PK and preliminary safety for high-priority TB drugs and regimens as soon as non-clinical prenatal and postnatal development (PPND) studies are completed with no negative signals.

Researchers, funders and regulators should collaborate to make the timely inclusion of pregnant women in TB trials a minimum requirement.

4. A pregnancy implementation plan should be developed early on, as for children (pediatric: <https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended>, <https://www.fda.gov/media/138489/download>, <https://toolbox.eupati.eu/resources/paediatric-medicine-paediatric-investigation-plan/>)

Regulators should request such a plan early on from industry, while adult phase 2 trials are being planned and implemented.

5. Women who become pregnant in pre-licensure trials should be given the option to make an informed choice to stay on study drug(s) (with reconsent) and contribute pregnancy pharmacokinetic PK and safety data if the two following conditions are met: (1) non-clinical FEED and EFD studies are completed, with no negative signals; and (2) dosing is established in non-pregnant adults.

Research groups, funders, regulators and civil society should ensure that this option is included in any therapeutic trial

6. Experts on TB in pregnancy should be included in expert groups⁷ to identify “high-priority” TB drug regimens for pregnant women, as for non-pregnant women, as is the case for children and adolescents. Experts should also be included in panels deliberating UNHLM requests to ensure that governments undertake commitments relevant to pregnant women affected by TB.

Policy makers and others should include experts and researchers in maternal TB, in addition to paediatric TB, in such panels. National TB programmes should report on progress made on TB indicators for pregnant and postpartum women.

7. Consultation should be undertaken with TB trial research groups, community stakeholders and regulatory authorities to inform research priorities and better understand preferences of pregnant women for TB prevention and treatment for both them and their infants. Women of childbearing potential affected by TB should, themselves, be involved in the identification of priority research questions, study design, recruitment, conduct and dissemination of results. Targeted qualitative research amongst pregnant women affected by TB should be undertaken by research groups in close collaboration with civil society.

Researchers, civil society, funders should collaborate on designing key data elements and to ensure that such data is collected in consultation with pregnant women before trials are planned and implemented

Specific requests for priority TB treatment regimens where pregnant women were excluded and where there are critical data gaps:

1. Drug-resistant TB: BPAL and BPAL-M: 6 -month all oral treatment of MDR and XDR-TB in adults: there is an urgent need for PK and safety data and pregnancy outcomes

⁷ e.g WHO Target Regimen Profiles for Tuberculosis Treatment, similar to the Conferences on Antiretroviral Drug Optimization (CADO) and the Pediatric Antiretroviral Drug Optimization (PADO) groups

- Regulators, funders and industry should work with researchers to generate this data as a priority
2. Drug-susceptible TB (4-month TBTC Study 31 short regimen regimen): Rifapentine + HZE/ RPT+Moxi +HZ
Researchers, regulators and funders should have a consultation which includes pregnant women, on the risk/benefit studying pregnant women on this regimen
 3. Drug-susceptible TB infection: The PK and safety of 1HP and 3HP should be studied as a priority
Researchers and funders should undertake trials on the safety, PK and effectiveness of 1 HP and 3 HP during pregnancy
 4. Drug-resistant TB infection: The PK and safety data on delamanid and levofloxacin should be studied in pregnant and postpartum women as a priority
Researchers and funders should undertake PK and safety studies which include pregnant and postpartum women receiving levofloxacin and delamanid, respectively, for MDR-TB prevention
 5. The pharmacokinetics and safety data on all priority first line and all licensed 2nd line TB drugs used as standard of care should be urgently determined and shared, where lacking.
Researchers and funders should undertake PK and safety studies which include pregnant and postpartum women receiving bedaquiline, delamanid, levofloxacin, moxifloxacin, linezolid, clofazimine, terizidone and rifapentine

TB vaccine research

Given the unprecedented number of TB vaccine candidates already in or soon to enter phase III trials, the following are key priorities:

1. TB vaccines developers should commit a combined cross-study effort to collect standardized information on maternal, infant, and pregnancy outcomes among women who become pregnant after enrolling in vaccine studies.
2. TB vaccines developers should design for inclusion by committing to generate supporting evidence, such as DART studies, early enough to enable the inclusion of pregnant women in efficacy trials.
3. TB vaccines developers should commit to collecting improved data on TB incidence and IGRA positivity during pregnancy, by incorporating pregnancy into the preparatory epidemiological studies that will precede phase III trials.

TB vaccine developers, researchers and regulators should prioritize the earlier inclusion of pregnant women in TB vaccine trials and jointly develop a standard approach (master protocol) for inclusion and data collection

Programmatic implementation and surveillance

1. Surveillance data on TB and pregnancy and the postpartum period, including treatment outcomes. should be included in national TB programs and in clinical research, where more detailed data can be collected. National TB programmes should consider including pregnancy status and trimester as an indicator in TB treatment and TB prevention (TPT) registers. Where feasible, pilot or demonstration projects should be implemented to assess the feasibility and utility of such data.

NTPs should work towards the inclusion of pregnancy indicators for TPT and TB treatment.

Researchers should ensure that planned WHO-commissioned global data curation on MDR-TB IPD and meta-analysis in adults, adolescents and children should also include pregnant women going forward.

2. Policy makers and TB programmes should ensure that current TB screening recommendation relevant to pregnant women in current WHO TB screening guidelines: <https://www.who.int/publications/i/item/9789240022676> are better implemented and tracked

WHO encourages NTPs to improve screening for TB in pregnant and postpartum women as per current recommended WHO screening guidelines

3. Researchers and industry should be encouraged to more systematically report on pregnancy safety data and contribute data through the development of a centrally coordinated global TB pregnancy registry. This should include pregnant women included in trials and women who become pregnant on studies. Data should include TB treatment outcomes, maternal and infant outcomes (clinical trials and observational studies). Active surveillance should be expanded to collect better quality drug safety in pregnancy to enable systematic and rapid detection of adverse maternal, pregnancy and birth outcomes, especially rare events, such as birth defects.

Regulators, industry and researchers should urgently collaborate and share data to support the implementation of a centrally coordinated global trial registry for TB during pregnancy and the postpartum period