MODULE 3: PREGNANT AND BREASTFEEDING WOMEN

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1. INTRODUCTION

The number of children newly infected with HIV has decreased by 47% since 2010, although 160 000 children acquired HIV in 2016 *(1)*. This decline is mainly related to treating women living with HIV for their own health and to reduce the risk of vertical HIV transmission *(2)*. Combination antiretroviral therapy (ART) is a highly effective strategy for preventing the vertical transmission of HIV, reducing the risk from 20–45% to less than 1% in non-breastfeeding populations *(3)*. However, information on antiretroviral (ARV) drug pharmacokinetics and maternal and fetal safety during pregnancy, as well as placental transfer, distribution into breast-milk and infant exposure are required before pregnant and lactating women can safely and effectively use these drugs.

Unfortunately, pregnant and breastfeeding women are generally excluded from pre-marketing clinical drug development programmes *(4)*. In the past decade, the United States Food and Drug Administration (FDA) has continued to emphasize the need for including women (pregnant and non-pregnant) in development programmes, issuing guidance for industry on establishing pregnancy registries and drafting guidelines for conducting pharmacokinetic and pharmacodynamic studies among pregnant women and draft guidance for studies among lactating women *(5,6)*.

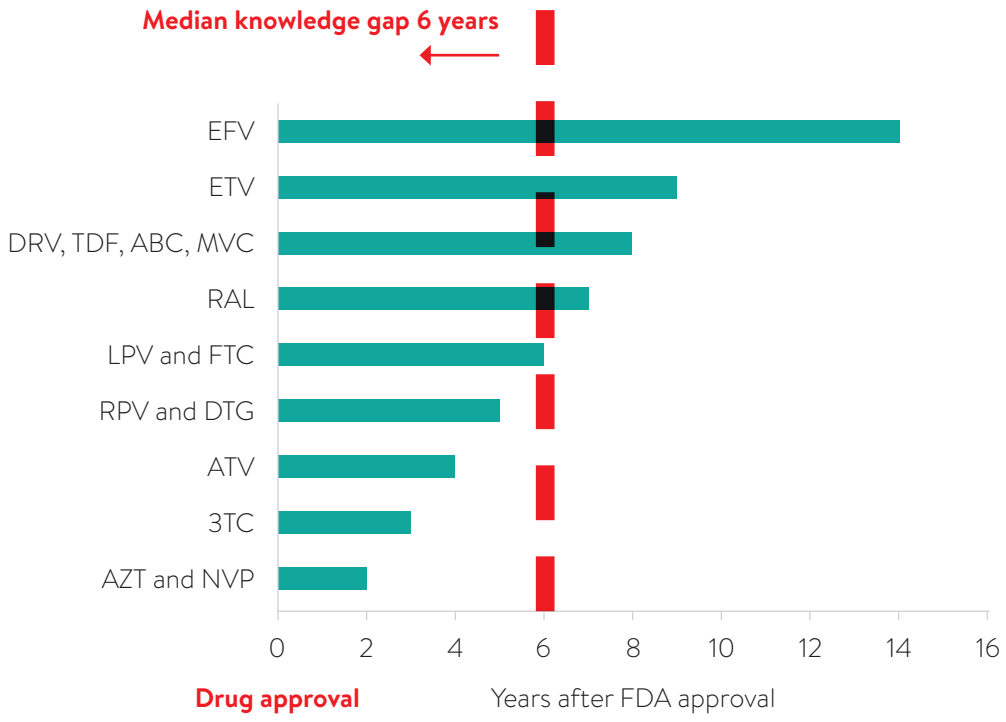
Nevertheless, no current legislation or regulations formally provide incentives for or mandate drug studies among pregnant women *(7)*. Several post-marketing surveillance initiatives and clinical trial networks (usually in the form of public–private partnerships) investigate the pharmacokinetics and report on the safety of ARV drugs during pregnancy *(8–10)*. Nevertheless, the data from these studies usually become available years after FDA licensing. Looking at clinical trials reporting on the pharmacokinetics and safety of the main ARV drugs during pregnancy, the median time to first data (the time between FDA approval and publication of the first prospective clinical trial) exceeds six years.

