

## EXECUTIVE SUMMARY

# Ending the evidence gap for pregnant women around HIV & co-infections:

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## A CALL TO ACTION

The PHASES Working Group  
Pregnancy and HIV/AIDS: Seeking Equitable Study

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This work is a product of The PHASES Working Group. PHASES is a grant-funded project led by faculty at the University of North Carolina at Chapel Hill alongside co-investigators at Georgetown University and Johns Hopkins University with contributions from Working Group members.

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The recommendations, interpretations, and conclusions expressed in this work do not necessarily reflect the views of the institutions with which Working Group members are affiliated.

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# Ending the evidence gap for pregnant women around HIV & co-infections: A call to action

## EXECUTIVE SUMMARY

### The PHASES Working Group

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## Introduction

**G**lobally, at any given time, 1.3 million women are living with HIV while pregnant.<sup>1</sup> HIV brings special risks during pregnancy. The risk of perinatal transmission is the most well known, and its prevention is widely recognized as a continuing, critical goal for global health.<sup>2</sup> More recent evidence has also pointed to the risks maternal HIV carries to offspring even when the child does not become infected: higher rates of preterm birth, poor fetal growth, stillbirth,<sup>3</sup> and worse outcomes that may stretch into childhood.<sup>4-7</sup>

For women living with HIV, pregnancy is also a time of heightened risk for their own health. HIV increases the risk of deadly obstetrical complications, such as sepsis—a life-threatening reaction to infection—after delivery.<sup>8,9</sup> Pregnancy-specific changes to heart function, lung capacity, and immune response make pregnant women more susceptible to some of HIV’s most deadly co-infections. Tuberculosis is a leading cause of maternal mortality among women living with HIV; malaria, HIV, and pregnancy together form a deadly combination.<sup>9</sup> Overall, women living with HIV face up to a tenfold increase in the risk of dying during pregnancy and the postpartum period compared with women not living with the virus.<sup>9</sup>

For women living in areas of high HIV prevalence, pregnancy is also a time of heightened risk for acquiring HIV in the first place.<sup>10</sup> Biological changes in pregnancy, as well as challenges in negotiating partner condom use during pregnancy, increase the likelihood of infection upon exposure to the virus and put pregnant women at especially high risk.<sup>10,11</sup>

Pregnant women, in short, are among those most in need of safe and effective preventives and treatments for HIV and co-infections. Yet they are among the least likely to have robust, timely evidence to inform decisions around use of medications. While the HIV research community has a notable history of conducting research with pregnant women—from efforts in the 1990s to address prevention of perinatal transmission to more recent vanguard studies—critical and systemic patterns of exclusion in the broad HIV/co-infection space nonetheless persist.

“ *Pregnant women are among the least likely to have robust, timely evidence to inform decisions around medication.* ”

Pregnant women have been excluded from most drug development trials of new interventions, including most large trials of pre-exposure prophylaxis (PrEP) to prevent HIV,<sup>12–15</sup> new antiretroviral therapies,<sup>16,17</sup> and drugs for HIV’s deadliest co-infections: tuberculosis (TB) and malaria.<sup>18–20</sup> Most post-approval research continues to exclude pregnant women and to remove women who become pregnant during a clinical trial from the study drug. Research specifically dedicated to pregnant women, while increasing, remains highly uneven across areas of need and often occurs only years after the drug in question is approved. And when the research agenda does attend to pregnancy, attention can focus disproportionately on fetal outcomes, without equal or adequate attention to issues around the pregnant woman’s own health.

## Key evidence gaps and their costs

The resulting evidence gaps and delays are significant—and put pregnant women and their children in harm’s way.

**First are issues of dosing.** Most HIV and co-infection drugs come to market with no pregnancy-specific dosing information—despite the fact that the pregnant body can radically change how drugs are processed.<sup>21–24</sup> When data are gathered in studies conducted after the drugs are approved, it is usually with long lag times, years after being prescribed to pregnant women.<sup>22,25</sup> Other times, they are lacking still. Pregnancy-specific dosing data are almost completely lacking for combinations of antimalarials and antiretrovirals in pregnant women,<sup>26,27</sup> and again for TB treatment during pregnancy.<sup>18,28</sup>

“ *The resulting evidence gaps and delays are significant—and put pregnant women and their children in harm’s way.* ”

