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COMMENTARY

Responding to the Call to Action: Framework to Accelerate Clinical Data Generation for Antiretroviral Use in Pregnant Individuals with HIV

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INTRODUCTION

An estimated 1.2 million people living with human immunodeficiency virus (HIV) become pregnant each year, and approximately 300,000 initiate antiretroviral therapy (ART) during pregnancy [1]. Moreover, > 120,000 preventable new HIV transmissions occurred among children in 2022, mostly due to lack of ART during pregnancy or breastfeeding [1]. Clinical data demonstrate that perinatal transmission risk can be reduced to ≤ 1% when effective ART, combined with other prevention strategies, is used during and after pregnancy [2].

Clinical data on individual antiretroviral agent use during pregnancy or lactation have been delayed or sparse, partially because pregnant individuals have long been categorized as a vulnerable population [3], which adds ethical considerations (e.g. challenges in weighing potential risks and benefits to the pregnant individual and foetus) and legal concerns (e.g. cautious interpretation of federal guidance for "not greater than minimal" risk) [4]. Moreover, regulatory authorities do not require clinical pregnancy data for marketing approval, mandating only non-clinical data and descriptions of restricted use in specific populations, such as pregnant individuals, in drug labelling [5]. This cautious approach has resulted in the de-prioritization of data generation in pregnant individuals before marketing approval of antiretroviral agents; consequently, most HIV drug labels include no clinical data regarding use in pregnancy or during lactation. One study reported that median time from regulatory approval of antiretroviral agents to first published pharmacokinetic data in pregnancy was 6 years [6].

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This paucity of timely pregnancy data during clinical development presents challenges for individuals of childbearing potential when it comes to making decisions that could impact the health of parent and child and for prescribers who offer advice in an information vacuum. Individuals who become pregnant while taking antiretroviral agents for the treatment or prevention of HIV may be switched to older regimens with available data, even though switching could result in loss of virologic suppression or acquisition of HIV due to inferior efficacy or undesirable side effects that compromise adherence. If the new antiretroviral regimen is not fully suppressive, risk of disease progression, opportunistic infections and vertical transmission is heightened. Alternatively, continuing an antiretroviral regimen during pregnancy without supporting data could lead to incorrect dosing because of potential pharmacokinetic differences during pregnancy [7]. For example, plasma concentrations of some antiretroviral agents are lower during certain trimesters of pregnancy [8]. Such variance could lead to inadequate viral suppression or new transmission events due to lower exposure or introduce new safety and tolerability issues due to higher exposure; even typical exposures could lead to unidentified safety signals [8, 9]. Uninvestigated drug–drug interactions (DDIs) between antiretroviral agents and drugs commonly used during pregnancy may also impact the effectiveness of either drug. Altogether, these challenges present compelling ethical arguments in favour of accelerating antiretroviral research in pregnancy.

Over the past 5+ years, these ethical considerations have been the basis for encouraging antiretroviral research in pregnancy in prelicensure clinical trials. Based on results from the Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) project [10], the World Health Organization (WHO), International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and International AIDS Society (IAS) issued a call to action urging the inclusion of pregnant and lactating individuals in prelicensure clinical trials so that pharmacokinetic and preliminary safety data for all new antiretroviral agents during pregnancy are available upon drug approval [11]. The basic principles of this call to action are to (1) "[consider] pregnant individuals as a complex population rather than a vulnerable population; (2) [move] from 'protecting from research' to 'protecting through research'; and (3) [promote] fair inclusion in, rather than presumptive exclusion from, clinical drug trials" [10, 11].

To address the need for earlier and more robust data in individuals of childbearing potential, ViiV Healthcare assembled a task force in 2021 to propose a framework on how this may be accomplished. The task force included experts in clinical and non-clinical pharmacology, safety and regulatory affairs, patient affairs, paediatrics, epidemiology and post-approval surveillance. With the goal of including pharmacokinetic and preliminary safety data in pregnancy for all new antiretroviral agents in new drug application/marketing authorization application submissions and proposed labelling, this framework petitions clinical development teams to support greater inclusion of pregnant and lactating individuals and those of childbearing potential in clinical trials for more equitable investigation of new therapies for the treatment or prevention of HIV.