Partly depending on treatment alternatives, many pregnant and breastfeeding women and potentially their (unborn) infants inevitably use (or have used) untested ARV drugs. Untested here refers to the fact that health-care professionals had no data available on pharmacokinetics and safety during pregnancy or breastfeeding to inform treatment strategies *(4)*. Excluding pregnant and lactating women from participating in medical research results in a lack of knowledge about the risks and potential benefits of products that will be available for their use once on the market.

Early data on the pharmacokinetics and safety of ARV drugs in pregnancy and lactation gathered under rigorous scientific conditions are critically needed. This would place fewer women and their fetuses at risk compared with the much larger number of pregnant and lactating women who are exposed when drugs reach the market without evaluation *(11)*.

In short, including pregnant and breastfeeding women in clinical research is critically important, and the period between FDA approval and the first clinical pregnancy and lactation data should be minimized or eliminated (Fig. 3.1).

Fig. 3.1. Time between approval and the first published pharmacokinetic data in pregnancy for various ARV drugs



2. CHALLENGES

Research involving and treatment of pregnant and breastfeeding women raises ethical and scientific questions. Although regulatory agencies encourage the study of drugs among pregnant and breastfeeding women, they are generally excluded from drug development programmes, leading to knowledge gaps when drugs come to market. Nearly all drugs are licensed without any data describing their use in pregnancy, including safety for the mother and child when used during pregnancy and breastfeeding, whether effective exposure is achieved during pregnancy with standard nonpregnant adult dosing and to what extent the drug crosses the placenta and is excreted in breast-milk. The lack of research leads to pregnant and breastfeeding women and their infants using ARV agents that have not been tested on them.

2.1 Ethical concerns about exposing pregnant women and their fetuses to ARV drugs being developed

Since the risks to the fetus and the infant posed by most new chemical entities or approved drugs cannot be sufficiently ruled out, pregnant and breastfeeding women are generally excluded from (pre-marketing) clinical trials *(12,13)*. Although no one questions the relevance of these ethical considerations, this leads to the following point.

2.2 ARV drugs are widely used "untested" among pregnancy and breastfeeding women

Since pregnant women are excluded from clinical trials during the development phase, a substantial knowledge gap remains regarding the pharmacokinetics and safety of ARV drugs during pregnancy, placental transfer of agents and transfer into breast-milk following drug marketing. Consequently, many pregnant and breastfeeding women will inevitably use (or have used) "untested" ARV drugs.

2.3 Using ARV drugs in pregnancy may be associated with birth defects or other adverse birth outcomes: preterm birth, fetal growth restriction and gestational diabetes

An essential element of pregnancy-related clinical pharmacology is the effect on the fetus of mothers using therapeutic agents. Maternal drug effects, such as an increased risk of preterm labour or impaired maternal glucose homeostasis, may profoundly affect the well-being of the fetus. Individual drugs cross the placenta to a greater or lesser extent, exposing the fetus to potential direct therapeutic and/or toxic drug effects. Exposure during the first trimester may impact fetal organogenesis and result in teratogenicity, although to date there is no confirmed association between exposure to ARV drugs and increased birth defect rate *(10)*.

Fetal (or placental) exposure to ARV drugs may provide beneficial effects such as pre-exposure prophylaxis to mother-to-child HIV transmission but may also result in fetal toxicity, such as bone marrow suppression or mitochondrial dysfunction *(14)*.

