APPROACHES TO OPTIMIZE AND ACCELERATE PHARMACOLOGY STUDIES IN PREGNANT AND LACTATING WOMEN

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The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network and the WHO-convened Paediatric Antiretroviral Working Group (PAWG) organized a workshop to reach consensus on designing, analysing and interpreting pharmacology studies of pregnant and lactating women with HIV and associated conditions. This workshop brought together academic researchers, clinical experts and key stakeholders involved in pharmacokinetic studies and in silico modelling of antiretroviral drugs among pregnant and lactating women. The workshop, entitled Approaches to Optimize and Accelerate Pharmacokinetic Studies in Pregnant and Lactating Women, was held on 13–14 June 2019 in Washington, DC, USA and gathered more than 40 experts from the IMPAACT Network as well as regulatory agencies, nongovernmental organizations, other researchers working in this arena and stakeholders in high-, middle- and low-income countries.

BACKGROUND

Pregnancy is associated with a wide range of physiological, anatomical and biochemical changes that substantially affect the pharmacokinetics of therapeutic agents. For women living with HIV this can often result in lower antiretroviral drug exposure, which can increase the risk of maternal viraemia and, in turn, increase the risk of transmitting HIV to the infant. Indeed, the clinical relevance of these changes during pregnancy was recently demonstrated by warnings from the United States Food and Drug Administration and European Medicines Agency on the use of the cobicistat-boosted regimens in pregnant women. These recent warnings highlight two critical issues: (1) that regulatory authorities view the risks for infants of maternal pharmacotherapy during pregnancy seriously and (2) the importance of collecting pharmacokinetic data on antiretroviral drugs in pregnant women in a prospective, systematic and controlled way. Of note, darunavir + cobicistat was initially registered by the United States Food and Drug Administration in 2015 and elvitegravir + cobicistat in 2012, but no data on their use during pregnancy were available at the time of approval, and the risks associated with their use during pregnancy were not identified until 2018. This underscores the need to expedite the study of antiretroviral drugs in pregnancy and during lactation, with an ultimate goal of generating pharmacokinetic and safety data during pregnancy and lactation substantially earlier along the drug development and approval timeline.

In the past decade, the United States Food and Drug Administration and European Medicines Agency have emphasized the need for including women (pregnant and non-pregnant) in clinical development programmes, issuing guidance for industry on how to conduct pharmacokinetic and pharmacodynamic studies among pregnant and lactating women and on establishing pregnancy registries. The utility of in silico (population and physiologically based) modelling and simulation is also being explored to expedite drug approvals. There is still, however, general lack of legislation or regulations that formally incentivize or mandate drug studies among pregnant women, as have been put in place for children. The workshop was particularly timely in the context of ongoing work by technical groups such as the Task Force on Research Specific to Pregnant Women and Lactating Women of the United States National Institutes of Health, which identified 15 recommendations, several of which call for more research among pregnant and lactating women.

Pharmacokinetic studies among both pregnant and lactating women vary in designing, analysing and interpreting the results. Current pharmacokinetics studies among pregnant and lactating women use a post-marketing opportunistic study design almost entirely, studying new antiretroviral drugs for pregnant women already receiving these drugs as part of clinical care. These post-marketing pharmacokinetics studies are conducted by only a few research teams, primarily in high-income countries, in which the new antiretroviral drugs are available but the number of pregnant women living with HIV is relatively low and breastfeeding is currently not recommended. Consequently, the populations with the highest pregnancy rates among women living with HIV in settings in which breastfeeding is recommended are not widely studied. This current practice of delaying these pharmacokinetics studies among pregnant and lactating women until post-marketing leads to an inequitable delay for this special population to benefit from these new medicines.

Several potential solutions have been identified to address these issues, but no consensus on the standard procedures has been reached. For this reason, the IMPAACT Network and the PAWG collaboratively convened a workshop to agree on and define key standards for generating pharmacology data for antiretroviral drugs to be used among pregnant and lactating women for HIV prevention and treatment.

OBJECTIVES

The objectives of the workshop were:

- to expand on the existing principles outlined in the **WHO Toolkit for research and development of paediatric antiretroviral drugs and formulations** and reach a consensus on the optimal design and analysis of pharmacology studies in pregnant and lactating women, with a focus on antiretroviral therapy; and
- to review the product pipeline, including approaches to long-acting and novel delivery platforms, and identify key gaps for use in low- and middle-income countries and immediate opportunities to undertake optimal studies and rapidly close the knowledge gap earlier.

METHODS

Pharmacology experts undertook preparatory work in collaboration with WHO. Before the workshop, critical gaps in designing, analysing and interpreting pharmacology studies among pregnant and lactating women were defined and summarized. Current practice and potential innovations were reviewed together with ongoing related workstreams led by other stakeholders.

The workshop took place over 1.5 days, starting with a plenary session to review the background and objectives. Breakout sessions were designed to facilitate critical review and innovative thinking to explore the design, analysis and interpretation of pharmacology studies among pregnant and lactating women. Report-back and plenary discussions enabled the group to reach consensus on some key principles and follow-up actions.

OUTCOMES

The workshop participants all agreed on the importance of protecting pregnant and lactating women through clinical research and not from clinical research. Considerations for studying the pharmacokinetics of antiretroviral drugs among and lactating women, were developed and are summarized below.

ETHICAL RATIONALE AND TIMING OF PHARMACOKINETICS STUDIES

Pregnancy

Since most antiretroviral drugs are registered and marketed without contraindication for pregnant and lactating women, prescribers and the individual woman need to weigh the (mainly unknown) benefit and risks of using the specific drug in pregnancy. The group emphasized the strong desire to perform pharmacokinetics studies in pregnancy during the clinical development of a drug (pre-marketing). To achieve this, reproductive toxicology studies need to be performed earlier along the drug development timeline, and ethics committees need to shift their approach to consider the importance of protecting the woman's health as well as the health of the fetus.

