

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

A CALL TO ACTION

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

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

The PHASES Working Group

Pregnancy and HIV/AIDS: Seeking Equitable Study

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1. Introduction

Since the early 1990s, pregnant women have been an important focus for HIV-related research. The urgent need to identify an intervention to prevent perinatal transmission led to what was then unprecedented recruitment of pregnant women into research trials, producing groundbreaking results for the protection of infants.^{1,2} Confidence from those experiences encouraged the HIV research community to be more willing than researchers focused on other diseases to pursue research with pregnant women. Further, the clear imperative to use antiretrovirals (ARVs) during pregnancy for large populations of women living with HIV led to a dedicated registry, the Antiretroviral Pregnancy Registry, aimed at gathering data on newborns exposed to ARVs during gestation.³ In many ways, then, the HIV community has been a vanguard for conducting research with pregnant women.

Despite these important advances, critical evidence gaps are ongoing. 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,⁴⁻⁷ new antiretroviral therapies,^{8,9} and drugs for HIV's deadliest co-infections: tuberculosis (TB) and malaria.^{10,11,12} 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 was 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.

This puts women and the children they bear in harm's way. Without timely pregnancy-specific data on safety, drugs may be used that carry unacceptable risks to the fetus or pregnant woman. Without pregnancy-specific data on how drugs interact with the distinctive physiology of pregnancy, pregnant women may be given doses that are too low—leaving them and their offspring unprotected from disease—or too high—exposing one or both to dangerous toxicities.

“ *Perhaps most profoundly, delays in gathering evidence can mean a delay in pregnant women’s access to next-generation drugs.* ”

Perhaps most profoundly, delays in gathering evidence can mean a delay in pregnant women’s access to next-generation drugs. In the context of inadequate data, case reports of adverse outcomes can lead to recommendations to use lesser options, even where the reports are consistent with baseline rates of those outcomes. Without a commitment to careful follow-up research, cautions from preclinical animal studies—meant only to inform preliminary assessments—can calcify into ongoing recommendations against the use of a drug that in fact may be far safer or more effective, for woman and fetus, than the alternatives. Finally, when pregnant women are included in the research agenda, a focus on fetal outcomes that is not balanced by an investigation of women’s own health outcomes leads to guidelines and clinical decisions based on only half the story.

Multiple organizations now affirm the critical need and importance of responsible research with pregnant women, both in general and for HIV and co-infections specifically. Influential organizations include the Council for International Organizations of Medical Sciences, the World Health Organization, the International AIDS Society, and the U.S. National Institute of Health’s Office of Women’s Health, among others.^{13–18} These organizations underscore that pregnant women deserve a more robust and timely evidence base to better protect them from undue risks and to ensure timely access to new medicines. Yet a complex set of barriers, including regulatory, oversight, and funding patterns, as well as confusion about the ethical principles that should frame such research, has made it difficult to make adequate 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. It 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.* ”

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 (for full details, see appendix A).

The Guidance presents 12 recommendations directed toward securing better, earlier, and more systematic evidence, with priority for activities that will decrease delays in pregnant women’s access to important medications and give equitable attention to pregnant women’s own health needs. These recommendations are directed to multiple stakeholders in the research and advocacy communities addressing HIV and key co-infections across the arc of drug development and post-approval contexts, including pharmaceutical companies and regulatory agencies, research agenda setters and funders, researchers and those involved in research oversight, and community research advisors.

Section 2 lays out a statement of the challenge, identifying priority needs, key evidence gaps and their costs, and barriers to progress. Section 3 identifies key ethical foundations for research with pregnant women based on wide-ranging, consensus commitments. Section 4 presents the 12 recommendations, with their specifications and rationales; and Section 5 provides appendices with further details and resources.

While this guidance is specific to HIV and key co-infections, many of the recommendations and analyses may provide helpful lessons to guide research with pregnant women around other diseases, especially those that are life-threatening and have high need of treatment or prevention during pregnancy. Further, while this guidance is specific to pregnancy, research on lactating women in HIV/co-infections is also important:^{10,15,26} in many contexts, women breastfeed longer than

they are pregnant, and transmission occurring in the postnatal period underscores the need for effective and tolerable drugs that can be used during breastfeeding.²⁷ While research with lactating women presents some distinct ethical and regulatory issues, many of the recommendations and analyses of this guidance may provide lessons for expanding critically needed research with lactating women. Finally, though the term “women” is used throughout this guidance, it is important to recognize that some who experience pregnancy do not identify as women. This guidance is meant to be inclusive of all who experience pregnancy, regardless of gender identity.



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—beginning with the early agenda to prevent perinatal transmission and continuing with the commitment of the Microbicide Trials Network to include pregnant women in HIV prevention research, as well as trials such as DolPHIN-2, PROMISE, VESTED, the Botswana Tsepamo birth outcome surveillance, and more—that ethical and impactful research with pregnant women is possible.^{19–25} 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.

2. Statement of Challenge

Globally, at any given time, 1.3 million women are living with HIV while pregnant.²⁸ Many of their pregnancies are complicated by deadly co-infections, including tuberculosis (TB) and malaria.^{29,30} In addition, millions of women each year face pregnancy while at high risk of acquiring HIV. Yet there are critical, systematic gaps in pregnancy-specific evidence around treatments and preventives for HIV and its co-infections—from dosing to fetal safety to maternal outcomes—that threaten the health of women and their children. Below, we review the key needs, evidence gaps, their costs, and their causes.

2.1 Pregnant women: A priority population in HIV and co-infections

Protecting maternal and child health through HIV treatment

Access to safe and effective antiretroviral treatment (ART) is widely understood as a key priority for pregnant women living with HIV. The most well-known reason is the importance of preventing perinatal transmission. In the absence of any intervention, the rate of transmission from a woman living with HIV to her child during pregnancy or delivery ranges from 15–30%; with effective antiretroviral treatment, the global rate of transmission can be reduced to less than 5%.^{31,32} Preventing perinatal transmission is widely recognized as a continuing, critical goal for global health.³²

But **effective HIV treatment during pregnancy is critical beyond its role in preventing perinatal transmission—it is also essential to protecting the woman’s own health.** Pregnancy is a time of heightened risk from HIV. Some of this is due to pregnancy-specific changes to heart function, lung capacity, and immune response that make pregnant women more susceptible to certain co-infections that can be especially dangerous (see below). In addition, HIV increases the risk of deadly obstetrical complications.³³ Pregnant women with poorly controlled HIV are six times more likely to develop sepsis (a life-threatening reaction to infection) after delivery, and three times more likely to die from it, especially following cesarean delivery or abortion.³⁴ Pregnant women living with poorly controlled HIV face higher rates of

“ *Pregnancy is a time of heightened risk from HIV.*

death directly related to HIV.³³ Overall, women living with HIV face up to a ten-fold increase in the risk of dying during pregnancy and the postpartum period compared with pregnant women not living with the virus.³⁴ An estimated 6–20% of all maternal deaths worldwide are attributed to HIV,³⁴ underscoring the need for pregnant women to have access to the most effective ARVs available.

Maternal HIV also carries risks to offspring, even when the child does not become infected. HIV in pregnancy has been associated with higher rates of preterm birth, poor fetal growth, and stillbirth, with risks appearing to worsen among women at more advanced stages of the disease.³⁵ Recent studies have found worse outcomes stretching into childhood, including infant death, infectious morbidity, and growth problems.^{36–39} While causes are likely multifactorial, risks have been attributed in part to the effects that HIV has on the maternal immune system and placental function, as well as poor maternal health in general³⁵—a stark reminder that attending to the health of children born to women with HIV is not only about preventing perinatal transmission but ensuring the pregnant woman’s own good health throughout gestation.

HIV prevention

Treatment is not the only urgency. **Pregnancy also represents a time of heightened risk for contracting HIV infection in high HIV-prevalence contexts.**⁴⁰

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.^{40,41} By some estimates, the risk of HIV infection per sex act increases threefold during late pregnancy relative to nonpregnant periods.⁴⁰

Women who become newly infected with HIV during pregnancy also face higher risks of perinatal transmission.^{42,43} This is due to the high levels of viremia associated with seroconversion and missed opportunities for testing and treatment over the course of prenatal care.^{42,43} In southern Africa, new maternal infections are responsible for over one-third of perinatal transmission cases.⁴⁴ Key to eliminating new HIV infections among children is not just the use of ARVs to prevent transmission from pregnant women with known HIV infection, but preventing pregnant women from acquiring infection in the first place.^{45,46}

Maternal HIV co-infections: Fatal trios

No discussion of the impact of HIV is complete without attention to deadly co-infections, especially TB and malaria. **When pregnancy is added to the mix, the situation is even more grave.**^{11,47-50} Consider first TB. Changes in the immune system caused by HIV can make a person more susceptible to new TB infection, and more likely to convert latent TB to its active, more dangerous form.⁵¹ TB infections, in turn, can make HIV more difficult to control, increasing the risk of HIV disease progression.^{52,53} And managing HIV and TB in combination is made challenging by frequent interactions among drugs commonly used for each.⁴⁹ Outcomes for pregnancy are deeply affected. TB is a leading cause of maternal mortality among women living with HIV.³⁴ Pregnant women living with HIV who have incident TB infection are two to three times more likely to die than pregnant women living with HIV alone.^{34,54} Their newborns fare poorly as well, facing increased risks of premature birth, low birthweight, and perinatal death.⁵⁵

Turn next to malaria. Untreated malaria can increase HIV viral load, which is of particular concern when access or adherence to ART is low.^{53,56} HIV and malaria management also poses challenging drug interactions.^{11,47,50,57} And malaria, HIV, and pregnancy together form a deadly combination. Malaria is already extremely difficult to treat during pregnancy because the parasite sequesters or “hides” in the placenta.⁵⁸ It becomes yet more complicated for pregnant women also living with HIV.^{59,60} Pregnant women living with HIV and malaria infection face three times the risk of severe anemia, and five times the risk of death, compared with pregnant women infected with malaria alone.³⁴

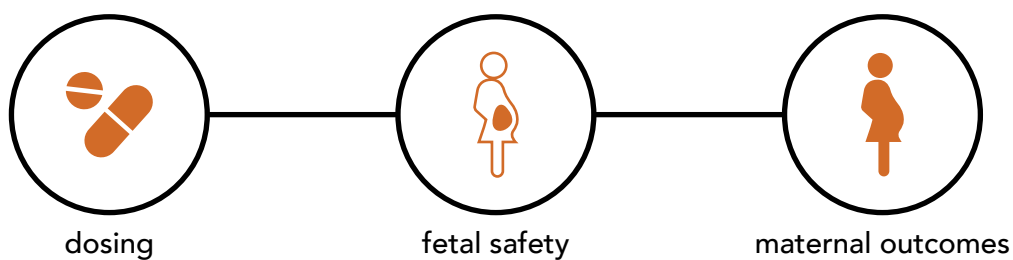


All told, pregnant women are among those *most* in need of safe and effective preventives and treatments for HIV and co-infections. Yet due to critical gaps and delays in gathering data specific to pregnancy, they are among the *least* likely to have robust, timely evidence to inform decisions around the use of medications.