2.4 Physiological changes in pregnancy may affect exposure to ARV drugs, and these changes may change drug efficacy

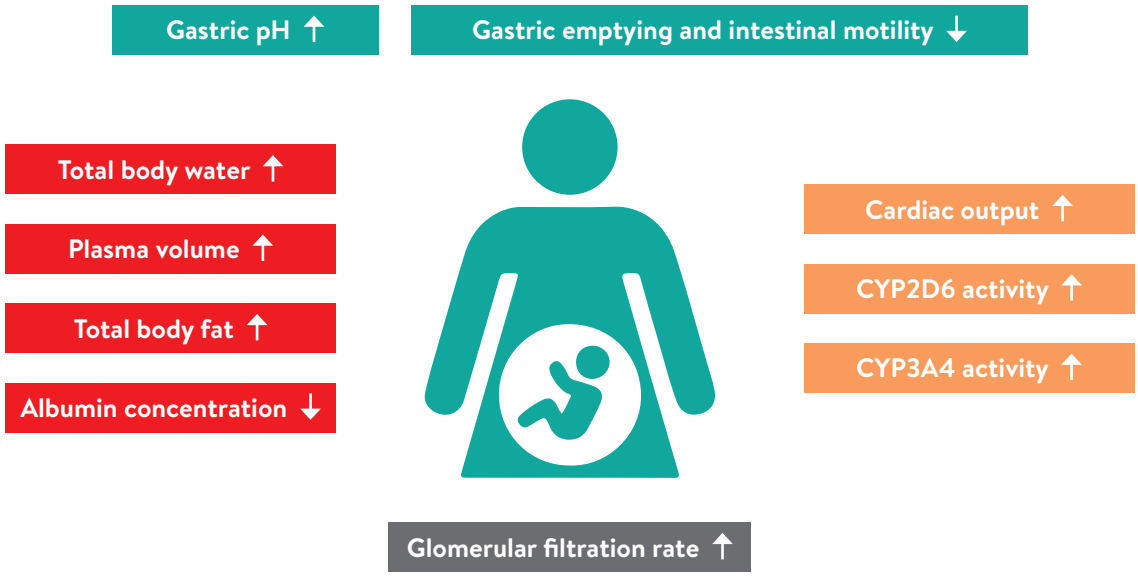
Pregnancy is associated with a wide range of physiological, anatomical and biochemical changes that substantially influence the pharmacokinetics of therapeutic agents *(15–18)*. Pregnancy is associated with prolonged gastric transit time, nausea and vomiting and dietary alterations that may alter drug absorption. Drug distribution may change in pregnant women because of changes in body composition, blood volume, protein binding and expression of transporters. Activity of drug metabolizing enzymes may increase during pregnancy (such as cytochrome 450 (CYP) 3A and uridine diphosphate-glucuronosyltransferase (UGT) 1A4) or decrease (such as CYP 2C19), affecting the intrinsic clearance of ARV drugs. Increases in cardiac output, renal blood flow and glomerular filtration rate during pregnancy may increase the elimination of renally cleared drugs.

In combination, these changes may result in alterations during pregnancy of the unbound pharmacologically active concentration of drug at the target site, leading to changes in drug response. Studying the pharmacokinetics of ARV drugs among pregnant women is necessary to ensure adequate drug exposure in this vulnerable population (Fig. 3.2).

2.5 Placental transfer, fetal exposure and disposition into breast-milk are unknown

Physiologically, placental transfer is the main determinant of fetal exposure *(20)*. Quantifying fetal exposure is key for evaluating potential fetal toxicity and therapeutic effect, since fetal exposure may have benefits in providing pre-exposure prophylaxis against maternal virus *(14)*. In general, quantifying human fetal exposure is not straightforward, since the fetus itself is not accessible for sampling throughout

Fig. 3.2. Pregnancy, physiology and pharmacokinetics



Created based on data from: Abduljalil et al. *(19)*.

pregnancy, so assessment of fetal drug exposure is generally limited to cord blood sampling at the time of delivery. Cord-to-maternal plasma concentration ratios are often computed based on time-matched samples collected at the time of delivery to provide a measure for fetal drug exposure relative to exposure in the mother. However, these relationships can be misleading because of the time-dependent distributional kinetics of drugs across the placenta (that is, placental transfer may vary during gestation).