To accelerate generation of this critical evidence, the pharmaceutical industry needs to perform pharmacokinetics studies during clinical development, and regulatory incentives could be explored for antiretroviral drugs that are likely to be used in pregnancy. However, these incentives should be designed to avoid any delay in marketing of new drugs or unnecessary contraindications in the label for people living with HIV.

Several options for when to perform these studies were discussed, all assuming that reproduction-toxicity studies would be completed and the findings would be negative and not hold back study in pregnancy. The most feasible and directly applicable approach is opportunistic, in which women becoming pregnant in Phase III (or even IIb) trials could be given the choice to stay on the study drug. One step further would be to not actively exclude pregnant women from participating in Phase III studies. The optimal approach would be a dedicated dose-finding pharmacokinetics study in pregnancy and lactation during Phase III or earlier, as soon as a dose is selected for non-pregnant individuals. Inclusion of pregnant women in Phase I studies would only be feasible if the woman is at risk of death without the investigational drug, but this approach was not considered to be applicable in the current antiretroviral drug landscape. Single-dose (or short-term multiple-dose) pharmacokinetics studies on top of optimized background therapy, to identify the pregnancy effect on the pharmacokinetics of the drug, could be performed during Phase III or earlier but may be more difficult to justify ethically since there is no benefit for the individual person. This might only be an option if harm is negligible and there is potential benefit for future pregnant women.

Lactation

The group noted that, in countries where formula feeding is widely available and accepted, women living with HIV are recommended not to breastfeed their infants, because of risk to the infant of acquiring HIV infection. The pharmaceutical industry therefore has little interest in studying the passage of the drug into human breast-milk during the drug development phase in these countries. However, in resource-limited settings in which breastfeeding is the preferred feeding option, this often occurs in the absence of information on exposure of the infant to antiretroviral drugs through breast-milk. The group agreed that knowledge needs to be generated on antiretroviral drug exposure of the infant through breast-milk, to assess potential toxicity, the role in decreasing perinatal transmission and the impact on selection of drug resistance.

The ethical and risk–benefit considerations in lactation studies differ from pregnancy studies, since toxicity to the fetus is no longer a concern, and in almost all cases, the drug exposure through breast-milk is lower than the exposure across the placenta. Therefore, the preferred method to obtain the necessary data on drug exposure to the breastfed infant is by studying breastfeeding mothers and their infants. To address the potential concerns that ethics committees often raise when assessing these studies, the group noted the key role played by regulators and policy-makers in adequately informing ethical review boards and ethics committees regarding the importance and need for these studies. Finally, the group reflected on the informed consent process as a complex topic to tackle: since the infant is also included in the study, mothers might be adolescents (considered emancipated minors), and paternal informed consent might be needed.

The group agreed that breast-milk studies, investigating transfer of the drug into breast-milk and assessing infant antiretroviral drug exposure, could be done during the clinical development as part of a pharmacokinetics study undertaken during Phase III, as an opportunistic design, among women who opt to breastfeed after delivery. Another option is to include lactating women in Phase III trials. To speed up data availability, these studies are preferably performed in settings in which breastfeeding is recommended as the preferred feeding option. Predicting drug exposure through human breast-milk has been challenging, but physiologically based pharmacokinetic modelling and simulation can be used to build on knowledge of drug physicochemical properties and transporter expression in the mammary gland to predict drug milk concentration time profiles before data are available from clinical lactation studies.

DESIGN AND ANALYSIS OF PHARMACOKINETICS STUDIES

Pregnancy

The current design of pharmacokinetics studies in pregnancy primarily involves intensive blood sampling (such as 6–10 timed blood samples per dosing interval) during the third trimester and postpartum. For assessing pharmacokinetics, it was thought that sampling during the first trimester was logistically challenging and the physiological changes are likely to be minimal, but this will depend on the pharmacokinetics characteristics of the individual drug under study. Performing additional intensive pharmacokinetics sampling during the second trimester would be advantageous; however, if only one intensive pharmacokinetics sampling visit was feasible, it was thought that the third trimester should take priority: the physiological changes associated with pregnancy would likely have the greatest clinical impact on drug exposure late in pregnancy. The primary endpoint of pharmacokinetics studies is often a specific pharmacokinetics parameter, such as area under the curve or maximum or minimum concentration, but the choice depends on the pharmacokinetic and pharmacodynamic characteristics of the drug.

Using a population pharmacokinetics approach is also a reasonable option in settings in which intensive pharmacokinetics sampling is not possible. Pooling pharmacokinetics data from both intensive and sparse sampling schedules would provide an optimal dataset for population pharmacokinetics analysis, whereby the impact of patient covariates could be assessed. In this context, documentation of food intake and use of concomitant medications such as antacids and herbal and mineral products are critical to inform the data analysis. It was also generally accepted that intrasubject comparisons –pharmacokinetics assessment during the third trimester and early postpartum period within the same women – is preferable to reduce variability. The use of historical controls was also widely discussed, and it was agreed that such comparisons are also acceptable, but careful consideration of the historical control group is needed. For example, drug exposure data from non-pregnant adults is often used, but it was thought that a control group including only non-pregnant women would be optimal for comparing subjects. It was also noted that real-time analysis and reporting of drug concentrations may facilitate enrolment and ethical approval of studies of new drugs during pregnancy.

In terms of study conduct, participant adherence checks before pharmacokinetics sampling was a major concern, as in all pharmacokinetics studies. In some cases, investigators could require direct observation of prior doses, such as doses over the previous 72 hours