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Advancing HIV Research with Pregnant Women: Navigating Challenges and Opportunities

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Abstract

Objective—Concerns about including pregnant women in research have led to a dearth of evidence to guide safe and effective treatment and prevention of HIV in pregnancy. To better understand why these evidence gaps persist and inform guidance for responsible inclusion of pregnant women in the HIV research agenda, we aimed to learn what HIV experts perceive as barriers and constraints to conducting this research.

Methods—We conducted a series of group and one-on-one consultations with 62 HIV investigators and clinicians to elicit their views and experiences conducting HIV research involving pregnant women. Thematic analysis was used to identify priorities and perceived barriers to HIV research with pregnant women.

Results—Experts discussed a breadth of needed research, including safety, efficacy and appropriate dosing of: newer ARVs for pregnant women, emerging preventive strategies, and treatment for co-infections. Challenges to conducting research on pregnancy and HIV included ethical concerns, such as how to weigh risks and benefits in pregnancy; legal concerns, such as restrictive interpretations of current regulations and liability issues; financial and professional disincentives, including misaligned funder priorities and fear of reputational damage; and analytical and logistical complexities, such as challenges recruiting and retaining pregnant women to sufficiently power analyses.

Conclusions—Investigators face numerous challenges to conducting needed HIV research with pregnant women. Advancing such research will require clearer guidance regarding ethical and legal uncertainties; incentives that encourage rather than discourage investigators to undertake such research; and a commitment to earlier development of safety and efficacy data through creative trial designs.

Keywords

HIV; Maternal Health; Pregnancy; Ethics, Research; Clinical Trials as Topic

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Author contributions

ADL, RRF, MOL and ACM conceptualized this work. ADL, RRF, CBK and RJC facilitated all consultations with HIV experts. CBK, RJC and EBN analyzed and synthesized the content from consultations. CBK and ADL drafted the manuscript. All authors contributed to the interpretation of the data and critically revised the article for important intellectual content.

Introduction

There is an urgent need for effective HIV prevention and treatment during pregnancy. An estimated 1.5 million women living with HIV give birth each year, and among the 2 million people each year who acquire HIV, about 1 million are women of reproductive age [1, 2]. Moreover, accumulating evidence indicates that women face an increased risk of HIV acquisition during pregnancy [3, 4].

Despite this enormous need, and the tremendous scientific advancements in prevention and treatment of HIV, there are major gaps in understanding how best to address the health needs of pregnant women living with or at risk for HIV. While the evidence for prevention of mother-to-child transmission (PMTCT) is robust, health outcomes focus nearly exclusively on the fetus. Little is known about which antiretrovirals or biomedical prophylaxis methods are safest and most effective in pregnancy [5, 6, 7]; while recent Southern African guidelines list pregnancy as a contraindication to pre-exposure prophylaxis (PrEP), WHO guidelines indicate “PreP can be used in pregnancy” alongside calls for further study [8, 9]. Data are similarly lacking for treatment of HIV co-infections like tuberculosis (TB) during pregnancy, despite the major contribution of multidrug-resistant TB to perinatal morbidity and mortality [10, 11, 12].

These gaps are part of a broader problem afflicting the management of illness during pregnancy [13, 14, 15, 16, 17]. Especially for HIV, the failure to build an adequate evidence base widens the health outcomes gap between pregnant women and other populations, contravening the commitment to “make sure no one is left behind” in the ambitious fast-track plan to end the epidemic by 2030 [18].

In 2013, we launched PHASES (Pregnancy and HIV/AIDS: Seeking Equitable Study), a project aimed at developing ethically responsible, action-guiding recommendations for advancing research to address these evidence gaps. To create guidance responsive to the needs, priorities, and experiences of HIV investigators whose work addresses issues relevant to pregnant women, we have been conducting engagement meetings and one-on-one conversations with experts in HIV research. Through consultations with more than 62 HIV experts working across multiple areas of investigation and global contexts, we solicited perspectives on the most significant barriers – perceived or real – to the conduct of HIV research in pregnancy. These experts were largely based at U.S. institutions, though 7 consultations were conducted in South Africa and of 62 experts consulted, nearly half conducted their research solely in international settings (predominantly in sub-Saharan Africa). To further explore both global and country-specific perspectives on this area, our project has ongoing consultations in South Africa, Botswana and Malawi.

