Beyond “Vessels and Vectors”: A Global Review of Registered HIV-Related Clinical Trials with Pregnant Women

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Abstract

Background: Since the early 1990s, the HIV research agenda has prioritized to some degree the inclusion of pregnant women. However, concerns remain regarding the extent to which pregnant women's own health needs are addressed, representation in trials of HIV preventives or treatments for comorbidities, and equitable study of newer medications during pregnancy.

Methods: We employed a keyword search of the International Clinical Trials Registry Platform to identify interventional HIV-related trials conducted with pregnant women between January 2001 and December 2015. Retained trials were coded according to several key variables (*e.g.*, study endpoints, trial phase, study compound) and analyzed using information provided in the database.

Results: In total, 63 trials studying use of a pharmacological compound during pregnancy were conducted across 35 countries and sponsored by 74 unique organizations, including pharmaceutical companies. Of trials analyzed, 86% (*n* = 54) listed maternal outcomes as a primary endpoint. More than 35% (*n* = 23) of trials assessed pharmacokinetic parameters of a study compound during pregnancy. Of 45 trials specifically studying HIV-related medication(s), just 4% (*n* = 2) focused on HIV preventives. One trial studied tuberculosis in HIV-infected pregnant women; 11 studied malaria. On average, medications were studied during pregnancy 4.4 years after licensure.

Conclusions: Our findings demonstrate that trials with pregnant women are conducted across a range of countries and sponsors, and much progress has been made to better address pregnant women's own health needs in HIV research. However, our findings confirm other concerns, for example, lack of HIV preventives studied and the lag between medication licensure and study during pregnancy.

Keywords: pregnant women, HIV, clinical research, PMTCT, pharmaceuticals

Introduction

IN 1996, FADEN, KASS, and McGraw popularized the phrase “women as vessels and vectors” in their work on the inclusion—or, more aptly, exclusion—of the interests of women, including pregnant women, from the HIV research enterprise.¹ Faden et al. demonstrated that HIV research conducted with women in the 1990s “reflected an interest in women as vectors or as vessels of transmission,” and when pregnant women were included, their participation was directed almost wholly toward addressing the health needs of the fetus.¹

Recently, however, HIV research has become a field in which research with pregnant women is actively pursued,² a contrast to both the broader research enterprise presently³ and

the HIV research enterprise historically.⁴ Although pregnant women are more widely and meaningfully included in HIV research now than they were 20 years ago, questions remain regarding the nature of their growing participation—especially the degree to which this participation addresses the health needs of pregnant women themselves. First are concerns that such research, with its genesis in studies focused on the prevention of mother-to-child transmission of HIV, has focused primarily on protecting the health of offspring with little regard for the health of the pregnant woman.¹ Second are concerns about the exclusion of pregnant women from HIV prevention studies despite their critical need for preventive interventions, noting unique social and biological risk factors that render pregnant women susceptible to infection.² Third are

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concerns about pregnant women's representation in studies of treatment for HIV coinfections, which can have devastating consequences on the woman and fetus alike.^{2,5} Fourth are concerns about timely access to evidence-based use of newer treatments for HIV during pregnancy—especially considering the many advantages of access to second- and third-generation medications for management of the disease²—given the pharmaceutical industry's general reluctance to include pregnant women in trials.

Despite persistent barriers to their inclusion,⁶ pregnant women have participated in HIV research to a greater extent than ever before. More than 20 years ago, Faden et al. investigated the number and nature of HIV research studies involving pregnant women.¹ To explore the extent to which the HIV research agenda has progressed from perceiving pregnant women as merely “vessels and vectors,” and the extent to which the HIV research agenda has addressed the health needs of women themselves, we undertook a robust, 15-year analysis of interventional clinical trials studying an HIV-related pharmaceutical during pregnancy. Much like the work of Faden et al. two decades ago, this review seeks to map the current landscape of HIV research with pregnant women, describing the number and nature of HIV-related research trials that include pregnant women.