2.2 Critical evidence gaps and their costs

A review of the literature and extensive consultation with experts reveals profound and consequential deficits in the evidence base for the treatment and prevention of HIV and co-infections during pregnancy. These deficits fall into three areas: dosing, fetal safety, and maternal outcomes. The costs of these evidence gaps are significant, including the potential for undiscovered risks, improper dosing, and critical delays in pregnant women's access to the benefits of next-generation treatments and preventives.

fig 1
Key
evidence
gaps



Dosing of approved drugs

The first key evidence gap concerns the proper dosing of drugs that need to be used during pregnancy. Changes to the pregnant body can radically affect a drug's absorption, distribution, metabolism, and excretion.⁶¹ These changes sometimes accelerate the processing of drugs, and at other times significantly reduce it. Further, pregnancy results in a decrease in plasma proteins that bind drugs.⁶² This can change the availability and potential toxicity of drugs that are highly protein-bound.⁶² Pregnancy-specific pharmacokinetic, or "PK" studies, are thus critical to ensuring accurate dosing during pregnancy and across trimesters of pregnancy.^{8,16,61,63}

Yet most HIV and co-infection drugs come to market with no pregnancy-specific PK data.^{26,64-66} Sometimes these data are gathered in studies conducted after the drugs are approved, but with long lag intervals, years after they have been widely prescribed to pregnant women; other times, such data are never gathered. The median lag time between ARV drug approval and the availability of

pregnancy-specific PK is six years.^{26,67} Evidence for the dosing of malaria drugs in pregnancy is similarly scant,^{66,68} and almost completely lacking for combinations of antimalarials and ARVs in pregnant women: no data to date are robust enough to inform dosing adjustments for the combined use of these drugs in pregnancy.^{47,69} Evidence gaps are even starker for TB treatment during pregnancy, for which pregnancy-specific PK data are almost entirely absent.^{10,70,71}

Not knowing the appropriate dose for drugs in pregnant women can be a serious problem. In the absence of timely PK data, pregnant women may be inadvertently underdosed—prescribed a regimen that will inadequately reduce HIV viral load or treat malaria. In other cases, they may be inadvertently overdosed. A standard adult dose may leave a pregnant woman with more medicine in her system than is needed to treat or prevent disease—which can expose her to heightened maternal and fetal toxicities, drug interactions, or side effects that can reduce her ability or willingness to take the medicine as frequently as prescribed, or lead her to switch to a less optimal regimen.^{61,72}

A recent example is cobicistat, a pharmacokinetic enhancer or “booster drug” used to increase the concentrations, and thus the effectiveness, of certain ARVs by interfering with the proteins that metabolize or break them down.⁷³ First approved by the U.S. Food and Drug Administration (FDA) in 2012, it is used in many fixed-dose drug combinations. For several years, cobicistat-containing regimens were prescribed to pregnant women living with HIV, using general population dosing information.⁷⁴ Recent studies (reported in 2018) that finally looked at pregnancy-specific PK found very low concentrations of cobicistat in pregnant women taking the drug at standard doses,^{75,76} and much lower concentrations of the ARVs they were meant to boost—up to 50% lower than had been observed in non-pregnant individuals.^{75,76} The observed low concentration of ARVs raised serious concerns about higher risks of HIV viral breakthrough, progression of HIV disease, perinatal transmission, and drug resistance.^{74,75,77} Pregnant women had been taking a drug that likely offered them inadequate protection against HIV disease.

Of note, when the data on PK in pregnancy were finally reported, warnings were issued against the drug without an effort to study what safe and effective dosing during pregnancy might be.⁷⁸ As a result, women who become pregnant while

taking cobicistat-containing regimens now face the well-known risks of switching regimens, and no longer have access to a drug combination that—with appropriate formulation and dosing—might be optimally tolerable and effective for them.



Fetal safety

The second key evidence gap concerns fetal safety. Most HIV and co-infection drugs come to market with only animal data to inform questions of fetal safety. Any in-human data is left to be gathered in postmarketing registries or through potential independent research that may occur. Given the widespread usage of ARVs during pregnancy, those efforts have yielded richer evidence than most drugs enjoy. For instance, the Antiretroviral Pregnancy Registry—an international registry jointly sponsored by manufacturers of FDA-approved ARVs—allows clinicians to voluntarily submit cases that prospectively follow pregnancies for fetal outcomes across ARVs to provide an early signal of potential teratogenic effects.³ Post-approval trials and independent observational research have also provided increasingly important evidence.^{23,79}

Despite these noteworthy efforts, in-human evidence on potential fetal risks for ARVs remains starkly limited and marked by extensive delay.⁸⁰ While the Antiretroviral Pregnancy Registry has produced important data, their usefulness is limited by low numbers due to its structure of voluntary reporting, with particularly small numbers from low- and middle-income country settings.⁸¹ And while ARVs are the subject of much independent research, controlled trials and active surveillance studies are ad hoc, rarely systematized across drug classes, and often only performed years after a drug's approval.⁸²

The gaps and delays are worse when we turn to HIV's co-infections. Despite overlapping populations, research progress regarding pregnancy and HIV has not transferred to co-infections, including TB or malaria.^{12,29} Without dedicated prospective registries, and with less historical experience of expanding research to pregnant women, an understanding of fetal safety beyond preclinical animal studies has been late in coming for both of these deadly diseases.^{29,48,83}

Gaps and delays in fetal safety assessment matter— for two reasons: inappropriate risk and barriers to access.

1. POTENTIAL FOR INAPPROPRIATE RISK TO THE FETUS

Of most obvious concern is the possibility that medications prescribed to pregnant women may be unsafe for the fetus. Drugs may carry risks of birth defects, such as changes to the structure of the heart, brain, or spinal cord. Less dramatic but still important are potential effects on the growth of the fetus and the pregnancy itself. For example, there is increasing realization of the need to assess ARVs for risks of pregnancy complications such as preterm birth, which can be especially deadly in low-income settings.^{79,80,84–86} Without timely research into fetal safety outcomes, decisions may be made to use a drug during pregnancy that carries inappropriate risk to the fetus.

TB prevention is a case in point. Isoniazid is a drug used to treat and prevent TB.⁸⁷ Since 2011, the World Health Organization (WHO) has recommended that isoniazid preventive therapy (IPT) be used in adults and adolescents, including pregnant women, living with HIV and at high risk of active TB.⁸⁸ Active TB can be deadly, especially during pregnancy.⁵⁵ Even though pregnant women are a critical population for active TB prevention, they were excluded from the large trials that assessed IPT.¹⁰ Eight years later, in 2019, the TB APPRISE trial, a large randomized study comparing the standard recommended IPT regimen for women living with HIV during pregnancy to IPT given 12 weeks after delivery, reported a surprising result.⁸⁹ There was no difference in the rates of active TB between women given IPT during pregnancy and those who received it after delivery, but babies whose mothers were treated during pregnancy did worse, with a higher incidence of adverse pregnancy outcomes, including stillbirth, miscarriage, and low birth weight.⁸⁹ Excluding pregnant women from IPT trials—and without a plan for timely follow-up research—led to recommendations that failed to account for the impact of a preventive drug on pregnancies complicated by HIV.

2. BARRIERS TO ACCESSING NEEDED DRUGS

Even where fears of fetal harm turn out to be unfounded, gaps in evidence around fetal safety are consequential. For there is a second, less well-appreciated cost to gaps in evidence around fetal safety: 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.** Thus, newer, more potent, and less toxic drugs may be recommended and used in nonpregnant individuals, with pregnant women initiated on less optimal older regimens.

For instance, the WHO has historically delayed endorsing new ARVs for use in treatment-naive pregnant women until in-human evidence of fetal safety is available. Women who are newly diagnosed during pregnancy—representing a large proportion of new diagnoses in low-resource settings as prenatal care is often a first point of entry to medical evaluation for women²⁷—are thus initiated on older, less optimal medications. Given the tendency to avoid switching medications, and many women's limited access to medical evaluation that might offer the opportunity for a change in drug regimens, HIV diagnosis during pregnancy can mean long-term consignment to less optimal drugs, particularly in low-resource settings.

Lesser data can also lead to uneven access. The WHO currently recommends PrEP for pregnant women at high-risk of HIV, based on reassuring safety data from the drug used in PrEP (tenofovir disoproxil fumarate, or TDF), including data from pregnant women using TDF to manage their HIV, exposures in HIV-negative women who became pregnant on PrEP trials, and HIV-negative pregnant women prescribed TDF to treat hepatitis B.^{90,91} Without evidence from controlled trials for use during pregnancy, though, country guidelines have varied widely.⁹² Eswatini specifically includes pregnant and lactating women in their 2018 PrEP guidance, but Malawi and Zambia specifically exclude pregnant and lactating women in their 2018 guidance.^{93,94} In South Africa, guidelines formally allow for physicians to counsel women at high risk of acquiring HIV to make their own informed decisions about PrEP use.⁹⁵ But reports suggest that, without evidence from controlled trials for use during pregnancy, PrEP is not available to pregnant women who use the public health system—precisely those most in need of effective prevention.⁹⁶

The DELIVER trial, now ongoing, is evaluating the safety of the dapivirine ring and oral TDF PrEP specifically in pregnant women, which will finally provide critically needed evidence.⁹⁷

Even in the absence of any concerning safety signals in preclinical drug development then, a lack of in-human fetal safety data can be a key barrier to pregnant women's access to critically needed drugs. And when early data do raise the possibility of a risk, the lack of follow-up research can calcify into restrictive policies for years—with high costs.

The history of the antiretroviral drug efavirenz (EFV) is a case in point.⁹⁸ First approved in 1998, EFV became a globally important first-line treatment for HIV. It was initially used with caution during pregnancy due to findings of birth defects in 3 out of 20 exposed monkeys.⁹⁹ In 2005, in response to four human case reports of birth defects in children whose mothers took EFV early in pregnancy, the FDA classified EFV as a potential teratogen, and warned against its use in women who are in their first trimester of pregnancy or who might become pregnant.¹⁰⁰ As a result of these recommendations, pregnant women who had been taking EFV were moved to other regimens (even after the window of potential harm had closed)—usually to nevirapine (NVP), which was more costly, carried concerns at the time about severe liver toxicity (requiring close monitoring in some cases), complicated national treatment guidelines and supply chains, and was similarly unprobed with regard to fetal safety.^{98,101} The switch to NVP also complicated the care of women being treated for TB, due to interactions between common TB medications and NVP.¹⁰¹ And, tragically, some women terminated desired pregnancies for fear of EFV-induced birth defects.¹⁰¹

Worries about EFV continued until new WHO guidelines were issued in 2012, based on accumulated reports from the Antiretroviral Pregnancy Registry, which indicated at most a low risk of birth defects for EFV, in line with other widely used ARVs at rates similar to the general population—seven years after the FDA issued its warning about the drug.^{101–104} The recent Tsepamo study—a large, prospective observational study in Botswana evaluating children exposed to EFV during pregnancy—demonstrated that, in fact, EFV carried *no* elevated risk of neural tube defects.¹⁰⁵ Had the original signal been pursued in a timely fashion, reassuring

evidence would likely have led to appropriate access to EFV for pregnant women. As the experience with EFV has so clearly demonstrated, early animal data and case reports uncoupled from timely, robust investigations can do more harm than good—for women and fetuses alike.

“ Since 2006, the WHO has recommended ACTs as first-line therapy for uncomplicated malaria in all populations except one—women in the first trimester of pregnancy.

Treatments for co-infections face similar issues. In the last two decades, artemisinin-based combination therapies (ACTs) have emerged as the most important and effective treatment for malaria.¹⁰⁶ ACTs have significant advantages over quinine, the primary alternative: higher cure rates, quicker clearance of malaria parasites, many fewer side effects, and avoidance of quinine’s well-known toxicities, which can include hearing loss, liver injury, and psychosis.^{106,107} Since 2006, the WHO has recommended ACTs as first-line therapy for uncomplicated malaria in all populations except one—women in the first trimester of pregnancy.^{106,108,109} Preclinical animal studies in rats and rabbits had raised the possibility that artemisinins were associated with fetal loss and skeletal and cardiac birth defects.⁸³ Over time, reports of pregnancy outcomes among women exposed (either inadvertently or intentionally) to artemisinin-based therapies surfaced no signals of increased rates of miscarriage, stillbirth, or birth defects compared with other antimalarial regimens.^{83,106} In the absence of formal follow-up studies, however, pregnant women have frequently been relegated to a considerably less effective and poorly tolerated alternative—even as they are among those at highest risk of death from malaria.