Roadblocks to Research

In our discussions, HIV investigators and clinicians endorsed a pressing need for more evidence to guide effective and safe treatment and prevention of HIV in pregnant women. Mirroring gaps discussed in the literature [19, 20, 21], they identified areas of need including pregnancy safety and dosing information for newer ARVs; optimal treatment

following PMTCT; safety and efficacy of emerging preventive strategies, such as microbicides, vaginal rings, oral pre-exposure prophylaxis (PrEP), and vaccines; treatment for HIV co-infections, including tuberculosis and malaria; as well as guidance for diagnostics. One commonly cited example was efavirenz, for which a lack of safety data in pregnancy resulted in reticence to use the drug, leading not only to limited treatment options for pregnant women, but also potentially poorer health outcomes given regimen changes and adverse effects associated with alternative ARVs. Within this context of limited evidence regarding pregnant women and HIV, these experts identified a wide range of barriers to gathering needed data.

Ethical Concerns: Risks, benefits and a "Catch-22" problem

HIV experts discussed ethical complexities of clinical research with pregnant women. They noted challenges in weighing potential risks and benefits of the research for the woman and the fetus, especially when the interests of one seemingly do not align with the other. Assessing relative risks and benefits across the two parties is further complicated by the dismal state of the evidence, giving rise to what one expert called a "Catch-22" dilemma: limited safety data on HIV-related drugs in pregnancy sparks concerns about unknown potential maternal-fetal exposure risks; this leads to reluctance to study pregnant women, in turn perpetuating the lack of safety data that could inform next steps for research. Some investigators also raised questions about obtaining meaningful consent, including but not limited to questions about the degree to which it is ethically appropriate or necessary to involve the biological father in the consent process.

Legal Concerns: Implications of confusing and complex regulations

Investigators frequently discussed how difficulties interpreting research regulations can impede research with pregnant women. Many discussed the U.S. regulations specific to the protection of pregnant women, human fetuses, and neonates known as "Subpart B" [22]. Despite Subpart B's statement that research with pregnant women is permissible, many investigators had experiences leading them to believe that oversight officials do not want pregnant women enrolled: often no justification was requested by oversight officials or required by IRB processes to exclude pregnant women from studies, and investigators noted that the general presumption was that pregnant women were ineligible, reinforcing the erroneous view that research with pregnant women is impermissible under current regulations. Several investigators described instances where research was thwarted by extremely cautious interpretations of "minimal risk" – a regulatory limit on risk for studies holding no prospect of direct benefit to the woman or her fetus. One investigator, aiming to delineate pharmacokinetic parameters of novel ARVs shared that, in her experience, regulators and some IRBs have held that a single dose of medication in pregnancy, even given at a fraction of the dose used clinically and in the third trimester, constitutes more than minimal risk.

Fear that IRBs would not approve studies discouraged some investigators from even attempting to include pregnant women in HIV research. This fear was exacerbated in multi-site trials, where approval from multiple IRBs was required.

Finally, some raised concerns about potential individual or institutional legal liability should the offspring be harmed during a study. Liability was also cited as a disincentive for collecting pregnancy-specific data that could be used for labeling, since this could open a pharmaceutical company to post-marketing liability should adverse effects be noted over time. This was particularly salient given the current emphasis on effects of in-utero exposures on long-term health outcomes of children.

Financial and professional disincentives

Many investigators discussed financial considerations as a source of reticence to include pregnant women. Some commented that, in their experience, pharmaceutical companies do not perceive pregnant women as a population likely to yield large returns on R&D investment. Furthermore, some noted that these studies can cost more to conduct, requiring longer-term follow up, provision of ancillary antenatal care, and potential legal costs linked to aforementioned liability concerns.

We also heard opinions that public funding agencies are biased against studies with pregnant women, with some calling these proposals “non-starters.” Many felt that the challenging funding climate, characterized by “donor fatigue,” coupled with the professional pressures to obtain grants and publish, discouraged them or their colleagues from attempting to include pregnant women, particularly when their study questions were not specific to pregnancy. A few voiced concerns about safeguarding their professional reputations, remarking that no investigator wanted to be perceived as exposing fetuses to harm or risk like the thalidomide debacle. In light of this reality, one investigator expressed frustration that the small number of HIV researchers interested in pregnancy – even collectively – cannot “beat a big enough drum” to be heard by funders or others shaping research priorities.

Analytical and logistical complexities

Investigators explained that including pregnant women in clinical research can be logistically challenging and analytically complicated. Data associated with women who are or become pregnant during a study must be analyzed separately, reducing sample size and statistical power. Additionally, some highlighted challenges in collecting data at fixed time points in pregnancy, noting that tracking down participants is difficult even without the added pressure of ensuring contact at particular pregnancy intervals. Recruitment can also be challenging, particularly when partners are involved in enrollment processes. Some researchers described going to great lengths in certain settings for “buy-in” from men to recruit pregnant women. Low enrollment also makes it difficult to run subgroup analyses for pregnancy-specific information. Loss-to-follow-up post-partum and longer-term was also a concern; some noted a common tendency for women to move to areas where they have greater family support after giving birth. While some of these challenges are also relevant to other populations, they were understood by the experts we interviewed as particularly relevant to decisions about whether to conduct research with pregnant women.

