Enhanced and Timely Investigation of ARVs for Use in Pregnant Women

Elaine J. Abrams, MD,[a,b] Lynne M. Mofenson, MD,[c] Anton Pozniak, MD,[d] Shahin Lockman, MD,[e,f,g] Angela Colbers, PhD,[h] Yodit Belew, MD,[i] Polly Clayden,[j] Mark Mirochnick, MD,[k] George K. Siberry, MD, MPH,[l] Nathan Ford, PhD, MPH,[m] Saye Khoo, MD, PhD,[n] Francoise Renaud, MD,[m] Marco Vitoria, MD,[m] Willem D. F. Venter, MD,[o] Meg Doherty, PhD, MD, MPH,[m] and Martina Penazzato, MD, MSc, PhD,[m] on Behalf of the PADO and CADO Experts Groups

Background: Concerns have been voiced that the exclusion of pregnant women from clinical trials results in a lack of safety and pharmacokinetic data for antiretroviral drugs (ARVs) in pregnancy, creating clear risks to pregnant women living with HIV (PWLHIV), and their infants.

Setting: The World Health Organization convened a Paediatric Antiretroviral Drug Optimization group meeting, December 10–12, 2018, in Geneva, Switzerland.

Methods: The group, comprised of clinicians, scientists, HIV program managers, regulators, and community representatives, were tasked to consider how ARVs are studied in PWLHIV, define alternative approaches to studying ARVs in PWLHIV, identify ways to shorten the timeline to determine safe use of new agents during pregnancy, and define strategies to collaborate with regulators and industry to change longstanding practices.

Results: Most new ARVs are not studied in pregnant populations until after drug licensure, primarily opportunistically among women who become pregnant while taking the ARV of interest. Acceleration of the timeline will require earlier completion of preclinical studies and a new paradigm, namely—under certain conditions—allow women who become pregnant while participating in phase III ARV studies the option of remaining on study and enroll pregnant women into phase III trials of new agents to obtain preliminary safety and dosing and efficacy data.

Conclusion: A revision of the current approach to the study of antiretrovirals in pregnant women is urgently needed to improve timely access and safe use of new agents during pregnancy.

Key Words: HIV, pregnancy, antiretroviral, pharmacology, clinical trials

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INTRODUCTION

With more than 19.2 million women living with HIV worldwide aged 15 years and older (majority of reproductive potential) and an estimated 720,000 women older than 15 years old newly infected with HIV in 2019, there is a public health imperative to obtain safety and pharmacokinetic (PK) data on antiretroviral drugs (ARVs) in pregnancy.[1] In 2019, over 85% of the estimated one million pregnant women living with HIV

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From the [a]ICAP at Columbia University, Mailman School of Public Health, Columbia University, New York, NY; [b]Department of Pediatrics, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY; [c]Research Program, Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC; [d]HIV and Sexual Health Clinic, Chelsea and Westminster Hospital NHS Foundation Trust and LSHTM London, London, United Kingdom; [e]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA; [f]Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, MA; [g]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana; [h]Radboud University Medical Center, and HIV Institute, Nijmegen, the Netherlands; [i]Division of Antiviral Products, US Food and Drug Administration (FDA), Silver Spring, MD; [j]HIV i-Base, London, United Kingdom; [k]Department of Pediatrics, Boston University School of Medicine, Boston, MA; [l]Division of Prevention Care and Treatment, Office of HIV/AIDS, United States Agency for International Development (USAID), Washington, DC; [m]Global HIV, Hepatitis and STIs Programme, World Health Organization, Geneva, Switzerland; [n]Department of Pharmacy, Research Institute, University of Liverpool, United Kingdom; and [o]Ezintsha, Wits Reproductive Health Sciences, University of Witwatersrand, South Africa.

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Correspondence to: Martina Penazzato, MD, DTMH, MSc, PhD, Global HIV, Hepatitis and STIs Programme, WHO, Avenue Appia, 20, CH-1202, Geneva, Switzerland (e-mail: penazzatom@who.int).