The story for TB is even more emblematic of the costs of “caution.” Bedaquiline is a newer oral drug heralded as a potential game-changer for TB treatment, including its ability to treat multidrug-resistant TB (MDR-TB), which has previously required prolonged treatment with TB drugs given by injection.¹¹⁰ It is not, however, currently recommended for use in pregnant women.¹¹¹ Although preclinical animal studies did not raise concerns of fetal risk, pregnant women were excluded from drug development trials, and the resulting lack of data has led to a delay in endorsing its use during pregnancy.^{110,111} This is particularly problematic, as options for pregnant women are already starkly limited by concerns about the teratogenicity of other drugs used to treat MDR-TB. (Aminoglycosides, for example, are associated with permanent hearing loss and kidney damage in prenatally exposed

children.)¹¹² With mortality rates from untreated TB as high as 40% among pregnant women (and likely higher for those co-infected by HIV), waiting for fetal safety data has left pregnant women at high risk of mortality without good options for treatment.¹¹²

“ Evidence delays leave pregnant women among those last in line to receive the benefits of next-generation drugs.

All told, **delays in gathering robust fetal safety data**, including delays in conducting post-approval observational studies, **carry deep costs even when—as often happens—the drug in question turns out to have a favorable risk-benefit balance.** Findings of teratogenicity, in particular, are extremely rare: most drugs finally tested in pregnant women bring reassuring evidence. But the wait for such reassurance can be a long one. Evidence delays leave pregnant women among those last in line to receive the benefits of next-generation drugs. A commitment to evaluating fetal safety outcomes is needed, not only to reduce risk to the fetus, but to ensure pregnant women’s timely access to preventives and treatments that are critical to their health, and the health of their children.



Maternal outcomes

The third evidence gap relates to pregnant women’s own health needs. The fetus is not the only focus of concern for potential pregnancy-specific drug risks. Drugs may carry risks that are specific to—or specifically heightened for—pregnant and delivering women. Drugs can be associated with higher rates of life-threatening preeclampsia, hemorrhage after delivery, or liver toxicities during pregnancy.

“ A focus on fetal outcomes tells only half the story.

In 2015, for example, a large observational study in the United Kingdom and Ireland found that among women on ART, pregnancy increased the risk of liver enzyme elevation by 70%, and more than tripled the risk of severe liver enzyme elevation compared with nonpregnant women.¹¹³ Such elevations require close monitoring and symptom assessment, as severe elevations can herald life-threatening obstetrical complications.¹¹³

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. **This is problematic not only as an issue of potential harm, but also of equity.** A focus on fetal outcomes tells only half the story.

There is also a more general need to attend to the complex interactions of drugs, disease, and pregnancy. Although the once ten-fold risk of HIV-related mortality in pregnancy has been reduced by the widespread use of ARVs,^{34,114} women living with HIV still have a markedly elevated risk of dying during pregnancy and in the postpartum period compared with women not living with the virus.^{34,115,116} Yet little is known about why this is, in part because of a “jarring lack” of data.³⁴

fig 2
Three
costs

Without research, pregnant women...

- may be given drugs at the **wrong dose**.
- may be given drugs that carry **unacceptable risk**.
- may be **denied access** to critically needed drugs.

2.3 Causes of evidence gaps

Many factors contribute to the costly evidence gaps outlined above.

Drug development and approval pathway

As previously noted, drug regulators do not generally require systematized evaluation of drugs in pregnant women for approval of a new drug, even when use and exposure are predicted for this population. Other than drugs seeking a “pregnancy-specific indication”—typically drugs that would be used exclusively during pregnancy, such as those for managing or preventing labor—the only studies required for market authorization of new drugs are certain preclinical animal reproductive toxicity studies.¹¹⁷ Some regulatory bodies currently face limits on their authority to require additional research on subpopulations due to concerns around delaying market entry. In the United States, for example, the FDA can require—as opposed to strongly encourage—specific postmarketing research on a subpopulation *only* under specific conditions, such as when strong evidence of significant harm has emerged.¹¹⁸

Pharmaceutical companies, in turn, have little incentive to conduct research with pregnant women absent a regulatory requirement. They also have many

disincentives against it, such as the added expense of including and monitoring pregnant women, questions about how to address pregnancy’s distinctive types and different rates of adverse events,¹¹⁹ and concerns about liability.^{15,120}

Instead, the drug approval process tends to rely on a system of postmarketing “adverse event” registries to gather pregnancy-specific data.¹⁶ Such registries carry serious limitations. Limited in general by low numbers and voluntarily reporting, they are also retrospective—inviting clinicians to share bad outcomes, rather than prospectively following a given number of pregnant women and reporting both reassuring and worrisome data. This approach carries a strong negative selection bias. Critically, such registries also lack a denominator of total drug exposures. This means that such registries, like the published “case reports” that surfaced with EFV, cannot be used to determine the prevalence of an adverse event, which carries with it a strong potential for misattributing adverse events to a study drug. This is especially problematic with pregnancy-specific data given the relatively high baseline rates of adverse events in pregnancy, including estimated baseline rates of serious birth defects of 3–6%, depending on geographic region.^{121,122}

Pregnant women as a research population

Also relevant are a set of issues around pregnant women as a research population, whether in drug development or post-approval research contexts.

“ *An abundance of myths and misconceptions persist.*

Myths and misconceptions. While most national and international guidance and regulations are permissive of research with pregnant women^{16,17,123,124} (see section 3), an abundance of myths and misconceptions persists. Many research oversight committees continue to believe that research with pregnant women is legally forbidden,^{96,125} and that their job is to summarily protect pregnant women from research rather than to help ensure that any proposed research meets appropriate criteria for their responsible inclusion.⁹⁶

Historical stance of protectionism on research with pregnant women. The historical designation of pregnant women as “vulnerable” research subjects—now overturned in many jurisdictions (see section 3)—has reinforced a sense that research with pregnant women is unacceptable.^{126,127} This stance, amplified in certain

contexts by a more general posture of paternalism toward pregnant women, has led to a very restrictive or conservative approach to research involving pregnant women.^{96,125}

Lack of training and experience. The conduct of interventional trials with pregnant women requires specific design considerations and support. Researchers often lack training or experience in approaching the issues raised by pregnancy, including specifics on trial insurance, protocols to allow admission or retention on study drug, pregnancy-specific monitoring, and personnel needed for the inclusion of pregnant women in research trials.^{96,126}

Legal and logistical challenges. Researchers report various issues that decrease the likelihood that they will pursue research with pregnant women, including challenges in obtaining trial insurance, concerns about legal liability or reputational risks should a trial have reports of adverse pregnancy outcomes, and the added burdens of navigating a potentially unfriendly committee oversight process.^{96,126}

Justificatory asymmetry. While regulations require protocols to justify the eligibility of pregnant women's enrollment or retention in a study, no justification is required for excluding them.¹⁵ This practice, underscored as problematic by groups such as CIOMS, means that any reason—or no reason at all—can suffice for exclusion, solidifying factors from habit to inconvenience into predictable patterns of exclusion.^{15,17}

Implicit patterns of reasoning around pregnancy

Certain implicit patterns of thinking around pregnancy, common in many aspects of personal life as well as in health care, can also affect the research context and the setting of research agendas.

Pregnant women as “vessels and vectors.” A longstanding concern is that when pregnant women are included in research, they are tacitly viewed as vectors of disease and vessels for the fetus rather than as ends in themselves.^{128,129} This framing can inadvertently lead to asymmetries in outcomes attended to in research design, investment in research agendas, and considerations in guidelines. The vessels-and-vectors frame can also unintentionally be reinforced by asymmetries in

expertise when designing or reviewing trials with pregnant women—for instance, having more representation of pediatric than obstetrical expertise. These tendencies can contribute to a narrow focus on the impact of a gestational intervention on child health and inequitable attention to pregnant women’s own health outcomes.

Pregnancy-specific risk distortions. Medical and public health analyses around risk in pregnancy are sometimes marked by specific cognitive biases. This includes a tendency to attend to the risks that an intervention may pose to the fetus without attending to the risks consequent to the fetus of *not* pursuing the intervention, as well as a tendency to attend to fetal risks without commensurate attention to potential maternal benefits.^{130,131} Ethics review committees sometimes fall prey to these risk distortions when assessing protocols that propose the inclusion of pregnant women in research.⁹⁶

Common pregnancy-specific risk biases

- Ignoring baseline rates of adverse events in pregnancy when reporting a study’s findings, which can lead to misattributing the cause of adverse events to the study drug
- Noticing the fetal risks of drugs without commensurate attention to the potential fetal benefits
- Noticing the fetal risks of drugs without commensurate attention to the benefits the drug may have for the pregnant woman
- Ignoring secondary medical benefits to the fetus that may result from the improvement of maternal health
- Inferring risks throughout gestation from risks that are biologically specific to one stage of gestation

3. The Ethical Foundations of Research with Pregnant Women

Responsible research with pregnant women is grounded in both the service of health and in moral commitments. In this section, we outline key conceptual shifts in the ethical framing of research with pregnant women, and the key ethical foundations that underpin them. These include principles of collective responsibility for addressing pregnancy-specific evidence delays, current regulatory and bioethical frameworks for the conditions under which pregnant women may ethically be included in clinical research, and principles of fair inclusion in research.

3.1 Conceptual shifts

There is now increasing consensus on the ethical imperative to conduct biomedical research with pregnant women. Influential organizations such as the Council for International Organizations of Medical Sciences (CIOMS), the Office of Research on Women's Health at the National Institutes of Health, new draft guidance from the U.S. Food and Drug Administration (FDA), and the Global Forum on Bioethics in Research have endorsed its importance.^{16,17,132,133} Professional organizations for both women's and children's health, including the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Society for Maternal-Fetal Medicine, among many others, have given forceful voice to the necessity.^{15,134,135} Recent guidances in other arenas, such as the PREVENT guidance for epidemic vaccine development, underscore the need.¹³⁶ In the HIV context specifically, both the International AIDS Society and World Health Organization (WHO) endorse the critical need for research with pregnant women.^{13,14}

Common to these efforts, and their appreciation of the costs to women and children of ignoring research during pregnancy, are certain key shifts in the ethical framing of research during pregnancy.

From “vulnerable” to “complex”

There is increasing recognition that the historical designation of pregnant women as a vulnerable research population has been problematic.¹³⁷ First, “vulnerable research population” is a term used for populations inherently unable to give valid consent or who are subject as a class to exploitation. Yet pregnancy does not itself limit the ability to reason; and while there are some contexts in which pregnancy may increase risks of exploitation, those factors are highly contextual and do not apply to the category of pregnancy in its own right. Second, it became clear that the designation had an unintentional but profoundly chilling effect on the pursuit of even highly responsible research into the health needs of pregnant women and the children they bear.^{138,139}

The bioethics literature and guidance from professional organizations now frame pregnant women as a “special” or “complex” population, by virtue of both the physiologic differences and ethical complexities that pregnancy entails, such as the need to consider the interests of both the woman and fetus. CIOMS explicitly states that pregnant women should no longer be categorized as a “vulnerable” population for research purposes.¹⁷ U.S. regulations on research for pregnant women have recently followed suit in revisions effective in July 2018, dropping the designation of “vulnerable” from this population.¹⁴⁰

Protecting pregnant women and the children they bear *through* research

“Traditional approaches to research during pregnancy actually increase risks to pregnant women and the children they bear.”