Methods

In January 2016, records were taken from the World Health Organization's International Clinical Trials Registry Platform (ICTRP), which compiles clinical trials registered in several national and regional databases.⁷

Two searches were conducted in the ICTRP database. First, a search of the ICTRP database was performed to identify all trials involving pregnancy and HIV. Trials under any stage of recruitment listing “HIV” as the study condition and including any of the terms “pregnancies,” “pregnancy,” “pregnant,” “natal,” “perinatal,” “neonatal,” “antenatal,” “postnatal,” “prenatal,” “perinatally,” “MTCT,” “PMTCT,” “maternal,” “partum,” “mother,” “mothers,” or “birth outcomes” in the trial title were eligible for analysis. A second search was conducted to identify additional trials under any stage of recruitment, listing “pregnancy” or “pregnant” as the study condition and “HIV” or “AIDS” in the trial title, which were added to all trials obtained from the first search.

Combined database results were then limited to those reporting their study start date between January 2001 and December 2015, capturing the preceding 15 years of research at the time of data collection. Remaining results were further restricted to studies classified as “interventional” and then restricted to those investigating a pharmaceutical product, excluding studies of behavioral interventions, procedures, and medical devices. Each remaining study was assessed for inclusion of pregnant women: trials were not included in analysis if pregnancy was listed as an exclusion criterion, or if pregnant women were recruited for a trial in which only their offspring were offered the study intervention.

All studies included in the final analysis were coded according to objectives, phase, type of study compound investigated, and study endpoint(s). Studies were also coded according to the Food and Drug Administration (FDA) approval date for any HIV treatment medications used in the trial (approval dates collected from AIDSinfo.nih.gov).⁸ For

studies conducted using more than one medication (*e.g.*, a trial investigating a combination of two or more distinct and individually approved medications to better manage HIV), the medication with the most recent approval date was used to assess the lag between medication approval and study start date. Thus, the results reported regarding lag between medication approval and study start date represent the most “generous” delay in the medication's study during pregnancy. In a few cases, ICTRP database information on trial location, inclusion and exclusion criteria, date of registration, study target enrollment, primary and secondary outcomes, sponsor and contact details, and source register were included where available.

Results

The first search yielded 231 records matching the search criteria. Two of the 231 records represented the same trial, leaving 230 unique trials. The second search yielded 23 additional records not identified in the first search. In total, 253 trials involving pregnancy and HIV were obtained. Of these, 207 trials listed an enrollment start date between January 2001 and December 2015. Of these, 168 were listed as “interventional” studies; 39 trials listed as “observational” were excluded. Notably, 14% ($n=5$) of the excluded observational trials assessed the pharmacokinetics (PK) of a study compound during pregnancy.

Of 168 interventional trials, only trials reported as investigating a pharmaceutical product (*e.g.*, medication, vaccine) were included for analysis, leaving 95 trials. Of these, 67 trials investigated use of a pharmacological intervention among HIV-infected pregnant women or investigated use of an HIV preventive in pregnant women. Of these 67 registered trials, 4 were withdrawn before enrollment and thus excluded (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/jwh). A total of 63 trials retrieved from the ICTRP were analyzed and coded (Supplementary Table S1). Of 63 studies, 67% ($n=42$) studied exclusively medications to treat HIV, 3% ($n=2$) studied exclusively HIV preventives, and 29% ($n=18$) studied exclusively the prevention or treatment of HIV comorbidities (*e.g.*, malaria) or investigated the efficacy of dietary supplements or hormones (*e.g.*, progesterone) on maternal and fetal health outcomes. One study investigated the PK both of HIV treatments and antitubercular medications during pregnancy, as well as PK of contraceptives during the postpartum period. For the purposes of this analysis, this study was considered a study of HIV treatment.

Of 63 studies, 3% ($n=2$) enrolled only HIV-uninfected pregnant women and aimed at HIV prevention, 87% ($n=55$) enrolled only HIV-positive pregnant women, and 10% ($n=6$) enrolled both HIV-positive and HIV-negative pregnant women.

Study start date (date of enrollment)

More than two-thirds of studies ($n=44$) began enrollment before 2010. The distribution of analyzed trials by study date demonstrates no appreciable trend (Fig. 1).

Study location

A total of 127 study locations were listed for the 63 trials analyzed, comprising 35 distinct countries. Nearly 25% of

FIG. 1. Interventional clinical trials to treat or prevent HIV or comorbid disease in pregnant women by year of study enrollment start date for all trials included in analysis ($n=63$).

registered studies ($n=15$) were conducted with at least one site in the United States (including Puerto Rico). Five or more studies were conducted in each of the following countries: Brazil, India, South Africa, Tanzania, Thailand, Uganda, United Kingdom, and Zambia.