The way forward? Toward a roadmap to navigate the challenges

This long list of challenges may seem discouraging, but there is good news. Our consultations suggest that evidence gaps for the HIV response in pregnancy are due neither to lack of will among investigators nor their failure to recognize the research and clinical needs of pregnant women. Rather, these gaps are largely a function of questions, disincentives, and barriers in the wider research environment resulting in patterns of resistance and uncertainty. Left unaddressed, they will continue to erode the prospects for a much-needed evidence base. While these challenges are significant, they are not insurmountable.

Recent history shows that the landscape is navigable. The PMTCT experience reminds us that research involving pregnant women can proceed. Moreover, a progressive vanguard of studies on preventives and treatments in pregnancy demonstrates what is possible through creative trial designs – and persistence [23, 24]. A “road map” clearly identifying when and how research with pregnant women can responsibly proceed will help pave the way for more successful HIV trials to promote the health of pregnant women and their offspring through evidence-based practice.

In developing this “road map,” our consultations point to at least three areas of need. The first is clearer guidance for investigators, IRBs, and regulatory agencies on what sorts of studies with pregnant women are ethically and legally permissible. These individuals face the difficult challenge of making decisions about research in the absence of a broadly recognized ethical framework for guiding clinical research in pregnancy [25] and ongoing debate about what it would entail [26]. Such guidance will require ethical and legal analysis of the conditions for responsible HIV research with pregnant women, informed by academic and regulatory experts and legal practitioners, and responsive to the priorities and concerns of those who might conduct or participate in needed studies. The guidance would attend to such issues as when it is permissible to impose fetal risk, how such risks should be interpreted and communicated given uncertainty, and when risks can ethically be traded off between woman and fetus. Establishing a clearer sense of ethically responsible research that attends to the legal complexities may also bolster investigators’ confidence that studies involving pregnant women will be allowed to proceed. This guidance should be accessible with practical tools, which might include sample protocols, case examples, and best practices for research oversight, including IRB processes that shift the evaluative stance from presumed exclusion of pregnant women to explicit discussion of and justification for decisions about pregnancy as an inclusion or exclusion criterion.

The second entails aligning incentives to encourage, rather than discourage, investigators to undertake this important research. This will necessarily include mobilizing investment in pregnancy-relevant research among key funders and building political will among those that control or influence the research agenda through focused advocacy efforts. Regulatory agencies can also play a significant role in shifting incentives. The recent move by the FDA to require study of sex differences in animal studies is a powerful example of what can be accomplished by focal regulatory interventions, and could serve as a precursor for policies

that would accelerate reproductive toxicity studies for drugs likely to be used by pregnant women.

Third is a commitment to generating safety and efficacy data through creative trial designs to interrupt the “Catch-22” of fetal risk uncertainty. Exposure registries, opportunistic studies, and combined Phase I/II trial designs can help bypass the vexations of “minimal risk” determinations – the first two because no additional risk is associated with the research, and Phase I/II because they involve prospects of direct benefit, allowing appropriately higher permissible risk thresholds. For example, the Microbicide Trials Network EMBRACE study (MTN-016) is a prospective observational cohort study of pregnancy outcomes, as well as growth parameters, major malformations and drug resistance in infants of women who either unintentionally became pregnant while in microbicide or PrEP trials or participated in a safety study of a HIV prevention agent during pregnancy [27]. Similarly, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network Study 1026s has helped characterize pharmacokinetics of newer antiretrovirals among pregnant women (and infants) taking medications for clinical indications [28, 29]. IMPAACT 2001, a Phase I/II trial, examines the pharmacokinetics, tolerability, and safety of once-weekly rifapentine and insoniazid for treatment of latent TB in pregnant women with and without HIV-infection [30].

Conclusion

Identifying a clear path forward for HIV research in pregnancy is crucial to the advancement of maternal and child health. The evidence garnered from such research is critical to identifying appropriate dosing, providing faster access to improved frontline medications, reducing reticence to prescribing beneficial interventions, and addressing treatment discontinuity.

Over the next three years, PHASES will develop and disseminate concrete, consensus-driven guidance for research with pregnant women. This guidance will provide criteria for ethically responsible HIV research in pregnancy across a range of risks, benefits, and trade-off scenarios; a portfolio of creative study designs and practical strategies that have successfully advanced needed research; and recommendations for when in the lifecycle of drug development, drug approval, and clinical use pregnant women should be included in studies. Importantly, the utility and acceptability of these materials will be vetted by a range of stakeholders and experts in HIV and women’s health. We hope this guidance will facilitate more successful, efficient, and ethical HIV trials addressing the needs of pregnant women, ultimately shifting the research agenda to improve clinical and public health practices for pregnant women and their children through the rigorous evidence base they deserve.

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