There is an increasing recognition that traditional approaches to research during pregnancy actually *increase* risks to pregnant women and the children they bear. At the population level, if evidence is not collected in the carefully controlled setting of responsible research, the potential risks of drugs are exported to the clinical setting, where they are magnified. At the individual level, exclusion from research keeps pregnant women from accessing studies that may offer real benefits to their health and the health of their children. While inclusion in research must always be responsibly assessed, research participation can be beneficial, and exclusion means exclusion from those potential benefits.

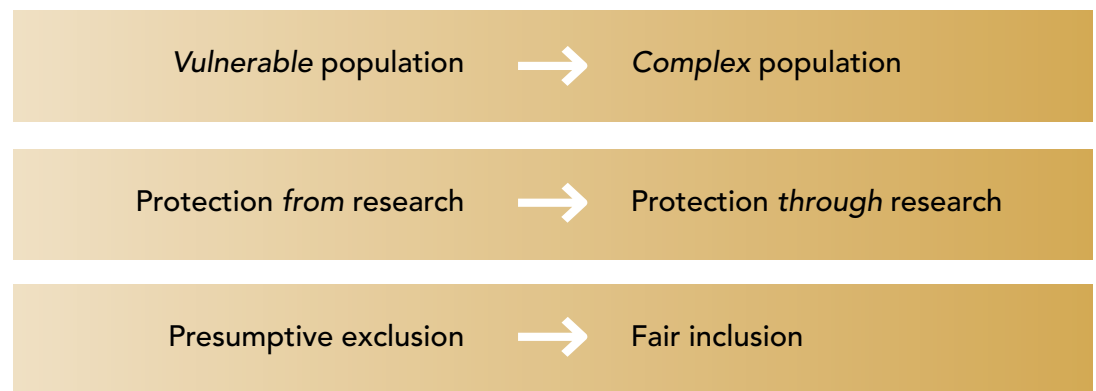
The last Ebola outbreak was instructive. Pregnant women were excluded from all drug and vaccine trials for Ebola, even as the disease they faced carried a near 100% mortality in pregnancy, with no other treatment options.¹⁴¹ The desire to contain research risk (or liability), in this case, left pregnant women and their children “protected to death.”¹⁴¹

Rather than thinking exclusively of an obligation to protect pregnant women *from* research, advocates of pregnant women and their children have urged a move to protecting them *through* research. As was found with the case of pediatric research, which has had a similar discussion of how to best address that population,¹⁴² the best way we can protect pregnant women and their fetuses is by responsibly conducting research and generating evidence that will inform their care.

From presumptive exclusion to fair inclusion

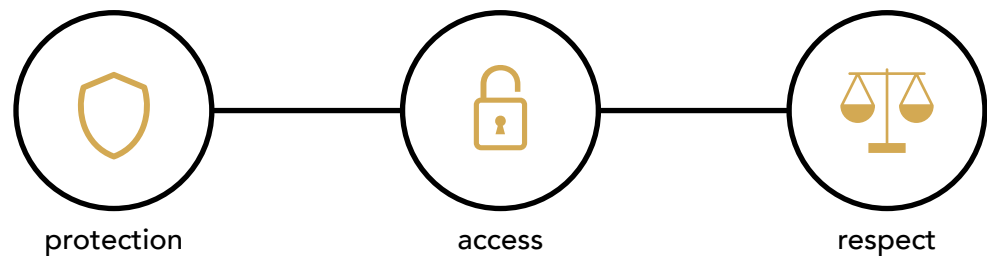
There is increasing recognition that the general practice of summarily excluding pregnant women from the research enterprise is unacceptable.^{15,143} As a population, pregnant women deserve to be equitably included in the research agenda,¹⁴⁴ for the generation of evidence to protect them and their offspring from avoidable risks and to address reticence toward the use of important, often first-line medications. They deserve representation in public and private investments to secure evidence for the safe and effective use of a drug when they are among those most

fig 3
Three
conceptual
shifts



in need of it.^{126,145} And they deserve fair opportunities of access to potential benefits that trials may offer.

fig 4
Three ethical foundations



3.2 The ethical responsibility to improve pregnancy-specific evidence

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. As is true for other subpopulations, data specific to the physiology of pregnancy is likely to entail some delay relative to data for the general population. But the current delays are extensive, severe, disproportionate to need, and without structures or plans to address them. When pregnant women are ignored in the research context, the potential risks associated with medication use are exported from the research setting into the clinical setting, where many more women and fetuses will be exposed to uncertain risks. Adequate research is therefore 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 the benefits of 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. But lack of research is a major barrier to pregnant women's timely access to first-line medications. Without in-human data, providers, practice guidelines, and public health systems can be reticent to endorse use of the drugs, even when they bring critical advantages over older drugs for disease states of urgent concern in pregnancy. And when early data do raise the possibility of a risk, the lack of follow-up research can calcify into restrictive policies for years. Better and more timely evidence is thus critical to avoiding delayed access to next-generation drugs.

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.

3.3 Special protections for including pregnant women in research

It is widely agreed that pregnancy brings with it distinctive ethical issues to the research context. Given that in utero exposure to study drugs can affect the health of the child born of that pregnancy, regulations and guidance on research with human subjects provide specific criteria for the inclusion of pregnant women in research.

Among the key guidance on criteria for research that includes pregnant women are: Guideline 19 of the International Ethical Guidelines for Biomedical Research Involving Human Subjects,¹⁷ issued by CIOMS in partnership with the WHO, which is nonbinding but strongly influential in many jurisdictions globally;¹⁴⁶ and Subpart B of the US Code of Federal Regulations,¹⁴⁷ which outlines requirements for research that receives funding from the U.S. government, wherever it takes place. In broadest form, the framework for determining when it is ethically

acceptable to enroll pregnant women in clinical research studies is shared by both guidances, based on consensus principles of clinical research ethics. These include standards of preliminary evidence needed before pregnant women are eligible to participate; standards of allowable research-related risk, especially to the fetus; and issues of consent and authorization.

Requirements for preliminary data

Before pregnant women are allowed in interventional research trials, both CIOMS and Subpart B guidances require that a degree of preliminary evidence about potential risks to the fetus is available to inform assessments of potential risks of fetal exposure.^{17,147} Just as preclinical evidence of general potential safety is required before first-in-human exposures, preclinical evidence around fetal development and reproductive toxicity is needed before first fetal exposures.¹⁴⁸ Data may come from animal models; be accrued from clinical use, including unintended exposures; or come from other data characterizing theoretical risk.⁸ In the context of investigational new drugs seeking approval, regulations outline specific preclinical animal reproductive toxicity studies—required ultimately for drug licensing—that must be completed in order for pregnant women to be eligible for inclusion or retention in trials.¹¹⁷

Of note, while these data can help characterize possible reproductive and gestational risk, they are imperfect predictors: drugs that do not demonstrate any risk in preclinical research may turn out to be harmful in human pregnancies, while reproductive harm in animals may not translate to any observable harm in humans. The purpose of requiring certain preliminary evidence before enrolling pregnant women is thus not to provide conclusions about risk or safety, but to help characterize potential risks, generate hypotheses for further study, and provide opportunities for preliminary concerns to be surfaced.

Standards for allowable research-related risk

Guidance and regulations also provide standards on how much research-related risk can ethically be permitted. Particular attention is paid to potential risks to the fetus and future child, given that they are unable to provide consent to research.

In general, the standard of acceptable research-related risk depends on whether the trial in question offers the “prospect of direct benefit.” Trials involving the prospect of direct benefit—sometimes called “therapeutic research”—are those in which the study intervention may provide participants with direct clinical benefit. When trials involve a prospect of direct benefit to either the woman or the fetus, the standard for allowable fetal risk is a proportionality standard. The potential risks of participation must be judged reasonable in relation to the potential clinical benefits offered by participation compared with available alternatives. Potential risk can thus be higher when the potential benefit is higher. In the context of pregnancy, fetal risk must be reasonable in relation to the potential clinical benefit to the woman, the fetus, or both. This includes secondary clinical benefits to the fetus resulting from the potential improvement to the woman’s health. This is the standard that governs the vast majority of proposed interventional trials with pregnant women.

Trials with no prospect of direct benefit, in contrast, are those in which such benefit cannot reasonably be expected. An example would be a single, subtherapeutic dose of a drug to assess pharmacokinetic (PK) values. When trials involve no prospect of direct benefit to either the woman or the fetus, research-related risks to the fetus are capped at a low threshold. In general, such trials can pose no more than “minimal risk” to the fetus—often defined by regulators as “the probability and magnitude of anticipated harms with those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”¹⁴⁰ CIOMS allows a slight elevation in permissible risk when the research in question is of particular importance.¹⁷

Consent

There is broad ethical consensus that competent participants above the age of majority should be the locus of consent for trials that entail risks and/or potential benefits to them. Pregnancy adds a layer of complexity, given the shared interests of two parents in the well-being of the offspring. Bioethical discussions emphasize the importance of respecting the pregnant woman’s agency and decisional authority while supporting the engagement of any other parent, and acknowledging the latter’s very real interests in the well-being of their offspring. However, adding

formal requirements for additional authorization by fathers, while well intentioned, can be problematic. Requiring formal paternal authorization as a precondition to a pregnant woman's ability to participate in research can be a significant barrier to her accessing trials that may carry important health benefits to her or the fetus. Concerns have also been raised that such requirements may not adequately account for the diversity of family structures and potentially complex relationship dynamics among couples.^{134,149,150}

Notably, research regulations on pediatric research indicate that, in most scenarios, one parent's formal authorization is sufficient for enrollment in research, even as engagement with both parents, where present, is understood as something to facilitate. According to CIOMS pregnant women above the age of majority should be the sole locus of consent for trials.¹⁷ U.S. regulations, in turn, have removed requirements for paternal consent except for rare cases in which research holds out the prospect of direct benefit to the fetus alone.¹⁴⁰

3.4 Principles of fair inclusion

Finally, responsibilities arise from another key facet of clinical research ethics: rather than conditions under which a research study *may* include certain participants, conditions under which it *should*. These are principles of fair inclusion.

Two principles of fair inclusion can be helpfully distinguished.¹⁵¹ The first is based on the need to ensure that study populations are diverse enough to support generalizable conclusions for the range of end users in health care settings. Widely regarded as an important principle,^{152,153} fair inclusion requires that study populations bear some semblance to the diversity of end users. Eligibility criteria that exclude affected subpopulations from study participation without adequate justification contravene the principle of fair inclusion.

The second is the principle of fair opportunity to access the benefits of therapeutic trials. Certainly, the primary goal of the research enterprise is knowledge gathering, not benefit conferring. That said, for trials that offer the prospect of net clinical benefit to participants, principles of fair opportunity must come into play.^{151,152,154} Under the principle of fair opportunity, therapeutic trials are obligated to avoid



Pregnant women should not be treated as an exception to these principles.

undue barriers to participation. The stronger the net benefit of trial participation compared with available options, the more accommodation can be required under the rubric of fair opportunity.