(PWLHIV) received ARVs.[1] With expansion of "treat all," increasing numbers of women are conceiving while already on antiretroviral therapy (ART).[2] The high unmet need for family planning in many settings, in parallel with greater child-bearing desires among people living with HIV on effective therapy, further contribute to high pregnancy rates among women on ART.[1] Pregnant women are generally excluded from phase I–III studies of investigational agents, and safety and PK data only become available years to decades after initial approval, if at all (Table 1). This delay is multifactorial, including the perception that studies in pregnancy are too high risk to conduct until drug licensure is secured. Consequently, pregnancy is often an exclusion criterion for enrollment and ongoing participation in trials of new agents.

Historically, pregnant women have been considered a "vulnerable" population and excluded from research of new drugs.[3] Intended to protect the fetus from harm, the exclusion of PWLHIV from early phase drug research has resulted in a paucity of pregnancy-specific safety and PK data for many ARVs that, once licensed, are inevitably used during pregnancy. Between 1920 and 2010, 91% of US Food and Drug Administration (US FDA) approved drugs had no data on safety and/or efficacy in pregnancy.[4] Although ARVs have been studied in pregnancy more than drugs for other major disease categories, the median time from US FDA approval to first published PK data in pregnancy has been 6 years (range 2–14 years).[2] Most dosing and safety data have been obtained from small postlicensing opportunistic PK studies supported within the PANNA (Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women) and IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) networks, enrolling pregnant women prescribed the ARV of interest in their routine care.[5,6] Although most of these "opportunistically studied" ARVs have demonstrated few clinically significant differences between pregnant and nonpregnant women, recent findings demonstrate the dangers of this approach. When coadministered with cobicistat, elvitegravir, darunavir, and atazanavir demonstrated significantly reduced plasma concentrations during pregnancy.[7] In light of these low exposures, ARVs boosted by cobicistat are no longer recommended during pregnancy.[8]

Concerns for a potential association of periconception exposure to the integrase inhibitor dolutegravir and neural tube defects have focused attention on the critical importance of defining the safety of new agents in women of reproductive potential and the need for appropriate postmarketing pharmacovigilance surveillance of drug safety in and after pregnancy to detect rare adverse maternal outcomes[9–11] and long-term infant and child health effects from in utero HIV and ARV exposures.

Over the last decade, critical work on ARV drug optimization has identified the most potent, safe, and cost-effective agents for HIV treatment.[12] Principles such as simplification and harmonization of ARV regimens across subpopulations have guided rapidly evolving global ARV guidelines, introducing safer and more durable regimens across all populations (including PWLHIV) to optimize individual outcomes while facilitating the scale-up of national ART programs within a public health approach.[13] There is an ethical requirement for ensuring there is an evidence base for the safety and efficacy of drugs that will be used by women of reproductive potential as well as pregnant women so that they are not excluded from receiving the new, potent regimens. Multiple stakeholders, including the community of people living with HIV, have voiced concerns about the exclusion of pregnant women from clinical trials and have joined forces to examine existing barriers and identify targeted solutions. Importantly, these concerns do not just apply to ARVs but to many other drugs which could be used in pregnant women to prevent or treat serious diseases such as tuberculosis, malaria, and epilepsy among others.[14] The framework for ARV studies can be the used as the basis for future consideration of studies in pregnant women of drugs for other disease areas.

The World Health Organization (WHO) convened relevant stakeholders within the Paediatric Antiretroviral Drug Optimization (PADO) group to consider how ARVs are studied in pregnant women, define and standardize optimal approaches to study ARVs in pregnant women, identify ways to accelerate the timeline to determine safe use of new agents during pregnancy, enable early engagement of the community of people living with HIV in pregnancy research (Fig. 1), and define strategies to collaborate with regulators and industry to change current practices. This article presents key findings from the meeting and sets forth principles and actions to improve timely access to new ARV medications for pregnant women. Although acknowledging that these issues extend to the study of drugs during breastfeeding, this work focuses primarily on studies during pregnancy (Fig. 2).