Research sponsors

The 63 analyzed trials listed 125 organizations as either “primary” or “secondary” sponsors, comprising 74 unique sponsors. Primary sponsors included the National Institute of Allergy and Infectious Disease (27%; $n=17$), Institut de Recherche pour le Développement (8%; $n=5$), and the Centers for Disease Control and Prevention (5%; $n=3$); 8% ($n=5$) listed a pharmaceutical company, namely Boehringer Ingelheim, Bristol-Meyers Squibb, GlaxoSmithKline, Janssen Scientific Affairs (grant administrator for Janssen Pharmaceuticals), or Pfizer, as the primary sponsor. None of these five studies listed any secondary sponsors. Just >5% ($n=4$) of studies listed a pharmaceutical company as a secondary sponsor. The Eunice Kennedy Shriver Institute of Child Health and Human Development served as secondary sponsor for 24% ($n=15$) studies.

Interventional study compounds

Of the 63 studies analyzed, 71% ($n=45$) studied an HIV treatment or preventive during pregnancy.

Across the 45 studies investigating HIV medications, 137 compounds, in total, were studied during pregnancy. The vast majority of studies investigated efficacy, safety, or PK of more than one study compound during pregnancy. A total of 34 distinct study compounds comprise these 137 medications (Fig. 2). Of the 137 medications studied, 37% ($n=51$) were fixed-dose combination (FDC) drugs, 20% ($n=28$) were non-

nucleoside reverse transcriptase inhibitors, 18% ($n=25$) were nucleoside reverse transcriptase inhibitors, 15% ($n=21$) were protease inhibitors, and 5% ($n=7$) were integrase inhibitors. Tenofovir gel ($n=2$), entry inhibitors ($n=1$), fusion inhibitors ($n=1$), and PK enhancers ($n=1$) each accounted for 1% of medications studied. Combined lopinavir and ritonavir and combined lamivudine and zidovudine accounted for 37% ($n=19$) and 29% ($n=15$) of the 51 FDC medications studied, respectively.

Of 45 studies investigating HIV treatments or preventives, 43 investigated medications already approved by the FDA. Two studies—the two studies that focused on maternal HIV prevention—investigated the use of a microbicide gel that is not yet approved for use by the regulatory agency. On average, the lag time between study start date and the most recent date of FDA approval for a medication used in the study was 4.4 years (*i.e.*, on average, most medications were studied in pregnant women 4.4 years after FDA approval). Of the 43 studies using FDA-approved HIV medications as the study compound, 7% ($n=3$) listed a study start date that preceded the FDA approval date of the most recently approved medication used; each of these studies utilized an opportunistic study design, and newer medications were added to the list of study compounds investigated as the trial progressed. Each of these studies investigated PK. Removing these studies from calculations of average lag time increased the lag to 5.3 years between study start date and the most recent date of FDA approval for a medication used in the study.

Phase

Of the 63 studies analyzed, 87% ($n=55$) reported study phase. Of these, 15% ($n=8$) were classified as phase I, 25%

FIG. 2. HIV medications studied during pregnancy with FDA approval (year in *parentheses*), drawn from 45 studies ($n = 137$). FDA, Food and Drug Administration.

($n = 14$) were classified as phase II, 35% ($n = 19$) were classified as phase III, and 22% ($n = 12$) were classified as phase IV studies. One study was classified as “phase I and II,” and another as “phase II and III.” More than 35% of trials ($n = 23$) assessed PK as an outcome. Of the 23 studies assessing PK, 22% ($n = 5$) were reported as phase I trials, 4% ($n = 1$) were “phase I and II,” 26% ($n = 6$) were phase II, 17% ($n = 4$) were phase III, and 30% ($n = 7$) were phase IV (Fig. 3).