➔ Guesswork on dosing can be costly. Pregnant women are sometimes inadvertently underdosed—prescribed a regimen that will inadequately reduce HIV viral load.<sup>29,30</sup> In other cases, doses may leave a pregnant woman with more medicine in her system than is needed, exposing her to heightened toxicities, drug interactions, or side effects that can lead her to switch to a less optimal regimen.<sup>31,32</sup>

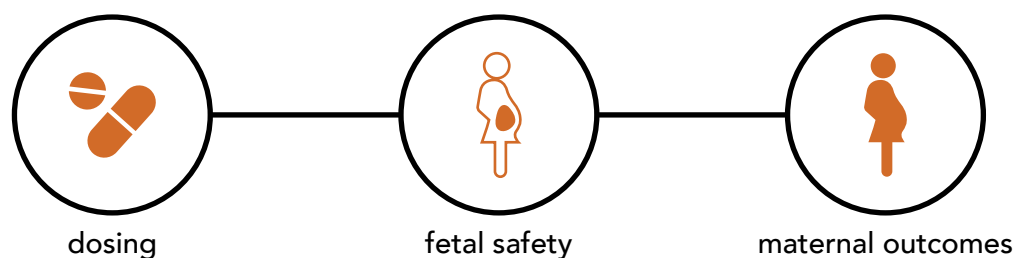
**Second are issues of fetal safety.** Most HIV and co-infection drugs come to market with only animal data to inform questions of fetal safety. In-human data is left to be gathered in postmarketing registries or potential independent research that may occur, and remains starkly limited and marked by extensive delay.<sup>33,34</sup>

➔ Gaps and delays in fetal safety assessment matter—for two reasons. Of most obvious concern is the possibility that medications prescribed to pregnant women may be unsafe for the fetus, carrying elevated risk of birth defects (teratogenicity) or potential effects on the fetus’s growth. A second cost exists even when—as often happens—the drug in question turns out to have a favorable risk-benefit balance: barriers to pregnant women accessing the benefits of new drugs. Providers and policymakers are often reticent to endorse the use of a drug during pregnancy until robust in-human data on fetal safety are available—which can take many years after drug approval. Gaps and delays in evidence leave pregnant women among those last in line to receive the benefits of next-generation drugs.

**Third are issues of maternal outcomes.** Few drugs used in HIV, TB, or malaria have a well-evidenced assessment of potential pregnancy-specific risks. Drugs prescribed for the benefit of fetal health may carry risks that are specific to—or specifically heightened for—pregnant and delivering women, such as elevated risks of life-threatening preeclampsia, dangerous liver toxicities, or hemorrhage after delivery.<sup>35</sup>

➔ This is problematic not only as an issue of potential harm, but also of respect for the independent value of the woman’s health. Without adequate research attention to maternal outcomes, a drug that is deemed safe and effective in terms of fetal health may in fact be harmful to the pregnant woman. A focus on fetal outcomes tells only half the story.

**fig 1**  
Key  
evidence  
gaps



## Ethical foundations

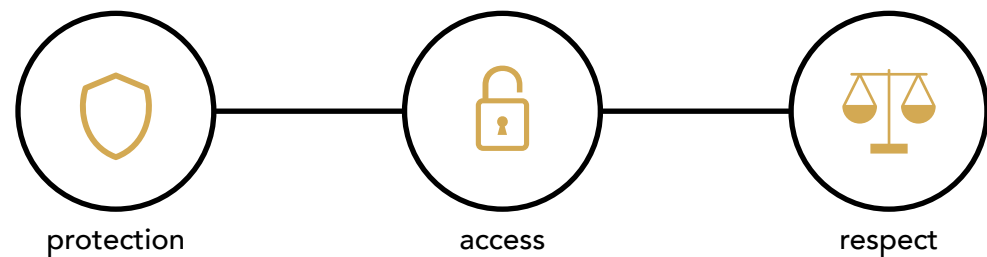
The ethical responsibility to address inequities in the evidence base for the use of medications during pregnancy is based on three ethical foundations.

**Equitable protection from drug-related risks.** An animating mission of all research is to gather evidence under carefully controlled and regulated contexts to decrease risks in the clinical care setting. Pregnant women, no less than any other population, deserve this protection against risks to themselves and their future offspring. Adequate research is essential to realizing the fundamental public health obligation of ensuring that the drugs taken by people—including pregnant women—meet an acceptable safety threshold.