DISCUSSION

Framework to Accelerate Data Generation

This framework proposes a strategy for clinical development teams to accelerate the generation of evidence informing the use of new antiretroviral agents in pregnant and lactating individuals (Table 1). This strategy focuses on generating non-clinical data, completing pharmacokinetic and modelling assessments earlier than prior development programs, including individuals of childbearing potential, and relaxing restrictions on contraceptives for these individuals in clinical trials. This proactive, evidence-based approach was designed so that pregnant and lactating individuals with HIV or those interested in pre-exposure prophylaxis for HIV could access the most efficacious, safe and convenient antiretroviral options broadly available to the general population.

Table 1 Basic framework to accelerate clinical data generation for antiretroviral use in pregnancy

	Action item
1	Develop a pregnancy data acceleration plan for each early-stage compound
2	Accelerate completion of reproductive toxicity assessments (EFD, PPND and FEED) and accelerate pharmacokinetic and modelling assessments
3	Phase 1b and 2 trials: include more individuals of childbearing potential (contraception or sterilization required) to allow meaningful data collection; must discontinue if pregnancy occurs
4	Phase 3 trials: recommend, but do not require, use of contraception by individuals of childbearing potential
5	Phase 3 trials: once effective dosing in individuals of childbearing potential is established and sufficient safety data are known, allow individuals to continue treatment if they become pregnant
6	Develop a regulatory strategy for each compound, and engage relevant health authorities through development (usual process) to align on process for an evidence-based pregnancy data acceleration plan; align early, if possible, on labelling options and requirements
7	Develop a data collection and statistical strategy for each compound that allows for early and consistent participation of individuals of childbearing potential in clinical studies, and for data handling options for individuals who become pregnant in phase 3 (e.g. sample size adjustments, pre-specified analysis plans, sensitivity analyses for primary or secondary endpoints, pharmacokinetic sampling strategies and study extension into the postpartum period)
8	Consider planning a dedicated trial during pregnancy and lactation to be conducted once sufficient safety data are available from phase 3 (pre- or post-approval)
9	Engage and consult with community representatives early and consistently
10	Publish data as early as possible to inform decision-making by healthcare providers

EFD embryo-foetal development, *FEED* fertility and early embryonic development, *PPND* pre- and post-natal development

Develop a Pregnancy Data Acceleration Plan for Each Early-Stage Compound

Upon selection of a candidate agent, safety governance and ethics committees should evaluate whether the target treatment population necessitates and/or feasibly allows for accelerated pregnancy data. If affirmed, a product-specific plan should be formulated outlining timelines for completion of necessary scientific, statistical and regulatory milestones to facilitate inclusion of individuals of childbearing potential, timing for relaxation of contraception requirements, retention of individuals who become pregnant in the trial and inclusion of pregnant individuals. Safety governance must be followed to ensure oversight of data supporting benefits and risks in this population, compliance with organizational standards, regulatory and labelling requirements and federal law. At each step of the development process, the plan should be re-evaluated and revised as data become available.

Accelerate Completion of Reproductive Toxicity Assessments and Accelerate Pharmacokinetic and Modelling Assessments

Planning for reproductive toxicology studies should occur early after the decision to enact a pregnancy data acceleration plan to ensure that the investigational agent will be available to support clinical development. Embryo-foetal development studies in two species should be completed in time for individuals of childbearing

potential to participate in phase 1b or 2 clinical trials, and additional fertility and pre- and post-natal development studies should be completed or ongoing before end-of-phase 2 regulatory meetings. Though this accelerated timetable carries some risk related to animal, financial and material resource utilization, it will facilitate a data-driven discussion in which contraception requirements and timing for inclusion of pregnant individuals in subsequent clinical studies can be defined and discussed with regulatory authorities. Additionally, after candidate selection, drug development teams should perform drug interaction risk assessments with commonly used hormonal contraceptives (to facilitate enrolment of individuals of childbearing potential into phase 1b/2 trials) and medications frequently given during pregnancy. Relevant DDI studies (in vivo or in silico, as appropriate) should be performed during phase 1 or 2a to guide use of concomitant medications for individuals of childbearing potential in later clinical phases. As absorption, distribution, metabolism and excretion data are collected during phase 1/2a, mathematical models (e.g. physiologically based pharmacokinetic models) should be developed to inform possible placental drug transfer, changes in pharmacokinetics during pregnancy and associated adjustments to dose or dosing regimen.