Study design

Of 63 studies, 63% ($n = 40$) were randomized, 35% ($n = 22$) were not randomized, and one study did not indicate randomization. Of 40 randomized studies, 58% ($n = 23$) studied HIV medications during pregnancy. All antimalarial trials ($n = 11$), all dietary supplement trials ($n = 3$), as well as each trial that addressed herpes simplex virus (HSV; $n = 1$), tuberculosis (TB; $n = 1$), and a hormone supplement ($n = 1$), were randomized. Of the 22 non-randomized studies, all except one (an influenza vaccine trial) studied HIV medications during pregnancy. Based on intervention studied, 94% ($n = 17$) of the 18 non-HIV medication studies were randomized, while just 52% ($n = 23$) of the 44 HIV medication studies were randomized (Fig. 4). More than 75% ($n = 17$) of non-randomized studies investigated PK of HIV medications (either as the primary outcome or as part of a safety/PK or efficacy/PK study). Notably, 14% ($n = 9$) of the studies in-

cluded in this analysis since they were listed as “interventional” in the ICTRP database actually relied upon a non-randomized, opportunistic study design in which the woman was already receiving the study compound through clinical care. All of these opportunistic studies assessed PK.

Trial enrollment ranged from 10 to more than >5700 study participants. Approximately one-third ($n = 20$) of studies recruited between 10 and 100 participants, 40% ($n = 25$) recruited between 100 and 500 participants, and 29% ($n = 18$) recruited more than 500 participants.

Study endpoints

Primary study endpoints were reported for 98% ($n = 62$) of trials or gleaned from original database registry summaries. More than half of all studies ($n = 33$) listed only maternal health outcomes (*e.g.*, placental malaria infection, maternal drug resistance, maternal PK) as primary study endpoints. Of these 33 studies, 33% ($n = 11$) did not investigate HIV medications.

One-third ($n = 21$) of studies listed both maternal and fetal outcomes as primary study endpoints. Only 13% ($n = 8$) listed exclusively fetal outcomes (*e.g.*, preterm birth, low birthweight, small for gestational age).

Just over 20% ($n = 13$) listed infant HIV status as a primary study endpoint. More than 80% ($n = 52$) reported secondary study endpoints; 27% ($n = 14$) listed infant HIV status as a

FIG. 3. Reported phase of trial, disaggregated by assessment of PK as an outcome ($n = 63$). PK, pharmacokinetics.

secondary endpoint. Overall, 43% ($n = 27$) of the 63 studies analyzed included infant HIV status as a specific primary or secondary endpoint.

Discussion

In this analysis of HIV-related trials with pregnant women reported in the ICTRP database, we found both promising trends and areas of continued concern. Most encouragingly, our analysis identified increased attention to the health interests of pregnant women themselves. While women in HIV research were once dubbed ‘vessels and vectors’ due to a narrow focus on PMTCT and perinatal outcomes—to the ex-

clusion of women’s own health interests early in the epidemic (CITE 1)—our findings indicate that women’s health interests are well represented among the modest number of HIV studies conducted during pregnancy in the past 15 years. Just over 85% ($n = 54$) of the 63 studies analyzed listed either maternal health outcomes alone or both maternal and fetal health outcomes as primary endpoints. Though interest in PMTCT remains a motivator for trials—infant HIV status was a primary or secondary endpoint assessed in nearly half of the studies (43%; $n = 27$)—data collection of maternal outcomes is largely included in these trials.

Also encouraging is the apparent attention to PK parameters among the studies identified, which stands in contrast to recent

FIG. 4. Type of intervention investigated (HIV medication versus other study compound), disaggregated by study design (randomized or nonrandomized; $n = 62$).

reports indicating that less than 2% of all PK studies published between 1967 and 2013 include pregnant women.⁹ More than 35% ($n=23$) of trials included in our analysis assessed PK of a pharmacological agent during pregnancy, suggesting both that PK studies during pregnancy are feasible and are conducted with some frequency in the context of HIV research. Notably, 30% ($n=9$) of these 23 PK studies utilized an opportunistic study design in which the woman was already receiving the study compound of interest through clinical care. Such trial designs often involve minimal research-related risk and, as such, are “low-hanging fruit” for generating evidence.²

Our findings also indicate a willingness to conduct research with pregnant women across 35 countries and 74 distinct sponsors, including 9 different pharmaceutical companies. Despite concerns that the pharmaceutical industry does not engage in research with pregnant women, our findings demonstrate that the industry does conduct trials to some extent. Still, the vast majority of studies were sponsored by governmental research institutions or universities. Many have noted a need for governmental intervention to fund, incentivize, and advance research in complex populations that are underrepresented in research¹⁰; this is likely to be true for research with pregnant women.