**Equitable access to first-line medications.** Pregnant women deserve timely access to the most effective advances medicine can offer, both for their health and the health of the children they bear. Delays and gaps in evidence are a major barrier to meeting this goal. A commitment to better, earlier evidence is critical to ensuring pregnant women’s equitable access to needed preventives and treatments.

**Equitable respect for pregnant women’s own health.** When research is conducted, it is crucial that attention to fetal and child outcomes do not overshadow attention to maternal outcomes. Drugs used during pregnancy are often prescribed or chosen in part to benefit the child. It is critical to ensure that such decisions reflect due consideration of the woman’s health as well. Not to do so inadvertently treats a woman as a mere vector of disease or vessel for her child, not a person whose health and well-being matter in their own right.

**fig 2**  
Three ethical  
foundations



## A pathway to progress

The purpose of this Guidance is to provide concrete and immediately actionable recommendations, grounded in ethical principles and consistent with current regulations, for better advancing timely, needed, responsible research with pregnant women in the HIV/co-infection research agenda.

The Guidance represents the efforts of a 26-member international, interdisciplinary, and intersectoral working group, convened as part of the PHASES (Pregnancy and HIV/AIDS: Seeking Equitable Study) Project, a seven-year effort funded by the U.S. National Institutes of Health. The Working Group includes experts in bioethics, public health, law, obstetrics and maternal-fetal medicine, pediatrics, HIV research, infectious disease, and pharmacology, as well as community advocates for women living with HIV; and includes members from Botswana, Kenya, Malawi, South Africa, Switzerland, Uganda, the United Kingdom, and the United States.

The Working Group's deliberations were informed by extensive research conducted by the PHASES Project. Project-based efforts include a qualitative study with 140 pregnant and recently pregnant women in the United States and Malawi; commissioned country-specific legal briefs; a series of workshops with representatives from North America, South America, sub-Saharan Africa, Southeast Asia, and Europe; and consultations with over 150 subject area experts, including HIV and co-infection researchers, clinicians, research oversight officials, legal scholars, regulators, and policymakers from around the world.

The 12 resulting recommendations are directed to multiple stakeholders in the research and advocacy communities addressing HIV and key co-infections, including pharmaceutical companies and regulatory agencies, research agenda setters and funders, researchers and those involved in research oversight, and community research advisors. Together, these recommendations aim to advance the three key ethical objectives of equitable protection, access, and respect.



# RECOMMENDATIONS



## Building capacity

### 1. Affirm the need for research with pregnant women

Organizations with influence over the development, research, regulatory approval, guidance development, and use of HIV/co-infection drugs should affirm the imperative for responsible research with pregnant women to achieve a timely and equitable evidence base.

Common misperceptions about pregnant women's eligibility for research participation, coupled with a historical culture of risk aversion around pregnancy, have led to patterns of excluding pregnant women from research that far outstrip regulatory restrictions and ethical constraints. Anticipating difficulty in approval, researchers and funders who might otherwise be interested in conducting such research may be discouraged from conceiving or proposing research with pregnant women. While resources, both human and financial, will be needed to enable such research, affirmation of the critical need for and ethical appropriateness of such research is thus a critical effort in its own right. Key stakeholders and agenda-setters can play a key role in changing the research culture from exclusion to integration of pregnant women in the HIV/co-infection research agenda.

### 2. Formalize a global network for advocacy and resources

The global HIV/co-infection research and advocacy communities, supported by funders, should formalize a network dedicated to advancing needed research with pregnant women. This network should facilitate research with pregnant women by creating a portfolio of shared resources to empower researchers to pursue, and enable oversight committees to effectively evaluate, studies that meet the needs of pregnant women.

While there are helpful advocacy efforts, tools, and educational resources around research with pregnant women in the HIV/co-infection space, their efforts are dispersed and often based on temporary funding. Funders of HIV and co-infection research and global health programs can strongly increase needed research by providing financial resources for a longer-term advocacy and resource network whose dedicated purpose is to support pathways to research with pregnant women.

### 3. Enhance training

Those involved in the conduct, monitoring, oversight, and community consultation of research in the HIV/co-infection space should be provided training in the ethical and legal issues relevant to research with pregnant women.