METHODS

The PADO group has been involved in informing development and introduction of ARVs for the treatment and prevention of HIV infection in children and for the treatment of HIV infection in PWLHIV in low-income and middle-income countries (LMIC). Individuals from the PADO group were convened by the WHO (PADO 4)[15] on December 10–12, 2018, in Geneva, Switzerland. Participants from 15 countries included representatives from WHO expert advisory groups (eg, Paediatric ARV Working Group, Adult ARV Working Group, and HIV Drug Resistance Network-ResNet) and from partnerships in the area of ARV drug optimization. Building on outcomes of the Conference on Antiretrovirals and Drug Optimization 3 (CADO 3) meeting,[16] the group met in plenary and working group sessions.

The outcomes were shared for input from a broader community of adult ARV expert members of the adult HIV treatment working group[17] at their annual meeting, resulting in strong endorsement of the meeting outcomes. Therefore, the article represents the view of a broad constituency of global ARV experts.

TABLE 1. Summary of New Antiretroviral Agents and Planned and Ongoing Studies in Pregnant Women Living With HIV

Compound	Class	Status/Phase	Dosing Schedule	Indication	Planned + Ongoing Studies in PW
Tenofovir alafenamide	NRTI	Approved in FDCs	25 mg + 10 mg boosted once-daily	Treatment	IMPAACT 1026 IMPAACT 2026 and PANNA (PK studies), IMPAACT 2010 efficacy and safety study
Bictegravir	INSTI	Approved in FDCs	50 mg oral once-daily (FDC with emtricitabine/tenofovir alafenamide)	Treatment	IMPAACT 2026, PANNA, gilead
Doravirine	NNRTI	Approved as single + in FDC	100 mg oral once-daily	Treatment	IMPAACT 2026 and PANNA PK studies
Ibalizumab	mAb	Approved	Single loading dose 2000 mg IV Maintenance dose 800 mg every 2 wk	Treatment (multidrug resistant)	Unknown
Cabotegravir	INSTI LA	Phase III completed Submitted to FDA—rejected Dec 2019	400 mg IM (600 mg rilpivirine injection) every 4 or 8 weeks	Treatment PrEP	ViiV (includes PK substudy-women to to remain on CAB studies if pregnant)
Dapivirine	NNRTI	EMA decision pending FDA and SAHPR submissions planned	25 mg vaginal ring 1 mo	PrEP	Deliver: 750 women dapivirine vs. tenofovir/emtricitabine (includes efficacy, safety and PK mother + child)
Fostemstavir	Attachment inhibitor	FDA decision pending	600 mg oral twice-daily	Treatment (multidrug resistant)	BRIGHTE study (women becoming pregnant were given option to continue. Outcomes published)
UB-421	Attachment inhibitor	Phase III	IV every 1 or 2 wk	Treatment (monotherapy substitution for virologically suppressed adults)	Unknown
Leronlimab	CCR5 antagonist	Phase IIb/III	Weekly SC inj	Treatment	Unknown
Islatravir	NRTTI	Phase III Phase IIa Phase I	0.75 mg once-daily oral (FDC with doravirine) 60 mg once monthly oral 62 mg annual implant	Treatment PrEP	Unknown
ABX464	Rev inhibitor	Phase II	Oral once-daily	Treatment	Unknown
Abivax					
Albuvirtide	Fusion inhibitor	Phase II	LA IV 2/4 wk	Treatment (maintenance)	Unknown
GSK 3640254	Maturation inhibitor	Phase IIa	Oral once-daily	Treatment	Unknown
GS 9131—prodrug for GS 9148	NRTI	Phase II	Oral once-daily	Treatment (activity against NRTI resistant virus)	Unknown
VRC01/VRC01LS	Therapeutic vaccine, bNb	Phase II	LA IV or SC 1/3 wk	Treatment + PrEP	Unknown
GS-6207 (analog of GS-CA1)	Capsid inhibitor	Phase II	LA SC 6-monthly	Treatment (multidrug resistant)	Unknown
GS-CA1	Capsid inhibitor	Phase I	LA SC	Treatment	Unknown
Combinectin	Combined adnectin/fusion inhibitor	Phase I	LA SC once-weekly	Treatment	Unknown

IMPAACT 1026 and 2026 and PANNA are post-marketing opportunistic design PK studies in pregnancy.[5,6]

Table updated March 2020, so some compounds further in development/approval then when discussed at the meeting.