Include More Individuals of Childbearing Potential in Phase 1b and 2 Trials

International Council for Harmonization guidelines allow for individuals of childbearing potential using barrier or highly effective hormonal contraceptives with no DDI risk to participate in first-time-in-human studies of ≤ 14 days [12]. Additionally, preliminary reproductive toxicity data are sufficient for inclusion of up to 150 individuals of childbearing potential in phase 1 and 2 studies of ≤ 3 months, provided highly effective contraceptives are used [12]. Thus, the opportunity to enrol individuals of childbearing potential in early-phase clinical trials already exists. Embracing this opportunity depends on the completion of DDI studies relating to contraceptives. If an individual becomes pregnant during these initial studies, however, they will immediately halt additional dosing and discontinue participation upon clearance of the study drug. During the period after dosing has stopped and before clearance of the study drug, the opportunity to continue as part of an ad hoc pharmacokinetic sub-study should be provided, particularly when the antiretroviral agent under study is a long-acting drug. When possible, safety outcomes should be documented for both the person giving birth and the newborn after dosing has been stopped.

Eliminate Contraceptive Requirements and Allow Individuals Who Become Pregnant the Opportunity to Continue Participation in Phase 3 Studies

Provided the safety and efficacy data generated in early-phase studies have an acceptable benefit–risk profile, phase 3 study protocols should recommend rather than require contraceptive use by individuals of childbearing potential. Detailed guidance for contraception recommendations in clinical trials and labelling has recently been proposed by the PreClinical Development Expert Group of the European Federation of Pharmaceutical Industries and Associations [13]. Healthcare providers should discuss benefits and risks with individuals who become pregnant, and they should be permitted to re-consent and continue study treatment. Due to potential changes in drug exposure during pregnancy [7], development teams should also consider requesting additional consent for intensive and longitudinal pharmacokinetic sampling to capture trimester-specific data and ensure drug exposures remain within the therapeutic target range throughout pregnancy. If not already available, bioanalytical techniques capable of assessing pharmacokinetics in breast milk and from low-volume neonate samples (e.g. heel stick) should be developed to monitor post-delivery pharmacokinetics. Data collected from pregnant individuals, cord blood and neonates can be used as a component of model-informed drug development to guide future dosing recommendations during pregnancy and to facilitate further investigation of neonatal indications.

Develop a Regulatory Strategy for Each Compound and Engage Relevant Health Authorities through Development to Align on Process for Evidence-Based Pregnancy Data Acceleration Plan

The call to action recommends that institutional review boards and ethics committees have access to non-clinical developmental and reproductive toxicity data to facilitate critical review of the justifications provided in clinical trial proposals for or against the exclusion of individuals of childbearing potential [11]. However, there are currently no roadmaps, regulatory guidelines or established pathways for conducting clinical trials in individuals who are or may become pregnant to enable regulatory approval. Teams should consistently engage with regulatory authorities and revise the pregnancy data acceleration plan based on those discussions until a global harmonized approach has been established. Of key importance are the end-of-phase 2 regulatory meetings and equivalent scientific advice engagement, when each development team should discuss specific expectations with regulatory authorities that define sufficient data for inclusion of pregnancy recommendations in the product label.

Develop a Data Collection and Statistical Strategy for Each Compound that Allows for Early and Consistent Participation of Individuals of Childbearing Potential in Clinical Studies, and for Data Handling Options for Individuals Who Become Pregnant in Phase 3

During development of the pregnancy data acceleration plan, statistical considerations such as sample size, power and precision as well as sensitivity analyses for small and large trials need to be adjusted to account for potential pregnancies among participants and the impact of any pregnancies on study endpoints, while balancing pragmatic considerations such as enrolment feasibility. These adjustments will ensure minimal delay between availability of the antiretroviral agent and access for those who can benefit. For larger trials, it is important to establish the number of pregnancies that triggers initiation of a dedicated sub-study to evaluate drug pharmacokinetics, safety and efficacy (instead of only continuing ad hoc data collection) and, if applicable, randomization and blinding strategies. Endpoints and outcomes of pregnancy substudies will need to be stratified by pregnancy phase (trimester, delivery and postpartum) and potentially by study phase depending on study duration. Safety and tolerability analyses in pregnant individuals, such as those concerning weight gain, metabolic parameters and new safety signals, may require additional data handling rules. Details on safety analyses in infants (type and duration of collection) should also be included in the study design.