Furthermore, the trials analyzed reflect a willingness to implement a range of study designs. More than half of the studies in our analysis used a randomized trial design, and start date of medication administration ranged across gestational age, including 14 studies that began medication administration in the first trimester (when risk of pregnancy loss, as well as teratogenic harm, tends to be higher and aversion to such risk might be presumed to preclude such investigations). That said, 64% ($n=9$) of those 14 studies utilized an opportunistic study design, posing no increment of research-related risk to the fetus.

The results of this review also affirm some concerns that have been raised around HIV research, namely that HIV-related research with pregnant women focuses more on PMTCT and treatment for HIV than on preventing HIV infection in pregnant woman.² We found that the number of studies of HIV preventives among pregnant women, critical to the effort to combat HIV, trail far behind treatment studies. With a few exceptions (*e.g.*, Cohen et al., 2011¹¹), prevention trials, including safety and dosing of microbicides and pre-exposure prophylaxis regimens, have excluded pregnant women.^{12–15} Our analysis underscored this tendency: of 63 studies analyzed, 71% ($n=45$) specifically investigated any HIV medication use during pregnancy, yet only 4% ($n=2$) of these trials focused on prevention of HIV.

Further, though 61% ($n=11$) of the 18 non-HIV medication trials focused on malaria, a common co-infection to which HIV-infected pregnant women are particularly susceptible,¹⁶ only 6% ($n=1$) of the non-HIV medication trials focused on TB, a critical comorbidity for HIV and a significant contributor to maternal and infant mortality among HIV-infected populations.¹⁷

Our findings also confirm a tendency to delay studying medications in pregnancy until after FDA approval. Of the 43 studies of HIV therapeutics identified, all involved compounds that were already licensed for use in the general population. On average, study start date occurred an average of 4.4 years after the most recent FDA approval of the HIV medication being studied. Further, few recently approved medications have been

tested in pregnant women; though 14 HIV medications were approved for use by the FDA between 2010 and 2015, only 50% ($n=7$) of these HIV medications were studied in pregnant women. These seven medications were included in just 6% ($n=4$) of the 63 trials. Moreover, three of these four trials utilized an opportunistic study design. Only one study (conducted in 2004) utilized a medication that had been approved in the same year. Of the 45 studies investigating HIV medications, only 22% ($n=10$) studied medications that had been approved within 3 years of the study start date. Our findings thus reflect continued reliance on post-market study for safety during pregnancy, indicating an ongoing need to emphasize the importance of implementing studies during pregnancy earlier in the drug development cycle when appropriate.

Our study is strengthened by the use of the ICTRP database, which gathers data from more than 15 primary registries, thereby collating a more holistic picture of global research.⁷ The study is further strengthened by the use of two separate search strategies to maximize the number of eligible studies captured in the search. Additionally, we reviewed every study protocol and individually coded the narrative descriptions of each trial in addition to analyzing information automatically collected in the database fields.

This study is limited, however, by the poor search functionality within the ICTRP database. Both search strategies identified only studies that specifically include pregnant women; thus, studies that may have recruited women irrespective of pregnancy status were not identified. Further, incompleteness and a lack of standardization within the study records impacts the accuracy of our findings, including inconsistent patterns in the characterization of observational studies as “interventional,” suggesting that other observational studies may have been excluded. In addition, regulations for source registers that contribute to the ICTRP database vary by jurisdiction—for example, while registration of all “applicable clinical trials” conducted in the U.S. is required by law,¹⁸ registration of clinical trials is not legally mandated in Australia and New Zealand.¹⁹ Because not all ICTRP primary registries require registration of clinical trials, generalizability of our findings is limited due to potential underreporting of trials conducted.

Conclusions

In summary, the findings of this study are encouraging: research with pregnant women in the context of HIV is conducted with some frequency and through a variety of sponsors, locations, and study designs. Our findings provide evidence to assuage some common concerns regarding the nature of clinical research during pregnancy, most notably attention to and priority for the health needs of women themselves as well as study of PK parameters among pregnant women. However, important opportunities for improving the evidence base remain, including advancing research on HIV prevention strategies for pregnant women and investigating safety and efficacy of study compounds during pregnancy earlier in the drug development cycle.

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Contribution to Authorship

M.O.L. and A.D.L. conceptualized this work. M.N.W. and A.S.C. performed the data collection and analysis. K.A.S. advised on data collection and analysis. M.N.W., M.O.L., and A.S.C. prepared the first draft. All authors contributed to the writing and editing of the final article.

Author Disclosure Statement

No competing financial interests exist.

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