FDA, US Food and Drug Administration; FDC, fixed dose combination; EMA, European Medicines Agency; IM, intramuscular; INSTI, integrase strand transfer inhibitor; IV, intravenous; LA, long-acting; mAb, monoclonal antibody; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; NRTTI, nucleoside reverse transcriptase translocation inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PW, pregnant women; SAHPRA, South African Health Products Regulatory Authority; SC, subcutaneous.

People living with HIV have been strongly involved in clinical trials and policy decisions since the early days of the epidemic. The PADO and CADO groups have underscored the importance of community engagement as an essential component of clinical research and drug development.

Recommendations from PADO emphasized the critical importance of direct engagement of communities of women living with HIV early in designing studies including working with existing national, regional community advisory boards, organizations of women living with HIV and setting up an appropriate advisory board for the study; supporting treatment and prevention literacy training to ensure that trial participants and their activists understand the science of HIV and the research interventions; involving women living with HIV and their activists in the development of informed consent forms written in plain language and; producing appropriate, acceptable and meaningful study-related material.

FIGURE 1. Community engagement. full color online

RESULTS

Regulatory Framework

Ethical codes and regulations have been established to protect human subjects who participate in research.[18] Guidance has also been published to help researchers conduct studies ethically and within the framework of established regulations. The recently published US FDA guidance, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry" discusses scientific and ethical issues to consider for inclusion of pregnant women in clinical trials and emphasizes the need to facilitate the inclusion of women (pregnant and non-pregnant) in clinical drug development programs[19] (Fig. 3).

- Historical delays continue to occur and there is an imperative to accelerate better ARV access for pregnant women with HIV
- Need for a fundamental paradigm shift in attribution of risk: use of new ARVs in clinical care without dosing or safety data in pregnant women puts them and their fetuses at risk of potential harmful interventions, suboptimal treatment and/or failed prevention of maternal disease and mother to child transmission.
- Earlier completion of pre-clinical reproductive toxicity studies is essential to accelerate subsequent evaluation of ARVs in pregnant women with HIVHIV
- Pre-drug-approval conduct of pregnancy pharmacokinetic (and safety) studies for promising new drugs (e.g. during phase III trials of new ARVs in non-pregnancy individuals) is critical to ensure optimal treatment for women living with HIV.
- Optimal design of pharmacokinetic studies in pregnancy should include intensive PK studies with full pharmacokinetic curves in the 3rd (and preferably also in 2nd and 1st trimester, and 4 weeks postpartum for comparison) as well as sparse sampling studies contributing to population PK models and determine covariates influencing PK changes.
- Full understanding of birth defects and long-term safety can only be established through active and robust surveillance where rarer adverse outcomes (and outcomes related to peri-conception or early first trimester exposure) can be documented.
- Implementation of this framework requires sustained and effective partnership:
    - with regulators to further enable earlier investigation of medicines in pregnancy;
    - with industry to more systematically generate evidence through clinical development of new drugs;
    - with researchers to promote innovative study design and foster cooperation for optimal implementation of studies;
    - with donors to ensure resources are available to support the clinical and operation research required;
    - with governments to enable responsible research by supporting ethical review board decisions and long-term efforts to undertake active pharmacovigilance and data sharing; and finally,
    - with the community of women living with HIV to foster their early involvement in research and to keep global stakeholders accountable.

FIGURE 2. Principles for accelerated investigation of new ARVs in pregnant women living with HIV. full color online

Highlights from US FDA Draft Guidance
Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials
Guidance for Industry ([1])

Inclusion of pregnant women in clinical trials requires careful risk-benefit assessments and must incorporate both ethical and scientific considerations.

1. Ethical Considerations guided by US federal regulations 45 CDR Part 46; 21 CFR Parts 50, 56, and 312
   - Where appropriate, data are available from nonclinical studies, including reproductive studies, and from clinical studies in nonpregnant adults to assess risks to pregnant women and fetuses.
   - The risk to the fetus is caused solely by interventions that has prospect of direct benefit for the woman or the fetus; or, when no prospect of benefit is expected, the risk to the fetus is not greater than minimal and the purpose of the research is to develop important biomedical knowledge which cannot be obtained by any other means.