Lack of information or misunderstandings about the design and permissibility conditions of research with pregnant women represent a strong barrier to needed research. Those involved in research and its oversight may lack understanding of the regulations, ethical frameworks, and best practices around research with pregnant women, which could offer confidence to pursue and approve research that meets appropriate ethical and regulatory standards. Confusion around regulatory and ethical eligibility criteria, in particular, can keep researchers from contemplating, oversight committees from approving, and community partners from endorsing needed research with pregnant women. Capacity building in this area, which can take advantage of or build on excellent existing modules, is thus essential to enabling needed research.



## Supporting inclusion

### 4. Design for inclusion

Researchers designing trials addressing HIV/co-infections should commit to a goal of integrating pregnant women wherever possible and optimizing opportunities to gather pregnancy-specific data.

Because pregnant women are such significant, distinctive, and important end-users of preventive and treatment drugs for HIV/co-infections, it is critical that trials make best use of opportunities to gather pregnancy-specific data. As part of the research community's collective responsibility to provide adequate protection and reduce delays in access to needed drugs for pregnant women, researchers designing trials of HIV/co-infection treatments and preventives should proactively seek designs that will allow for the inclusion of pregnant women and optimize opportunities for gathering pregnancy-specific data. Inclusion in trials can create valuable knowledge-gathering opportunities, including opportunities to provide the in-human data that guidelines often look for before recommending use during pregnancy.

## 5. Review for and facilitate inclusion

Regulatory review sections, research ethics committees, and funders of HIV/co-infection research should require proposed clinical trial protocols to provide justification whenever pregnancy is indicated as a criterion for exclusion or removal from a trial, and should proactively support and incentivize inclusive designs.

Currently, regulations require protocols to justify the eligibility of pregnant women's enrollment or retention in a study, but no justification is required for excluding them.<sup>36</sup> Regulatory review sections, research ethics committees, and funders of research can be important drivers of cultural change away from the summary exclusion of pregnant women in research by shifting this justificatory burden. They can also encourage and facilitate inclusive designs through specific incentives and supports: funders can incentivize research with pregnant women through preferential funding; regulatory review sections can facilitate matchmaking between independent academic researchers and interested industry partners; and RECs can proactively work with investigators to identify approvable designs.

## 6. Ensure equitable research on pregnant women's own health

Agenda setters in HIV/co-infection research should commit to equitably promoting the study of pregnant women's own health needs as a key pillar of effort and funding. Research into fetal safety outcomes should be matched by relevant maternal outcomes assessments to ensure that decisions about whether and which options to pursue during pregnancy are made with equitable consideration of the pregnant woman's health.

Pregnant women are entitled to have their own health needs taken into account, not just the health needs of the fetus, in decisions of whether and which drugs to use. Without research directed at both maternal and fetal outcomes, it will be impossible for clinical care or public health programs to offer guidance that accounts for the full profile of considerations needed to ethically serve the interests of both pregnant women and the children they bear. This is especially important given the historical patterns in HIV, which in early years attended centrally to the pregnant woman as a vector of HIV transmission rather than an end in herself. Adopting a commitment to equity is thus essential.



## Achieving priority research

### 7. Integrate pharmacokinetic (PK) studies

Plans for pregnancy-specific pharmacokinetic (PK) studies should be integrated into new drug development plans and performed as early as possible, ideally before licensure, for all new preventives and treatments anticipated to be used during pregnancy.

While pregnant women's access to drugs should not be made contingent on the availability of pregnancy-specific PK data, new drugs should reach market with pregnancy-specific dosing information in hand at the time of licensure, or as soon as possible after regulatory approval. Shifting the timing of available PK data in pregnancy to the time the drug is being reviewed for approval as a routine matter

will help ensure appropriate dosing across drug options upon rollout. This recommendation can be achieved through commitments from the drug industry, encouragement from regulators, and support from funders.

## 8. Enhance post-approval safety evaluations

The HIV/co-infection research community should commit to a more robust and regularized structure of post-approval safety evaluations to ensure both adequate pharmacovigilance and pregnant women's timely access to important drugs. This includes expanding prospective registries, conducting timely prospective observational studies for drugs in widespread use during pregnancy, and conducting prospective cohort studies of unintended exposures to probe safety signals that stand in the way of pregnant women accessing important drugs.

Enhancing safety data specific to pregnancy is important to making informed clinical decisions and counteracting reticence in prescribing based on poorly characterized risk. While pregnant women's access to new drugs should not be further burdened with yet greater evidence requirements than practice and guidance developers already impose, the HIV/co-infection community should move toward a standard of practice to expand prospective adverse event data collection, assure the timely, post-approval safety studies of drugs with widespread use in pregnancy, and timely pursuit of safety signals.