There is increasing realization that pregnant women should not be treated as an exception to these principles.¹³¹ When pregnant women are among those who will be using drugs to treat or prevent a disease, they must have adequate representation, in the aggregate, in research assessing the safety and dosing of those drugs.^{9,126} And when individual trials offer the potential of critical direct benefits, they have a responsibility to carefully assess the needs of potential participants—including those who are pregnant.¹⁵¹

3.5 A pathway to progress

Work is underway in many quarters to make progress on research with pregnant women. In the United States, for instance, the Task Force on Research with Pregnant and Lactating Women (PRGLAC) is tackling structural issues, including the organization of regulatory pathways for drug development in pregnancy, agencies' practices and their legislative authorities, and ideas for bolstering industry incentives and liability reforms that can reduce disincentives.¹⁵ Guidance from projects such as PREVENT have offered focal recommendations for improving research with pregnant women in their respective health contexts.¹³⁶

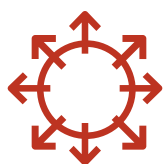
In the HIV/co-infection space, in particular, there is much cause for optimism. Vanguard trials and studies, such as DolPHIN and several studies from the IMPAACT Network,^{20,21,89} provide compelling examples of exemplar designs, including giving equal priority to maternal outcomes and fetal outcomes, that illustrate just what is possible. The WHO's Paediatric Antiviral Working Group has recently expanded its efforts to include advocacy for needed research with pregnant women, including for their own health outcomes.¹⁵⁵ In the co-infection space, researchers at the Medicines for Malaria venture are shifting the paradigm in drug development by prioritizing molecules that may have acceptable safety in pregnancy, conducting early developmental and reproductive toxicology tests, and moving forward for development only the compounds that show no concerning pregnancy-specific safety signals.^{156,157} The Kigali Statement, written by a group of

African women living with HIV in response to initial, restrictive WHO guidelines on dolutegravir¹⁵⁸ (now revised),^{159,160} is a potent reminder that the needs of women, including pregnant women, must be attended to; that robust evidence and equitable access to drugs are central to those needs; and that policy decisions need to be woman-centered.¹⁶¹ It is also a reminder of the power of women's voices to effect change.

To harness this momentum, we outline 12 concrete, specific recommendations that are immediately actionable within the current regulatory context. Together, these recommendations aim to advance the three key ethical objectives of equitable protection, access, and respect.

4. Recommendations

This guidance outlines specific, concrete, and immediately actionable steps, consistent with current regulatory frameworks, for the HIV/co-infection research community. Together, the recommendations aim to decrease the likelihood that drugs used in pregnancy carry undue risks, increase pregnant women’s timely access to needed drugs, and advance equitable representation of pregnant women’s own health outcomes in studies. The recommendations address multiple stakeholders across the arc of drug development and post-approval research, organized around building capacity, supporting inclusion, achieving priority research, and ensuring respect.



Building capacity

1. Affirm the need for research with pregnant women
2. Formalize a global network for advocacy and resources
3. Enhance training



Supporting inclusion

4. Design for inclusion
5. Review for and facilitate inclusion
6. Ensure equitable attention to pregnant women’s own health



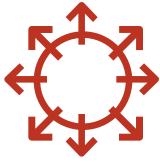
Achieving priority research

7. Integrate pharmacokinetic (PK) studies
8. Enhance post-approval safety assessments
9. Address legacy evidence gaps



Ensuring respect

10. Respect and support women’s decisional authority
11. Ensure fair access to life-saving experimental drugs
12. Contextualize risk findings



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 (see recommendations 5, 6, and 9), affirmation of the critical need for and ethical appropriateness of such research is a critical step in its own right. 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.

Key organizations should publicly affirm the importance of an adequate and equitable evidence base to guide the use of preventives and treatments in pregnant women, the necessity of research with pregnant women to achieve that evidence base, and the existence of pathways for ethically and legally responsible research.

These include national, regional, and global network research organizations working in HIV and/or co-infections; advocacy groups for women living with HIV; regional community advisory boards (CABs), especially those working in HIV-endemic regions; global policymakers; relevant study sections of drug regulatory authorities; and major purchasers of HIV/co-infection drugs.

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 (see appendix B), 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.

Specifically, **the global HIV/co-infection research community** should coordinate, and funders provide resources to support, an ongoing network to sustain advocacy for the critical need for research with pregnant women, and to coordinate an open-access portfolio of resources to support researchers and oversight bodies in the design, review, implementation, and monitoring of such research.

Resources to be considered include examples of innovative trial designs and sample protocols; templated language and strategies for trial insurance; curated portals to available data sources for monitoring baseline adverse events; translational toolkits for research ethics committees (RECs), community advisory boards, and Data and safety monitoring boards (DSMBs); examples of best practices for community engagement; and contacts for in-country organizations available to help develop appropriate translational tools suitable for their own context.

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 permissible 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—understanding that can provide confidence to pursue and approve research meeting 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 excellent existing modules (see appendix B), is thus essential to enabling needed research.

Because of the importance and complexity of this key population, as well as the diversity of research areas in which their needs can appear, training on the importance of ethically acceptable criteria for research with pregnant women should be added to training and in-service programs as follows:

Large institutional sponsors of biomedical research, such as national research-sponsoring organizations, should add training on research with pregnant women to the suite of research training required for funding eligibility.

Accrediting bodies for ethics committees should amend their certification requirements to include training on research with pregnant women.

Organizations involved in local capacity-building in research ethics, as well as regional community advisory boards involved in research literacy programs, with support from their funding partners, should add required modules on research with pregnant women to their programs.

Large research units with significant responsibility for research on HIV or co-infections, along with RECs and drug regulatory sections that frequently review protocols for HIV/co-infection drugs, should incorporate training on research with pregnant women into ongoing in-service programs. This training should include training on innovative trial design and interpretation of pregnancy-related adverse outcomes, risks, and signal events to encourage the appropriate pursuit and approval of trials that can enroll pregnant women.



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.

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. 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. Inclusion in trials creates valuable knowledge-gathering opportunities, including the chance to provide in-human data that guidelines often look to before recommending use during pregnancy.

Inclusive trial designs

A wealth of trial designs exist that can garner much-needed pregnancy-specific data. Designs include targeting the enrollment of pregnant women, reducing the use of pregnancy as an exclusion criterion in general population studies, giving women who become pregnant during a trial the opportunity to continue on the study drug when ethical eligibility requirements can be met, and tracking outcomes for unintended exposures.

To collectively achieve the needed evidence base for pregnant women, the HIV/co-infection community should commit to the following:

Proactively pursue inclusion. HIV/co-infection trials should end the presumption of excluding pregnant women. While there are contexts in which pregnant women’s inclusion in a trial is not advisable or feasible, the community should move to a system of intentional assessment for and priority of inclusion. This includes serious consideration of the needs of this population, its potential ethical eligibility, and the evidential value that inclusion in the trial could afford.

For larger trials, intentional assessment should move to a presumption of inclusion. The larger the trial and the greater the potential advantages of the drug being researched, the stronger should be the presumption of inclusion. Inclusion may take the form of positive recruitment of pregnant women in numbers adequate to power for specific maternal and fetal outcomes, if feasible. It may also include reducing the use of pregnancy as an exclusion criterion, allowing pregnant women in the study population. Even where studies are not powered to draw pregnancy-specific conclusions, data generated can create opportunities for detecting signals, generating hypotheses, or adding descriptive data to the profile of in-human experience—evidence that guidelines often wait for before endorsing the use of a new drug by pregnant women. Such descriptive data are especially helpful when accompanied by historical experience, previous data on exposures, or when aggregated across trials.

Move up preclinical animal reproductive toxicity studies. Drug developers should conduct the preclinical animal reprotoxicity studies needed for pregnant women’s research inclusion as early as possible after initial safety and dosing studies are completed. The current practice of delaying definitive animal reprotoxicity studies to the last stage of drug development precludes pregnant women from participating in Phase III trials. Increasing pregnant women’s inclusion in such trials can be an important source of information to surface cautions and reduce delays in pregnant women’s post-approval access. Increased use of available in-vitro models, such as placental transfer models, can also enhance opportunities to enroll pregnant women by helping to characterize or rule out a drug’s biologically plausible risks.

Retain women with incident pregnancy on study drug. All protocol designs of HIV/co-infection drugs for which adequate preclinical toxicology animal safety data is available should allow women who become pregnant while on a protocol the opportunity to remain on the study drug as long as their participation carries a favorable risk-benefit ratio. Retention on the study drug should include a robust counseling process to cover or review issues not explicitly addressed or attended to in the consent process prior to pregnancy.

Capture outcomes from incident trial exposures. At a minimum, all HIV/co-infection trials involving women of reproductive potential should capture and analyze relevant fetal and maternal outcomes of incident pregnancy exposures. This includes trials for which pregnancy appropriately serves as an exclusion criterion but pregnancy occurs during the course of the trial, and trials that allow women who become pregnant to continue on the study drug but will have some women who choose not to do so. Exposure data may be collected in the context of the clinical trial or as a separate prospective observational study of pregnant women exposed to a product in the context of a trial, and should include relevant maternal—not just fetal—outcomes (see Recommendation 6).

Data harmonization and pooling. Using standard sets of indicators, outcomes, and definitions across various studies can be a powerful tool for maximizing knowledge by combining small amounts of data from each while helping to avoid misattribution of adverse events to study drugs. Trial networks should develop data harmonization protocols and expand data pooling registries to maximize useful aggregation across trials and studies that gather small numbers of pregnancy exposures—on both fetal and maternal outcomes—to maximize the knowledge that can be gained through such efforts.

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.

Regulatory review sections, RECs, and funders of research can be important drivers of cultural change by shifting the justificatory asymmetry that currently exists in research with pregnant women (see section 2.3). They can also encourage and facilitate inclusive designs through specific incentives and supports: funders can incentivize research with pregnant women with 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. All should require clear and specific justification wherever pregnancy is proposed as an exclusion or removal criteria.

RECs reviewing HIV/co-infection research should require proposals to provide clear and specific justification wherever pregnancy is proposed as an exclusion or removal criteria. RECs should also work proactively with researchers to find designs that can appropriately include pregnant women. The practice of excluding pregnant women should be especially strongly questioned with trials conducting research on already approved active ingredients. Unless adequate evidence supports contraindication in pregnancy, trials with formulations of approved active ingredients, including trials seeking new formulations or indications, should not affirmatively exclude pregnant women unless clear, specific, and adequate justification can be provided, such as an unfavorable risk-benefit ratio relative to alternative available interventions.

When reviewing protocols that propose inclusion or retention of pregnant women, RECs should remember not to base their decisions regarding clinical trial eligibility on risk alone, but on risk in relation to the potential benefits of participation (see section 3: Ethical Foundations). This includes prevention trials. Assessments of the inclusion of pregnant women in prevention trials should be made on the available

evidence of potential benefits and risks to the pregnant woman and fetus/future child, rather than a categorical distinction between treatment and prevention.

Funders of HIV/co-infection research should require clear and specific justification wherever pregnancy is proposed as an exclusion or removal criterion. Funders should also encourage pregnancy-specific evidence gathering by adding incentives for such inclusion in their funding calls, preferentially designating resources to projects that take on the added risk and resource needs of including pregnant women, and providing adequate resources to cover the expanded costs of studying this population.

Regulatory review sections of HIV/co-infection drug development research should require clear and specific justification wherever pregnancy is proposed as a criterion for exclusion or removal from a study drug. While some regulatory bodies are limited in their ability to require a subpopulation study as part of the approval dossier, areas of encouragement and facilitation are possible. Regulators should proactively encourage industry partners to maximize options for including pregnant women, such as helping to foster industry-independent collaborations, and offering strategies for allowing pregnant women to participate in trials. Such strategies include statistically sequestering adverse events data from pregnant participants due to the regularly higher rates of certain adverse events during pregnancy, such as nausea, rather than aggregating them with general population data.

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 is impossible for clinical care and 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 research, which in early years attended centrally to the pregnant woman as a vector of HIV transmission rather than as an end in herself. Adopting a commitment to equity is therefore essential.

Funders and research agenda setters in HIV/co-infections should commit to equity of attention to and funding for the promotion of pregnant women’s own health needs, including assessing risks and potential benefits of drugs that are likely unique to or exacerbated by pregnancy. Agenda setters should ensure that research into the profile of risks and potential benefits to the fetus is matched by an understanding of the risks and benefits to the woman. Support for research on pregnant women’s health needs should be at least as strong as that for research addressing child outcomes, and should be commensurate with prioritization criteria, such as the burden of disease compared with other subpopulations in need of research dollars.