2. General guidelines for including pregnant women in clinical trials (pre-market)

Examples of circumstances where inclusion of pregnant women with a disease or condition requiring treatment is ethically justifiable

- Enrollment into an investigational trial:
  - Completed adequate nonclinical studies (including studies on pregnant animals), and
  - The proposed clinical trial holds out the prospect of direct benefit to the pregnant woman and/or fetus, and not otherwise available outside the research setting (e.g., lack of approved effective treatment option to the pregnant woman)
- Women who become pregnant during clinical trials:
  - Adequate nonclinical studies are completed
  - When a pregnancy occurs during a clinical trial, and if fetal exposure has already occurred, a woman should be allowed to continue the investigational drug if the potential benefits of continued treatment for the woman outweigh the risks to the fetus or the mother. Pregnancy outcome data should be collected regardless of whether the drug is continued.
  - When a pregnancy occurs during a clinical trial, unblinding should occur to allow for counseling. Pregnant women who choose to continue in the clinical trial should be re-consented to reflect the additional risk-benefit considerations.

FIGURE 3. US Food and Drug Administration draft guidance for industry on considerations for inclusion of pregnant women in clinical trials. full color online

Clinical Studies of New Antiretroviral Agents in Pregnant Women

Studies have demonstrated that although ARVs generally have similar efficacy in pregnant women and nonpregnant adults, ARVs have variable associations with adverse pregnancy outcomes, including risks of still birth, preterm delivery, and low birth weight.[20] The purpose of ARV clinical studies in pregnant women is to establish the PK and safety of ARVs, collect virologic outcomes, and evaluate pregnancy outcomes; efficacy is extrapolated from the non-pregnant adult trials, if the exposures in pregnancy are similar to the exposures observed with the marketed dose for the non-pregnant adult populations. Currently, studies evaluating ARVs during pregnancy are conducted only after drug approval and marketing (phase IV), if at all. There is, however, a growing consensus that clinical trials in pregnancy, and the breastfeeding period should be conducted earlier in the drug development process (Fig. 4).[21,22] In addition, women living with HIV can play a critical role in informing the planning and design of such studies (Fig. 1).

Before an investigational ARV is studied during pregnancy, adequate nonclinical studies including reproductive-toxicity animal studies must generally be completed. In addition, data from nonpregnant participants in clinical trials, preferably including women, should be available to assess the PK, safety, and virologic activity of the drug before administration to pregnant women.[23]

Currently, although completion of initial animal safety studies is required before drugs are studied in humans, completion of all reproductive/developmental toxicity animal studies is not required until before drug approval; hence, completion of such studies is often delayed until phase III clinical trials are well underway. Earlier completion (eg, by the time the drug development stage enters phase IIb) of all reproductive/developmental toxicity animal studies is essential to allow earlier enrollment of PWLHIV into clinical trials evaluating investigational ARVs.

Therefore, as described by Roes et al in 2018, the earliest that pregnancy studies could be initiated would be after phase I and IIa study completion in nonpregnant individuals, when drug development enters phase IIb.[21] There may be exceptions to this rule for acute and life-threatening conditions in pregnant women for which there are no approved therapies and experimental therapies are being studied, such as was seen for treatment of Ebola virus infection.[24,25]

Evidence from phase IIb studies demonstrating ARV efficacy in larger numbers of nonpregnant individuals and guiding final dose selection is desirable before allowing participants who become pregnant to continue the phase III clinical trial, or before enrolling PWLHIV in phase III