Consider Planning a Dedicated Pregnancy Trial to be Conducted Once Sufficient Safety Data from the General Population Are Available from Phase 3

Even with relaxed contraception requirements, development teams should anticipate that the number of pregnancies during phase 3 trials may be too few to make generalizable conclusions on safety and dosing, even with non-clinical reproductive toxicology, pharmacokinetic and modelling data. Therefore, dedicated pregnancy trials may be necessary to generate informative data. In their call to action, the WHO committed to advancing priority antiretroviral agents into dedicated safety studies in pregnant individuals during phase 3 or immediately after approval [11]. With the proposed completion of reproductive toxicity assessments in time for inclusion in end-of-phase 2 regulatory submissions or soon after, this framework supports or potentially accelerates the WHO timeline. Dedicated pharmacokinetic and safety trials in pregnant and lactating individuals may begin once sufficient safety data and dosing have been established in non-pregnant adults, which may occur during phase 2 and/or early phase 3. However, if dedicated pregnancy trials cannot feasibly be performed in parallel with phase 3, planning for the pregnancy study should still begin during

phase 3 to facilitate immediate initiation after drug approval.

Engage and Consult with Community Representatives Early and Consistently

Community-based programs, in addition to traditional healthcare services, are a critical means of delivering continuous high-quality care to people with HIV [14]. These programs can provide accessibility and flexibility in situations where care at a professional healthcare facility may be prohibitively expensive or infeasible due to time constraints or travel limitations [15]. Pregnant participants will likely encounter such obstacles, limiting their ability to attend visits at clinical research sites [16]. Thus, development teams should engage with community advocates and representatives where available, as well as individuals of childbearing potential, on best practices and seek their input on study design since these groups may be instrumental in helping pregnant individuals remain fully informed, autonomous and on study. Moreover, community advocates can relay the needs and concerns of pregnant participants to development teams, whose input will help ensure that research questions and study designs provide answers for pregnant individuals and their physicians to help them make informed decisions. Community advocates, therefore, should be included early in the design process. Advisory boards should also be convened for evaluation of draft study protocols that consider community input as well as diversity targets in pregnancy studies.

Publish Data as Early as Possible to Inform Decision-Making by Healthcare Providers

Publication steering committee membership should expand, if necessary, to include members with expertise in obstetrics and paediatrics, who can guide publication planning and journal selection to maximize timely outreach to relevant healthcare providers. Data from each study with drug exposure in pregnant and lactating individuals should be made available in a pregnancy exposure registry upon conclusion of the initial study period and updated regularly. Prescribing information should also be updated with pregnancy data as they become available and include information on pregnancy exposure registries (if available), as well as a section for additional considerations based on reproductive potential (e.g. pregnancy testing requirements, contraception recommendations and infertility information related to the drug) and lactation in accordance with the Pregnancy and Lactation Labeling Rule [17]. In addition, if there are insufficient data to merit publication, alternative communication methods such as pre-print platforms, conference presentations, drug label revisions and pregnancy exposure registry updates may be considered.

CONCLUSION

This proposed strategy to accelerate non-clinical data collection, conduct early pharmacokinetic and modelling assessments and facilitate the inclusion of individuals who are or may become pregnant in clinical trials can improve the treatment of pregnant and lactating people living with HIV as well as those using pre-exposure prophylaxis by generating data on safe and effective antiretroviral agents. Additionally, this framework can be tailored and adapted for use in other therapeutic areas. Although the risks of antiretroviral drug exposure to the foetus must be carefully assessed, a proactive, evidenced-based and practical approach, such as the one described here, will allow people of childbearing potential, pregnant individuals and their healthcare providers to obtain the information they need to make informed decisions regarding available or investigational antiretroviral agents. Ensuring access to the safest and most efficacious antiretroviral drugs during pregnancy and lactation is critical to the elimination of vertical transmission.

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Declarations

Conflict of Interest. Vani Vannappagari, Scott McCallister, Beth Romach, Mark Bush, Dinesh Stanislaus, Charlotte Root, Christine Lampkin, Nneka Nwokolo, Ana Puga, Sebastian Moreira, Farzaneh Salem, Ralph DeMasi, Nassrin Payvandi, Kimberly Smith, Harmony Garges and Annemiek de Ruiter are employees of ViiV Healthcare or GSK and may hold stock in GSK.

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