Trials that include pregnant women should look for opportunities to expand the scope of data collected to include useful information about the woman as well as the neonate. At minimum, studies should be examined for opportunities to analyze data already being collected that can develop the evidence base for maternal as well as infant outcomes. Trials whose primary study aims concern neonatal/pediatric outcomes should include collection and analysis of data on relevant outcomes for the pregnant woman’s own health, including HIV/co-infection-specific outcomes during pregnancy and for a relevant horizon postpartum. Failing to assess the outcomes of study interventions on the health of trial participants not only misses an important opportunity to gain critically needed evidence, but risks treating pregnant women as “vessels and vectors” rather than as human beings whose own health needs merit consideration. If a study’s design or capacity precludes the inclusion of maternal outcomes, this should be noted in study publications as a limitation of the study’s findings, and identified as a future research need.

Data and safety monitoring boards (DSMBs) for trials involving pregnant women should ensure that stopping rules include relevant maternal and obstetric outcomes, and should not disproportionately weigh neonatal over maternal outcomes.

Guidelines recommending the choice of a drug during pregnancy for fetal/child benefit should be accompanied by a commitment to evaluate the implications of such guidance on the pregnant woman's own health. It is critical that decisions about whether and which option to use during pregnancy be based on equitable evidence regarding the drug's profile of risks and benefits to both the woman and her child, rather than the child alone. At each level, in order to inform decisions regarding the appropriateness of a contraindication of a drug for use during pregnancy or guidance on the use of a preferred drug, analysis needs to be inclusive of the risks and benefits that the drug may present to the pregnant woman as well as to the fetus.



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.

As a commitment going forward, 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. At a minimum, mathematical modeling studies of pregnancy-specific PK across the trimesters should be conducted for regulatory submission to provide preliminary dosing guidance, with confirmatory PK studies in pregnant women conducted as soon as possible.

It is important that pregnant women's access to new drugs not be further burdened by instituting yet higher evidence requirements than those already imposed by practice and guidance developers. Thus, while pregnant women's access to drugs should not be made contingent on the following, the HIV/co-infection community

should move toward a standard of practice where the following research commitments are assured.

The drug industry should commit to pursuing PK studies in pregnancy, either independently or in partnership with academic researchers, as soon as standard dosing and preliminary safety of a drug is confirmed in nonpregnant individuals. This includes a commitment to move up conducting definitive preclinical reproductive toxicity studies of HIV/co-infection therapeutics as soon as possible after preliminary efficacy of the drug is established (see recommendation 4).

Regulators should strongly encourage, require up to their authority, and facilitate industry/independent collaborations for pregnancy-specific PK as part of the drug-approval dossier for all HIV/co-infection drugs anticipated for use by the general adult population and not contraindicated for use in pregnancy.

Funders of independent research should support post-approval PK studies when they are not achieved by industry. If there are challenges to achieving PK studies prior to approval, industry should work with independent researchers and provide supportive funding for these needed studies.

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.

While increasing interventional trials with pregnant women is important, other data collection and observational studies are critical to ensuring the safety of drugs used in pregnancy as well as pregnant women's timely access to needed new drugs.

While safety data specific to pregnancy are important to making informed clinical decisions and counteracting reticence to prescribe based on poorly characterized risk, pregnant women's access to new drugs should not be further burdened with yet greater evidence requirements than practice and guidance developers already impose. Thus, while pregnant women's access to drugs should not be made contingent on the following, the HIV/co-infection community should move toward a standard of practice where the following data collection and research commitments are assured.

Expand prospective adverse event data collection. Registries are important pharmacovigilance efforts for gathering data on adverse events of drugs in clinical use. Reliance on retrospective registries, however, is highly problematic in the case of pregnancy exposure. Without denominators indicating the number of exposures, retrospective registries do little to contribute to the kind of evidence guideline developers look for when deciding whether or not to endorse the use of new drugs during pregnancy. Further, the well-known negative selection bias of such registries can fuel false alarms that may preclude pregnant women's access to important drugs. For this reason, the malaria and TB research communities should work to establish robust and ongoing global data collection modalities to collect outcome data similar to the prospective data collected in the Antiretroviral Pregnancy Registry. Funders, researchers, and government agencies should collaborate to establish sentinel site birth outcome surveillance in geographic areas around the world where high use of the drug of concern in pregnancy is anticipated. (See appendix B for WHO tools on development of birth defects surveillance.)

Assure timely, post-approval safety studies of drugs with widespread use in pregnancy. When new HIV/co-infection drugs are rolled out for use in large populations that include women who are pregnant or of reproductive potential, follow-up prospective observational studies should be pursued for pregnancy exposure. Such studies offer critical opportunities to collect data adequate for assessing the attributable risk of adverse pregnancy outcomes as well as the relative risk of a novel compound compared with alternative interventions. Prospective tracking of large numbers of pregnancies, with exposures at various times of gestation (from periconception on), offers a critical opportunity to gather much-needed evidence. Evidence collected from such studies can be used to address safety risks—to

pregnant women and children. It can also address lingering signal concerns that may lead to unevenness or volatility of access should later case reports of adverse events arise from ongoing, widespread clinical use of the drug during pregnancy. This is especially important given that the magnitude of exposures increases the likelihood of adverse events reports that, in the absence of quantified characterization of risk, can improperly lead to misattribution and denial of access to what may in fact turn out to be an important drug with a superior risk-benefit profile.

For these reasons, drugs for HIV/co-infections with widespread use in pregnancy should be evaluated through timely prospective and systematic studies with large sample sizes of pregnant women to assess the attributable risk of adverse pregnancy outcomes as well as the relative risk of this novel compound compared with other alternative interventions. This will often entail partnerships between independent researchers and the public health system of one or more countries where the drug is widely used.

Commit to the timely pursuit of safety signals. Without follow-up efforts to confirm or refute the existence and magnitude of a risk, unconfirmed safety signals—which can emerge in preclinical animal studies, in-human research, or later as unanticipated events in clinical care settings—carry a long tail of influence on policy recommendations and clinical decisions, shifting pregnant women—and sometimes women of reproductive age—to second-tier drugs. When the drug in question is an important one, it is critical to have timely follow-up studies to confirm whether increased risk is present and, if so, to quantify it in comparison with known benefits. In these instances, reliance on the accumulation of passive registry data results is unacceptable, as too much time is needed to accumulate evidence capable of confirming or dismissing the signal. The stronger the potential comparative advantage of the drug in question, the stronger the obligation to invest in timely cohort studies.

Research agenda setters should therefore commit to the pursuit of timely and responsive investigations of observed safety signals that preclude pregnant women's access to important drugs. These investigations may take the form of cohort studies of unintended exposures or, where the drug is used in specific contexts, prospective observational studies. In some cases, data aggregation and data

mining are possible. Investments in such follow-up studies should also be strongly considered where precautionary stances are leading to overly long delays in pregnant women's access to particularly important drugs.

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, we also need to review currently available therapies for evidence gaps that may significantly affect drug access, equity, or risk in the context of pregnancy. Such evidence gaps may relate to questions about whether a contraindication for use in pregnancy is appropriate, or may inform critical choices between and among treatment or prevention options. Given the scope of available pharmaceuticals, filling all evidence gaps will not be possible; priority should be given to the most pressing and impactful gaps, which may include a range of possible scenarios, such as inadequate evidence on maternal outcomes for drugs deemed safe for the fetus, inadequate data on fetal safety or maternal outcomes for drugs that are widely used to good effect outside the context of pregnancy, and 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. This includes research to provide evidence for currently approved preventives and treatments that were not previously evaluated in pregnant women for pregnancy-specific dosing, and for neonatal, obstetrical, or maternal outcomes. These efforts could include government- or foundation-funded research or investigator-initiated, industry-supported research.

Public research institutes as well as private and industry funders should develop and support dedicated requests for research proposals that address key legacy

and priority gaps. Priority should be based on the assessed negative impact of proposed gaps, informed by robust input from community advocates, and ideally based on a sound priority-setting process with agreed-on substantive criteria and a fair process. Study designs may include clinical trials, observational studies, secondary data analyses, mathematical modelling, and data pooling. Industry should participate in resource sharing and support investigator-initiated research efforts.



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 provide not just a small incremental benefit, but the only or best potential for a lifesaving intervention. Examples include compassionate use programs and monitored emergency use of medication, where access to the critical product is allowed under a regulated structure. Such programs have humanitarian obligations on top of evidence-gathering commitments, correspondingly less restrictive eligibility criteria, and a permissible increase in tolerance for uncertainty.

Pregnant women have been excluded from such special access programs even when the drug was the only potential life-saving option for them or their children. For instance, early in the 2013–2016 Ebola outbreak/epidemic, an expert panel urged the need to prioritize and preferentially allocate unregistered interventions to pregnant women due to the dire risks they and their newborns faced in the prior outbreak—fatality rates among pregnant women were 89–93% and fetal/neonatal mortality rates were 100%—and the lack of approved treatments or vaccines. Despite this recommendation, pregnant women were excluded from drug and vaccine trials for Ebola even when those trials offered their only access to potential life-saving interventions.¹⁴¹

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. Should a drug emerge that is capable of significantly reducing the high mortality rates of malaria during pregnancy, for instance, pregnancy should not preclude women from special access programs that may be initiated. 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. While community engagement is always important in research, and voluntary engagement with fathers an equally important aspect of research, strong caution should be used before considering adding formal paternal consent as a precondition to a pregnant woman's participation in research. Such formal preconditions can create problematic barriers to pregnant women's access to research that may be beneficial to themselves or the fetus, and do not take into account the highly contextual specifics of individual relationships.

Researchers should provide meaningful decisional support to prospective participants. This should include facilitating consultation and shared decision-making with partners, family members, or other personal support according to the woman's wishes. Researchers should also provide protections to mitigate the social

risks of their participation, which for pregnant women can include partner or family violence and abandonment.

Adolescent girls remain disproportionately at risk of acquiring HIV; these same adolescent girls are also at higher risk of pregnancy. Where participation in research carries the prospect of important benefit, and where standard parental consent requirements for participation in research would constitute a barrier to accessing participation, trials should seek a waiver from parental consent requirements where allowed by local jurisdiction.

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 for any research, but research with pregnant women brings special challenges and imperatives. Untoward events such as miscarriage and birth defects regularly occur in a pregnancy. However, when such events occur in a research context, 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.

Trial sponsors should proactively engage the local community and relevant health ministries on what is known about baseline rates of adverse maternal, pregnancy,

and neonatal events to help prevent the automatic attribution of adverse events to a study drug. This is particularly important because local baseline rates of such adverse events may not be known, and public concern can be heightened with reports of adverse events during pregnancy. Thus, it is imperative that researchers proactively and responsibly interpret, communicate, and translate trial results and outcomes, including reports of adverse events. Research sponsors should accurately and compassionately communicate adverse event signals and their possible meaning to participants, ensuring that they are treated as partners in the research, and address and appropriately contextualize any resulting worry or concern.

Those involved in the analysis and evaluation of evidence from research trials

involving women of reproductive age, including data safety and monitoring boards, should include individuals with expertise in obstetrics and gynecology, maternal-fetal medicine, pediatrics, and neonatology; and the analysis should be informed by and reflect available evidence about probable baseline rates of adverse events in pregnancy.

Researchers need to be careful not just in the methodology of their research, but in communicating their findings to help avoid well-known problems of misinterpretation, including over-reaction to weak findings. Communication of interim and final study findings should always be framed by relevant features, such as baseline risks of adverse events, clarity about absolute and relative risk, and comparisons with the potential benefits of the study drug relative to alternative options.