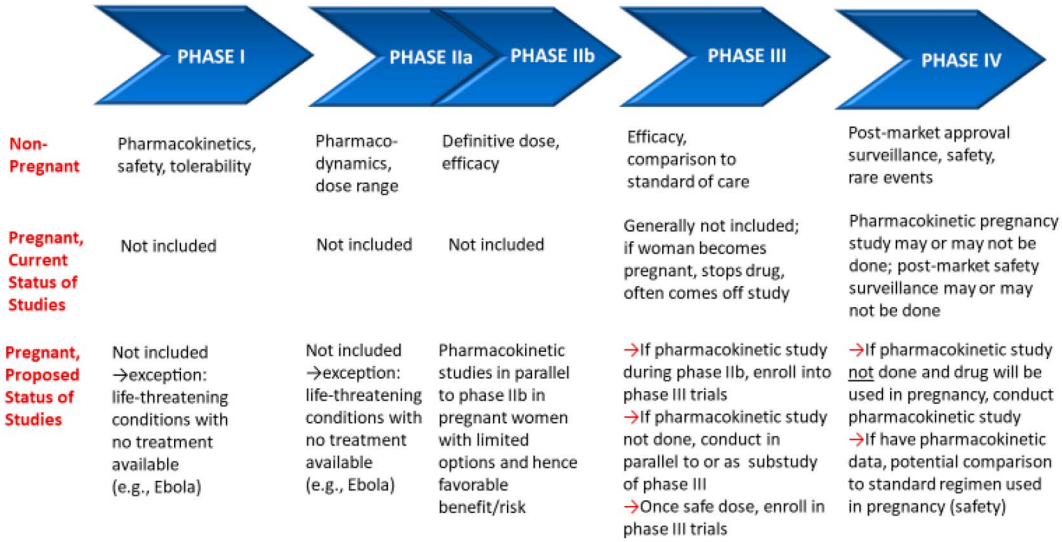

FIGURE 4. Proposed inclusion of pregnant women in clinical trial drug development phases. full color online

trials. For most investigational ARV drugs, PK and safety studies in pregnant women would be initiated during the phase III registrational trial in nonpregnant individuals.[21] However, enrollment of pregnant women into phase IIb clinical trials to collect PK and safety data could be considered when the benefit/risk considerations are favorable. For example, including treatment experienced PWLHIV who have no other treatment options in a phase IIb trial of a new agent. In such cases, initial enrollment could be limited to women in late pregnancy to minimize fetal exposure. If supported by the safety data, the trial could expand to allow inclusion of women in earlier stages of pregnancy, a strategy used successfully by the Microbicide Trials Network to evaluate the dapivirine vaginal ring in pregnancy.[26]

Currently, registrational ARV clinical trials exclude pregnant women from enrollment, mandate that women participants use effective contraception, and require that participants who become pregnant while on study discontinue study drug. To accelerate study of new agents, the WHO ART expert groups (PADO and CADO) adapted the "Roes framework" and proposed that nonpregnant women enrolled in phase III ARV trials who become pregnant during the trial should be able to remain on the study drug provided that (1) no signals were observed in preclinical reproductive toxicology studies, (2) safety and preliminary efficacy data from phase I and II trials in nonpregnant adults are supportive, and (3) consent is granted after documented discussion of risk and benefits based on available knowledge. Protocols should outline a priori implementation steps if pregnancy occurs and whether breastfeeding is allowed. Protocols should include systematic data collection on women who become pregnant during the trials, including PK data, maternal safety and virologic outcomes, and pregnancy, birth, early neonatal, and infant outcomes.

The purpose of enrolling pregnant women in phase III studies is not to evaluate drug efficacy but to establish PK and safety data during pregnancy. Such studies could be conducted as a separate parallel study or could be embedded into the phase III clinical trial design (eg, as a single-arm nonblinded PK substudy that enrolls small numbers of PWLHIV in the second and third trimesters). Similarly, as mentioned above, women who become pregnant while participating in ongoing phase III trials could also participate (with consent) in such a pregnancy/lactation safety and PK substudy. If too few pregnancies occur in the latter case, the safety and PK profile of the investigational ARV may be inadequately characterized. However, if supported by the

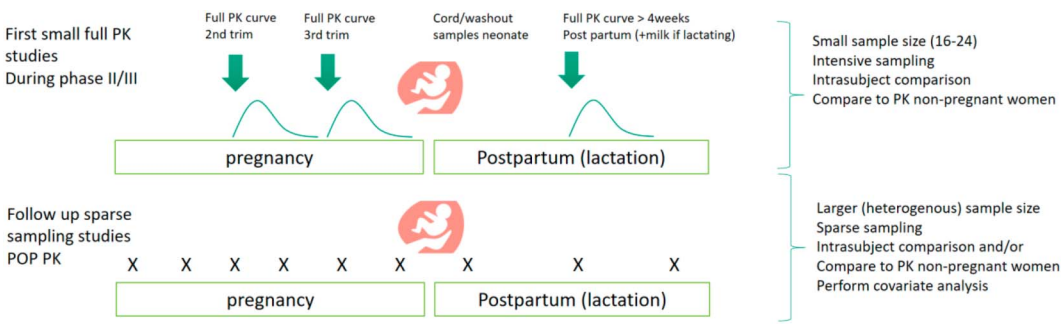

FIGURE 5. Proposed approach to pharmacokinetic studies of ARVs during pregnancy and the postpartum period. full color online