## 9. Address legacy evidence gaps

Currently approved preventives and treatments for HIV/co-infections should be reviewed for critical pregnancy-related evidence gaps that interfere with safe, evidence-based use in pregnancy; and research should be conducted to address those gaps.

Even as we advance more timely and robust evidence gathering for new drugs in pregnant women, currently available therapies should be reviewed for evidence gaps that may significantly affect drug access, equity, or risk in the context of pregnancy. Priority should be given to the most pressing and impactful gaps, which could

include a range of possible scenarios, such as inadequate evidence about maternal outcomes for drugs deemed safe for the fetus, inadequate fetal safety or maternal outcomes data for drugs that are widely used to good effect outside the context of pregnancy, or information on PK of approved drugs used in pregnancy. Funders of HIV/co-infection research can make a critical difference in supporting needed research with pregnant women by directing funding to this neglected subpopulation, especially in areas where industry's general market incentives are lowest.



## Ensuring respect

### 10. Ensure access to life-saving experimental drugs

Pregnant women should be guaranteed fair access to participate in trials and special access programs for experimental interventions that offer potential life-saving benefits in contexts where no or poor alternatives exist.

Sometimes, experimental drugs are the only option available in high-stakes contexts in which individuals face a life-threatening disease and have no or poor options for treatment or prevention. In such cases, experimental drugs may offer not just a small incremental benefit, but the only or best potential for a lifesaving intervention. The HIV/co-infection community should anticipate the potential for future game-changing drugs and the importance of ensuring fair access to pregnant women during their experimental stage. Pregnancy in itself should not be a reason to exclude a person from access to an intervention that is potentially life-saving, particularly in the absence of good alternative treatments, and especially when pregnant women or their neonates face higher than usual risks from the disease in question. Pregnant women should not be excluded from participating in such trials or programs unless there is demonstrable evidence that the risks outweigh the potential benefits to the women and their children.

## 11. Respect and support decisional authority

When a pregnant woman of legal standing is eligible to participate in research, her voluntary and informed consent should be sufficient to authorize her participation. Accommodations should be made to facilitate a woman's ability to engage the father, her family, or other personal supports, and to promote their understanding of the benefits and risks of research participation.

Pregnant women of legal age should be at the center of decisions about whether to participate in research. Researchers should also provide meaningful decisional support to prospective participants, including facilitating consultation and shared decision-making with fathers, partners, family members, or other personal support according to the woman's wishes. Strong caution should be used before adding formal paternal consent as a precondition to a pregnant woman's participation in research, as this additional layer of authorization can create barriers to pregnant women's access to research that may be beneficial to themselves or the fetus, and may not take into account the highly contextual specifics of individual relationships.

## 12. Contextualize risk findings

Those conducting HIV/co-infection research with pregnant women should anticipate possible adverse events and proactively develop communication strategies for adequately contextualizing them against baseline rates of such events. Communication of overall findings should take care to contextualize potential risks of an intervention against its potential benefits and the risk-benefit profiles of alternatives, and should include benefits to the woman and those that would accrue secondarily to her child should her health be benefited.

Clear risk assessment, communication, and translation is important in any research, but research with pregnant women brings special challenges and imperatives. Untoward events such as miscarriage and birth defects regularly occur in pregnancy. However, when such events occur in research contexts, unproven causal associations with the intervention may be presumed. Further, certain biases in risk

perception have been noted, including the tendency of over-weighting the risks of intervention compared with the risks of not intervening, as well as over-weighting risks to the fetus compared with benefits to the woman. For these reasons, all studies, including observational cohort studies, should develop thoughtful communication strategies before the research begins, and follow key practices for communicating risk.



The HIV research community has long been an exemplar of finding pathways to address complex and underserved communities. Moreover, the HIV research community has demonstrated for decades, continuing with current vanguard studies, that ethical and impactful research with pregnant women is possible.<sup>37–41</sup> As the global HIV research community continues to work together to end HIV and address its deadly co-infections, it is imperative to ensure equitable attention to a population so centrally affected by these diseases. Pregnant women and the children they bear deserve nothing less.

**To read the full report and guidance, see [hiv.pregnancyethics.org](http://hiv.pregnancyethics.org)**



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