Contextualizing risk

- Contextualize adverse events against baseline rates in pregnancy to avoid premature attribution of such events to a study drug.
- Contextualize uncertainties in comparison with similar uncertainties that may also persist for alternative options; indicate when potential benefits may still outweigh the risk even should a safety signal be confirmed.
- Contextualize risk findings against potential benefits of the intervention to fetus and woman alike, as well as the risk-benefit trade-offs of alternative options.

Glossary of Commonly Used Terminology

Antiretrovirals (ARVs). Medications used to manage HIV infection.

Council for International Organizations of Medical Sciences (CIOMS). An international non-profit organization jointly established by World Health Organization (WHO) and United Nations Educational, Scientific and Cultural Organization (UNESCO) that creates broad guidelines for the conduct of ethical research and is widely influential.

Co-infection. A separate infection that occurs at the same time. When different infections occur at once, they can impact each other and result in worse health outcomes.

Contraindication. A reason why a medication is recommended to be avoided in a patient or a population, including pregnancy, a co-infection, or other illness.

Equitable. Fair and reasonable. “Equitable treatment” means something is fair for all involved.

Evidence gap. When there is little or poor data or information around the use of a medication.

First-line medications. The medication regimen suggested by treatment guidelines as the best standard of care for a given condition.

Gestation. The period of pregnancy.

Interventional clinical trial. A research study in which participants are exposed to a preventive or treatment for purposes of assessing its impact.

Human immunodeficiency virus (HIV). A retrovirus that weakens the immune system when not managed by medication. Without appropriate antiretroviral treatment, HIV can progress to acquired immune deficiency syndrome (AIDS).

Malaria. A disease caused by a parasite spread by infected mosquitoes. Symptoms include fever, chills, and flu-like illness. Severe complications and/or death may result if left untreated.

Minimal risk. Contested definition, but it is generally agreed that a research study is minimal risk when the probability and magnitude of harm or discomfort anticipated in the research study are not greater than those encountered in daily life.

Neonatal. The period between birth and 28 days after birth. Neonatal mortality refers to infant deaths during this period.

Observational study. Research in which the investigator collects information about individuals without changing their medications or intervening in their care or environment. Observational studies may be *prospective* or *retrospective* (see respective definitions).

Obstetrical. Related to pregnancy and childbirth.

Perinatal. The time period around birth, including pregnancy, delivery, and the postpartum period. Perinatal transmission of HIV refers to HIV transmission that occurs during the perinatal period, also known as vertical transmission or mother-to-child-transmission.

Pharmacokinetics (PK). How the body impacts the effect of medication. The body can impact the amount of medication stored, used, or discarded, as well as the speed at which these processes occur. May be altered by factors such as pregnancy, age, health status, and gender.

Pharmacovigilance. The continued efforts to collect data about drug safety after the drug has been approved. This can take many forms, ranging from establishment of general registries to the conduct of observational studies.

Placenta. An organ that exists during pregnancy to connect the fetus and the pregnant woman and that facilitates the exchange of nutrients, oxygen, and waste. After the birth of the baby, the placenta is delivered.

Post-approval studies. Research studies conducted after a medication has been approved by regulatory bodies to assess continued safety and effectiveness; may be required by regulators.

Postpartum. The period after the birth of the child when the woman's body returns to a nonpregnant state.

Pre-exposure prophylaxis (PrEP). Medications used for the prevention of HIV infection.

Prospect of direct benefit. A potential clinical benefit to a participant in a clinical trial that results from the intervention being studied.

Prospective research. Research that enrolls a group of individuals and follows them *forward* in time, looking for health outcomes of interest. Usually provides more accurate (less biased) information than retrospective studies.

Registry. An organized system to store detailed information about people with a specific disease, condition, or exposure. Some registries are prospective, such as the Antiretroviral Pregnancy Registry, while others are retrospective, such as pharmaceutical drug registries.

Reproductive toxicity studies. Research studies designed to identify adverse effects of a substance on any part of the reproductive cycle, including effects on the fetus or offspring and impaired reproductive functioning in adults. Preclinical animal studies of reproductive toxicity are required before pregnant women are allowed in research trials.

Research-related risk. The possible harms that may occur to individuals as a result of their participation in a research study. Risks may be physical, psychological, social, legal, and/or economic.

Retrospective research. Research that identifies an outcome of interest (e.g., a birth defect) then looks *backward* for factors that might be related to that outcome (nutritional problems, medications, factors in the environment). Usually less accurate than prospective studies due to many sources of bias.

Safety signal. Preliminary data that raise the possibility or hypothesis that a drug may carry a health risk. The existence of a safety signal does not mean that an actual risk exists, but rather that more investigation is appropriate.

Surveillance. The systematic collection and analysis of data on injuries, illnesses, and deaths for public health purposes.

Trimesters. A full-term pregnancy is typically 40 weeks from the date of the woman's last period to delivery and divided into three trimesters: the first trimester is 0 to 13 weeks; the second trimester is 14 to 26 weeks, and the third trimester is 27 to 40 weeks. Each trimester is associated with different stages of fetal development and changes in the woman's body.

Tuberculosis. A potentially serious bacterial infection that primarily affects the lungs. Tuberculosis can be *latent* (asymptomatic and not contagious) or *active* (with symptoms and contagious).

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Appendix A: The PHASES Project

Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) is an interdisciplinary, research-driven project funded through the U.S. National Institute of Allergy and Infectious Diseases of the National Institutes of Health (R01AI108368) led by Dr. Anne Drapkin Lyerly, MD, MA, Principal Investigator (University of North Carolina at Chapel Hill), and co-Principal Investigators Dr. Maggie Little, BPhil, PhD (Georgetown University) and Dr. Ruth Faden, PhD, MPH (Johns Hopkins University). Along with the Project Director, Dr. Kristen Sullivan, PhD, MSW, MBA, MA, and collaborating with research partners in Malawi, Botswana, and the United States, the multi-institutional team conducted the empirical and conceptual research to inform the development of the Guidance, convened the PHASES Working Group, and directed the Guidance development process.

The PHASES Working Group, assembled in 2017, is composed of 26 international leaders in diverse fields, including HIV/AIDS and infectious disease, advocacy for women living with HIV, bioethics, law, public health, maternal and fetal medicine, obstetrics, pediatrics, and epidemiology. With multidisciplinary representation from southern and eastern Africa, Europe, Canada, and the United States, the Working Group was charged with authoring the PHASES Guidance together with the PHASES Project team.

Goal and geographic scope

With a particular focus on the United States and southern Africa, specifically Botswana, Malawi, and South Africa, the ultimate goal of the PHASES Project is to develop concrete, engagement-driven guidance for conducting HIV research in pregnancy that is responsive to identified priority areas, barriers, and opportunities. While we believe this Guidance has the potential for widespread applicability, it is our substantial engagement in these contexts through empirical research, consultations, and collaborative partnerships that have directly informed its development and therefore grounds the contexts where the Guidance may be most applicable.

Objectives and approach

Since the project's initiation in 2013, PHASES has prioritized deep engagement with the HIV research community as well as with affected women to develop a robust appreciation of the priorities and factors influencing the HIV research landscape and to capture a diversity of perspectives from a range of key stakeholders. Engagement with these groups has been critical to the development of responsive, concrete, and actionable ethics guidance. In service of advancing ethical research and developing the Guidance, PHASES' five objectives are to:

1. Identify priority evidence gaps for biomedical research addressing pregnant women in the prevention and treatment of HIV and co-infections.
2. Characterize the perceived barriers to and opportunities for including pregnant women and women who may become pregnant in HIV and co-infection biomedical research.
3. Characterize reasoning around participation in such studies from the viewpoints of affected women.
4. Conduct ethical and legal analyses of conditions for responsible HIV and co-infection biomedical research with pregnant women and women who may become pregnant.
5. Develop concrete, engagement-driven guidance for biomedical HIV and co-infection research in pregnancy that is responsive to the identified priority areas and viewpoints of key stakeholders.

Background work

In-depth interviews with expert stakeholders in the United States, Botswana, Malawi, and South Africa

We conducted in-depth interviews and focus group discussions with 150 HIV investigators, bioethicists, institutional review board chairs and members, research community advisory board members, legal and regulatory experts, and policy leaders. Through these interviews, we gathered information on the most pressing research priorities for pregnant women, identified relevant research ethics frameworks and

moral considerations, and surfaced both obstacles to and successful approaches for conducting HIV research with pregnant women (e.g., Krubiner, et al., 2016).ⁱ This work was led by the PHASES research team in the United States, Malawi, and South Africa; and in Botswana, in collaboration with Dr. Mary Kasule of the Botswana Baylor Children’s Clinical Center of Excellence.

In-depth interviews with pregnant women living with or at risk of HIV in Malawi and the United States

We conducted 140 in-depth interviews (70 in Malawi and 70 in the United States) with pregnant and recently pregnant women, living with or at risk of HIV. The aim of these interviews was to characterize reasoning around and experiences with clinical trial participation during pregnancy to ensure that the Guidance was informed by the views of actual and potential pregnant study participants^{ii, iii, iv} who are potentially most affected by changes in policies and practices under consideration.

Scholarly/conceptual ethical and legal research

Conceptual ethics scholarship explored concerns salient to clinical HIV-related research with pregnant women, including challenges surrounding current conceptual frameworks of minimal risk applied to pregnant women, requirements for informed consent, risk-benefit tradeoffs, and the development of an ethical framework for research with pregnant women carrying the prospect of direct benefit.

PHASES conducted research into legal barriers limiting research with pregnant women, focused on the United States.^v Additionally, legal experts in each of the countries of focus were commissioned to develop a brief addressing legal and regulatory issues specific to research with pregnant women in their respective countries.

i. Krubiner CB, Faden RR, Cadigan RJ, et al. Advancing HIV research with pregnant women: navigating challenges and opportunities. *AIDS*. 2016;30(15):2261–5.
ii. Sullivan K, Gilbert S, Mtande T, et al. Women’s views about rules governing reproductive issues in the context of biomedical clinical trials. *Journal of Empirical Research on Human Research Ethics*. 2017;12(5), 393–394.
iii. Sullivan K, Jaffe EF, Mtande T, et al. Malawian women’s experiences of rules regarding participation in HIV prevention and treatment clinical trials during pregnancy. *AJOG*, 2017;217(6):734–735.
iv. iv. Sullivan K, Little M, Rosenberg NE, et al. Women’s views about a paternal consent requirement for biomedical research in pregnancy. In press.
v. Mastroianni AC, Henry LM, Robinson D, et al. Research with Pregnant Women: New Insights on Legal Decision-Making. *Hastings Cent Rep*. 2017;47(3):38–45. doi:10.1002/hast.706

PHASES Team

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PHASES Vetting Meeting Participants, July 2018

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Country-Specific Legal Briefs

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We are immensely grateful to all of the women who participated in PHASES qualitative research interviews; stakeholders from Botswana, Malawi, South Africa, the United States, and Europe who generously shared their time to provide key context and insights about priority needs, barriers, and opportunities; and expert consultants in bioethics, research design, infectious disease, obstetrics and gynecology, clinical research regulations, fetal toxicology, and pharmacology who generously provided feedback on early drafts of the Guidance.

Guidance Design

Kelly Heuer PhD MA, Laura C. Johnson BA

Appendix B:

Additional Resources

Affirming statements, guidance, and reports for improving responsible research with pregnant women

ACOG Committee Opinion on the Inclusion of Pregnant Women in Research

This committee opinion provides a broad overview of the history and ethics of research with pregnant women and examines issues such as informed consent, contraception requirements, partner consent, and appropriate inclusion.

Ethical considerations for including women as research participants. Committee Opinion No. 646. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;126:e100–7. Available from: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2015/11/ethical-considerations-for-including-women-as-research-participants>

Ethical guidances on inclusion of pregnant women in vaccine research

These two guidance documents offer recommendations for advancing the ethical inclusion of pregnant women in vaccine research during epidemics and infectious disease outbreaks.