sparse initial PK and safety data, pregnant and lactating women could be able to directly enroll into the phase III study to collect data. Interim pregnancy related analyses could be conducted with early safety stopping rules as needed.

If studies in pregnant women have not been conducted to evaluate the PK and safety of an investigational ARV before approval, postapproval PK, and safety studies during pregnancy are required to establish safe and effective doses when used during second/third trimester (the current paradigm). Once PK/dose and safety are established to support ARV use during pregnancy, other trials could be conducted (when needed) to compare the safety/efficacy of the newly approved drug (in combination with other ARVs) and the current standard-of-care ARVs regimens. These studies should evaluate maternal health, pregnancy, and birth outcomes and, if possible, virologic outcomes and child health outcomes.[27] Such protocols could be designed as master protocols and amended to include new ARV regimens as they are approved.

Clinical trials in pregnancy will not be able to detect differences in rare adverse outcomes, including birth defects, because this requires large numbers of exposures from conception. Thus, robust birth surveillance systems should be established in LMIC to collect high-quality, systematic postmarketing surveillance of pregnancy outcomes to determine the safety of new antiretroviral agents and other medications used during pregnancy. Such trials are likely to occur in LMIC where millions of women are receiving ARVs.

Design of Pharmacokinetic Studies in Pregnant Women

Ideally, placental transfer of new ARVs should be studied during the preclinical phases of drug development using in vitro–in vivo extrapolations or ex vivo human cotyledon perfusion models to provide predictions of placental transfer and fetal exposure before human studies in pregnant women. Incorporating these data into pregnancy physiological-based pharmacokinetic (PBPK) models may help predict maternal and fetal exposure before actual exposure of pregnant women and fetuses to new ARVs.[28] However, pregnancy PBPK models are still under development and clinical pharmacology studies during pregnancy remain necessary.[29]

Clinical pharmacology studies should include intensive PK sampling over a dosing period. PK profiles should be obtained in the third trimester of pregnancy (minimum), second and first trimesters (if possible), with a postpartum reference curve (at least 4 weeks postpartum) for intrasubject comparison (Fig. 5). Collection of random samples during the entire pregnancy to support population PK modeling is recommended to supplement intensive sampling in a relatively small number of pregnant and postpartum women. For highly protein-bound drugs (>80% bound), unbound plasma concentrations should be determined. Plasma protein concentrations generally decrease during pregnancy, but the fraction that is unbound also changes for highly protein-bound drugs. As a result, total drug concentrations during pregnancy may not be reliable and assessment of exposure should be based on measurement of for unbound (active) drug concentrations.[30]

Several approaches to analysis and interpretation of data are suggested. Main parameters of interest are area under the curve (AUCtau), Ctrough (predose sample), and Cmax. The pregnancy effect should be reported as a percentage change, by trimester, compared with the specified time postpartum, with a confidence interval for these parameters. Furthermore, if a therapeutic target (eg, minimum Ctrough) has been defined for a certain drug, the percentage of women failing to achieve that therapeutic target should be reported per period (pregnancy and postpartum). Pregnancy and postpartum PK parameters should also be compared with historical data from nonpregnant (preferably female) adults, as drug exposure for some ARVs (eg, TAF) has been reported to be increased postpartum relative to nonpregnant adult data.[31] Data from intensive curves and sparse sampling can be combined in a population PK analysis to evaluate the impact of factors (such as weight gain and plasma albumin concentrations) contributing to a possible pregnancy effect. Furthermore, these population PK models can be used to predict the effect of adapting the drug dose in pregnancy.