The Ethics Working Group on ZIKV Research and Pregnancy. *Pregnant Women and the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation*. Baltimore, MD: 2017. Available from: vax.pregnancyethics.org

Krubiner CB, Faden RR, Karron RA, Little MO, Lyerly AD, et al. Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response [published online ahead of print, 2019 May 3]. *Vaccine*. 2019;S0264-410X(19)30045-3. Available from vax.pregnancyethics.org

Global Forum on Bioethics In Research

The 2016 Global Forum on Bioethics in Research meeting focused on the ethics of research in pregnancy. The meeting report is a part of a *Reproductive Health* supplement issue with a range of articles related to advancing ethical research in pregnancy.

Hunt, A., Banner, N. and Littler, K. The global forum on bioethics in research meeting, “ethics of research in pregnancy”: emerging consensus themes and outputs. *Reprod Health* 14, 158 (2017). Available from: <https://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-017-0431-1>

Improving Safe and Effective Use of Drugs in Pregnancy and Lactation:

Workshop Summary

This workshop summary includes an overview of existing U.S. surveillance systems for drug use in pregnancy and policy recommendations to advance ethical research in pregnancy

Riley LE, Cahill AG, Beigi R, Savich R, Saade G. *Am J Perinatol.* 2017;34(8):826–832. Available from: <https://www.thieme-connect.de/products/ejournals/html/10.1055/s-0037-1598070>

NIH Report from 2010 Workshop on Enrollment of Pregnant Women

This report summarizes recommendations around enrolling pregnant women in research made by a group of relevant experts at a 2010 NIH workshop.

Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. *Womens Health Issues.* 2013;23(1):e39–e45. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547525/>

NIH Report from 2010 Workshop: Next steps for testing microbicides and PrEP in pregnancy

This report summarizes recommendations for advancing the inclusion of pregnant and lactating women in HIV prevention research.

Beigi RH, Noguchi L, Brown G, Piper J, Watts DH. Performing Drug Safety Research During Pregnancy and Lactation: Biomedical HIV Prevention Research as a Template. *J Womens Health (Larchmt).* 2016;25(7):761-766. doi:10.1089/jwh.2013.4398. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4939378/>

PRGLAC Report

Recommendations made to the U.S. Secretary of Health and Human Services regarding research and the development of safe and effective therapies specific to pregnant women and lactating women.

Task Force on Research Specific to Pregnant Women and Lactating Women. Report to the Health and Human Services Secretary and Congress.; 2018. Available from: https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf

Tools for Research Design and Evaluation

Harmonizing Definitions

The Global Alignment for Immunization safety Assessment (GAIA) organization developed a special issue of *Vaccine* to harmonize obstetric and neonatal case definitions to improve trial design and data comparison between contexts.

Bauwens, J, Bonhoeffer, J, Chen, RT (Eds.) Harmonising Immunisation Safety Assessment in Pregnancy. *Vaccine*. 34 (49): 5991–6110. Available from: <https://www.sciencedirect.com/journal/vaccine/vol/34/issue/49>

Inclusion of pregnant women in antiretroviral drug research: what is needed to move forwards?

This article offers case studies and trial design recommendations about how to advance the inclusion of pregnant women in HIV treatment research.

Fairlie L, Waitt C, Lockman S, et al. *J Int AIDS Soc*. 2019;22(9):e25372. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6747006/>

Malaria in Pregnancy Consortium

The Malaria in Pregnancy (MiP) consortium has many available resources, including standard protocols for data collection in pregnancy and template forms for assessing and reporting pregnancy-related outcomes. The MiP also houses a free library of published and unpublished literature about malaria in pregnancy.

Resources available from: <https://globalpharmacovigilance.tghn.org/resources/mipc-resources/>. Library available from: <https://www.wwarn.org/tools-resources/malaria-pregnancy-library>.

Recommendations for Institutional Review Boards

This paper presents practical guidance for institutional review boards to evaluate for fair inclusion of pregnant women in clinical research.

Payne, P. (2019), Including Pregnant Women in Clinical Research: Practical Guidance for Institutional Review Boards. *Ethics & Human Research*, 41: 35–40. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/eahr.500036>

Toolkit for Research and Development of Paediatric Antiretroviral Drugs and Formulations

This toolkit was developed by WHO and UNITAID in collaboration with IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) network, PENTA (Paediatric European Network for Treatment of AIDS) foundation and experts from the Paediatric Antiretroviral Working Group. Module 3 addresses pregnant and breastfeeding women.

Schalkwijk S, Colbers A, Mirochnick M. Module 3: Pregnant and Breastfeeding Women. WHO. 2017. Available from: <https://apps.who.int/iris/bitstream/handle/10665/273151/9789241514361-eng.pdf?ua=1>

FDA Draft Guidance for Industry

This draft guidance represents the position of the U.S. Food and Drug Administration to date on the inclusion of pregnant women in research. Specific recommendations relate to trial design, obtaining pharmacokinetic data, obtaining safety and efficacy data, and monitoring research with pregnant women.

U.S. Department of Health and Human Services Food and Drug Administration. Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials. Guidance for Industry, Draft Guidance. April 2018. Available from: <https://www.fda.gov/media/112195/download>

Drugs@FaDA

A search engine for current labeling and a history of regulatory action of FDA approved drugs. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>

NIH Inclusion Outreach Toolkit

The United States National Institutes of Health “strongly encourages” the inclusion of pregnant women in appropriate research, and details supportive legal and ethical resources.

National Institutes of Health. NIH Guidelines: Inclusion of Women and Minorities. NIH Inclusion Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research. Available from: <https://orwh.od.nih.gov/toolkit/nih-policies-inclusion/guidelines>.

Pregnancy Registries

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry prospectively collects and evaluates data on the pregnancy outcomes of women using antiretroviral medications during pregnancy. Learn more at: <http://www.apregistry.com/Default.aspx>

ConCEPTION

ConCEPTION is a broad project funded by the Innovative Medicines Initiative, a private public partnership, that seeks to expand evidence around medications in pregnancy and breastfeeding and streamline access to this data by a range of stakeholders. Learn more at: <https://www.imi-conception.eu/>

World Health Organization: Central registry for epidemiological surveillance of drug safety in pregnancy

The World Health Organization and Special Programme for Research and Training in tropical diseases central registry for epidemiological surveillance of drug safety in pregnancy pools safety data issued from local or national pregnancy exposure registries and collected in birth outcome research programs on, HIV, TB, and malaria drugs, as well as drugs coadministered during pregnancy. Learn more at: https://www.who.int/tdr/research/tb_hiv/drug-safety-pregnancy/en/

World Health Organization: Birth defects surveillance

The World Health Organization, National Center on Birth Defects and Developmental Disabilities from the United States Centers for Disease Control and Prevention, and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) together developed resources for birth defects surveillance

including a facilitator training guide, a manual for program managers, and an atlas of selected congenital anomalies.

Available from:

https://apps.who.int/nutrition/publications/birthdefects_training_facilitators_guide/en/index.html

https://apps.who.int/nutrition/publications/birthdefects_manual/en/index.html

https://apps.who.int/nutrition/publications/birthdefects_atlas/en/index.html

Advocacy Resources

Coalition to Advance Maternal Therapeutics (CAMT)

The Society for Maternal Fetal Medicine created the Coalition to Advance Maternal Therapeutics (CAMT). CAMT was a leading force behind PRGLAC, and remains a strong advocate for research with pregnant and lactating women in the United States. Learn more at: <https://www.smfm.org/advocacy/camt>

Communique of the Kigali Dolutegravir Stakeholder Meeting of African Women Living with HIV

The Kigali Statement, written by a group of African women living with HIV in response to the potential fetal safety signal for dolutegravir exposure in early pregnancy and the restrictive WHO guidelines developed in response (now revised), articulates a joint position on behalf of women for access to optimal HIV treatment and prevention.

International Community of Women Living with HIV. Communique of the Kigali Dolutegravir Stakeholder Meeting of African Women Living with HIV. Afrocab. 2018. Available from: <http://www.afrocab.info/wp-content/uploads/2019/05/Kigali-Communique-.pdf>

The Global Coalition on Women and AIDS (GCWA)

The Global Coalition on Women and AIDS (GCWA) brings together all global civil society organizations working on issues related to HIV and women. Learn more at: <https://gcwa.unaids.org/>

International Community of Women Living with HIV

Since 1992, the International Community of Women Living with HIV (ICW) has been a global advocacy network run for and by women living with HIV. Learn more at: <https://www.facebook.com/internationalcommunityofwomenlivingwithhiv/>

MotherToBaby

MotherToBaby provides information from researchers in the Organization of Teratology Information Specialists (OTIS), a nonprofit that evaluates medication risk in pregnancy and breastfeeding.

Learn more at: mothertobaby.org

SisterLove, Inc.

SisterLove works to eradicate the adverse impact of HIV/AIDS and reproductive health challenges for women and their families in the United States and around the world through education, prevention, support, and human rights advocacy. Learn more at: <https://www.sisterlove.org/>

Afterword

The journey to this guidance has been long and generative. Foundational work around the urgent need to address evidence gaps about medication use in pregnancy began in the mid-2000s, when three of us (ML, AL, RF) founded the Second Wave Initiative. The vision of this collaborative was to forge a new paradigm for the responsible inclusion of pregnant women in research and development of an evidence base to better meet their needs.

In 2013, the Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) project was born, funded by an R56 from the National Institutes of Health (PI: Lyerly), as well as a developmental award from the UNC Center for AIDS Research. We are immensely grateful for the partnership of Liza Dawson, our original Program Officer, who shared our vision of a project that melded the normative conceptual, empirical, and policy aspects of this work and who spearheaded the call for this project to continue in earnest. In 2015, the PHASES Project was awarded an R01 (PI: Lyerly) and the work began more fulsomely.

In 2016, as work on the PHASES Project continued, three of us (RF, AL, ML) received a grant from the Wellcome Trust to develop ethics guidance for research with pregnant women in the distinctive context of vaccines and emerging infections. The resulting project developed two ethics guidances (PI: Faden): *Pregnant Women & The Zika Virus Vaccine Research Agenda: Ethics Guidance On Priorities, Inclusion, and Evidence Generation* was released in 2017, and, under an expanded leadership team (with Ruth Karron and Carleigh Krubiner), *Pregnant Women & Vaccines Against Emerging Epidemic Threats (PREVENT): Ethics Guidance for Preparedness, Research, and Response* in 2019. Development of both was instructive and synergistic to the process of developing the PHASES Ethics Guidance.

The development of the PHASES guidance was deeply and broadly collaborative, and would not have been possible without the unparalleled contributions of the exceptional PHASES Working Group members. This guidance further reflects a global effort beyond the international membership of our Working Group. Across

these past seven years, colleagues from around the world have given generously and tirelessly their time and effort. Our dedicated research partners in Botswana, Malawi, and South Africa have contributed countless hours and expertise to the development of this product. Efforts benefitted from the momentum of burgeoning global scholarship and advocacy promoting the interests of pregnant women through responsible biomedical research, including the 2016 Global Forum for Bioethics Research (GFBR) in Buenos Aires, Argentina that was focused on pregnant women and research; and the 2018 US Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC) in Washington, DC. Our guidance development process also took inspiration from the energy of the many passionate researchers that met with us and attended our workshops at the GFBR 2017 conference in Bangkok, Thailand and the AIDS 2019 conference in Amsterdam, the Netherlands.

Finally—and most critically—this guidance was motivated by respect for and deeply informed by the perspectives of pregnant women themselves. We are immensely grateful to all of the pregnant and postpartum women who shared their experiences and wisdom. Their narratives and insights strongly informed the guidance and have been essential in illuminating the ethical pathway forward.

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