ARV drug studies in pregnant women should include collection of cord and maternal blood samples at delivery if possible, to assess placental transfer of the drugs in vivo, and serial blood sampling of newborns over the first week of life to assess the washout elimination kinetics of drug transferred to the fetus across the placenta. Neonatal washout kinetic data provide crucial data for modeling and simulations to facilitate studies to determine ARV dosing regimens for neonates and infants.

Joining Forces and Aligning Efforts

Several recent initiatives have investigated the gaps in drug development and evaluations for use during pregnancy. Concrete actions have been defined to address these gaps including outlining key tenets for involvement of the community of PWLHIV (Fig. 1).

In the United States, the 21st Century Cure Act mandated a taskforce to assess the landscape of research on drugs in pregnancy and provide recommendations. The Task Force on Research Specific to Pregnant Women and Lactating Women published its recommendations in September 2018.[32] These recommendations included (1) removal of pregnant women as a vulnerable population in the common rule with a request to the FDA to align with this approach and (2) modifications to recognize the autonomy of a pregnant woman and the evolution of family structure so that one parental signature be required for research to benefit the child (aligning with parental consent for paediatrics). The task force released recommendations to allow enrollment of pregnant women into clinical trials even without the prospect of any direct benefit (eg, a PK study) if the risk to the fetus is not greater than minimal. The task force continues to operate with a focus on 4 areas: research, training, regulatory issues, and discovery.

The PHASES (Pregnancy and HIV/AIDS: Seeking Equitable Study) Group was formed to identify ethical

solutions to advance research at the intersection of women's reproduction and HIV prevention, treatment, and management. A number of recommendations were made by PHASES, including inclusion of women living with HIV of reproductive-potential or who are pregnant when designing phase III clinical trials (see earlier clinical studies section), the importance of guaranteeing access to life-saving experimental treatments to pregnant women with no alternatives, and a shift from the current paradigm to require justification if pregnant women or women of reproductive-potential are excluded from phase III trials rather than the current approach of justifying inclusion.[33]

WHO strongly advocates for countries to establish and strengthen epidemiological surveillance of drug safety during pregnancy alongside ART programmes.[34] WHO recommended enhanced monitoring and surveillance of toxicity[35] and has recently provided to countries standardized tools to collect such data systematically. WHO also supports continuation of birth surveillance studies such as the Tsepamo Botswana as a general model for studying the safety of drugs in pregnancy and call for rapid investments in this area.[9]

DISCUSSION

Recognizing the historical delays and the imperative to accelerate ARV access in PWLHIV, we examined the current approach, identified the barriers, and put forward a set of principles and a new framework for studying new ARVs in pregnant women earlier and faster (Figs. 4 and 5).

These principles are based on a fundamental paradigm shift in attribution of risk and align well align with what has been put forward by the PHASES group.[33] The outdated concept that it is risky and unethical to enroll pregnant women into clinical trials of investigational drugs needs to be replaced with the recognition that the exclusion of pregnant women in such studies results in "off-label use" of drugs lacking dosing or safety data. This puts the women and their infants at risk of potential harm for adverse events as well as suboptimal prevention of vertical transmission and treatment of maternal HIV disease.

Earlier completion of preclinical reproductive-toxicity studies coupled with preapproval conduct of PK and safety studies in women who become pregnant on study for promising new drugs will enable enrollment of pregnant women into phase III trials and accelerate the timeline for PK and safety data in pregnancy (Fig. 4). Optimal studies in pregnancy should include intensive PK studies with full PK curves in the third trimester (and preferably also in second and first trimester, and 4 weeks postpartum for comparison) and sparse sampling studies contributing to population PK models (Fig. 5). Recognizing the unique characteristics of the mother–infant dyad, studies of examining pregnancy, birth, newborn, and infant outcomes also need to be conducted. Finally, full understanding of rare toxicities, birth defects, and long-term safety can only be established through active and robust surveillance where rarer adverse outcomes can be documented.

Implementation of this framework requires sustained and effective partnerships among stakeholders, regulators, industry, researchers, donors, ethical review boards, and, importantly, with the community of women living with HIV. Stakeholders can build on the emerging consensus that it is time to change the research paradigm to include pregnant women in premarketing studies. Data gaps need to be addressed ethically and rapidly to generate the evidence required to guide safe use of new ARVs in pregnant women and support broad adoption of life-saving treatments.

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