Cord blood sampling provides the best available proxy for fetal exposure in humans, but the data resulting from cord blood sampling are generally limited to a single sample collected at one time point late in pregnancy. This sampling limitation complicates population pharmacokinetic analysis of such data *(21,22)*. Data on fetal exposure from animal models may be informative but of limited translational value because of interspecies variability in placental structure and function *(23,24)*.

Transmission of HIV from mother to child after birth via breast-milk remains a major problem in regions where formula feeding is not safe, affordable or practical. The provision of maternal ART through the period of breast-feeding has been shown to significantly reduce breast-milk HIV transmission by reducing breast-milk HIV concentrations and/or by providing prophylaxis to the infant who ingests the ARV drugs present in breast-milk *(25)*.

Waitt et al. *(26)* investigated whether infant exposure to ARV drugs during breastfeeding is quantitatively important. They concluded that this might be the case for some nucleoside reverse-transcriptase inhibitors and non-nucleoside reverse-transcriptase inhibitors but not for protease inhibitors.

Exposure to ARV drugs during breastfeeding could result in toxicity to the infant. Should the infant acquire HIV infection via breast-milk, infant exposure to low concentrations of ARV drugs during the breastfeeding period could result in the infant developing ARV drug resistance, limiting future therapeutic options *(27,28)*.

3. SOLUTIONS

Adequate ART for mother and child during and directly after pregnancy is vital in preventing mother-to-child HIV transmission. The following approaches and solutions can be used to ensure adequate treatment. Following these recommendations, information will become available for health-care professionals on adequate treatment regimens during pregnancy in a timely, informative and efficient manner.

3.1 Ethical concerns about exposing pregnant women and their fetuses to ARV drugs being developed

Regulatory authorities and ethical committees should require and support the inclusion of pregnant women in pre-marketing clinical trials. At the very least, women enrolled in Phase II or III clinical trials should not be removed from the study drug if they become pregnant during the trial, if preclinical reproductive toxicology studies were negative. Fortunately, the consensus is shifting, and support for including pregnant women before marketing is growing *(11,13)*.

Incentives from regulatory authorities are important to include pregnancy as part of the clinical development plan for ARV drugs, given the substantial anticipated use among women of childbearing age. This plan should ensure that the necessary data are obtained through studies in pregnancy and/or breastfeeding to support the use of drugs in pregnant women, including:

- safety data from both mother and child, with long-term follow-up after in utero and/or breast-milk exposure; and
- pharmacokinetic and pharmacodynamic data: viral load monitoring, CD4 counts, pharmacokinetics in pregnancy, placental passage, passage into breast-milk and exposure of neonates and other infants.

Dedicated clinical pharmacology studies involving pregnant and lactating women can be initiated once initial safety and efficacy have been demonstrated among non-pregnant adults *(4)*. These studies could include the women from pre-marketing trials and continue to include more pregnant women for adequate power with respect to a prespecified clinical endpoint, such as undetectable viral load at delivery. These studies may be opportunistic (women who become pregnant while receiving a specific drug can be included without changing treatment) or may be intervention studies (search for the optimal dose in pregnancy) initiated by academia or the pharmaceutical industry. To accelerate inclusion rates and include women in the settings where the disease is most prevalent, these studies should be performed in relevant populations in both high-income and low- and middle-income countries. Centres of excellence should be established in the low- and middle-income countries.

3.2 Using ARV drugs in pregnancy may be associated with birth defects or other adverse birth outcomes: preterm birth, fetal growth restriction and gestational diabetes

The safety of ART and pregnancy outcomes should be closely monitored during pharmacokinetic studies that include pregnant women. However, clinical studies specifically designed to detect safety issues during pregnancy require large numbers of study subjects and are therefore not feasible. Instead, post-marketing surveillance studies are used that follow women and newborns exposed to ARV drugs during pregnancy, such as the Antiretroviral Pregnancy Registry (http://www.apregistry.com). For sufficient power to detect

relevant effects (mainly birth defects), these studies typically require hundreds of subjects exposed to these agents *(10)*. Guidance on designing and executing these studies is described elsewhere *(29)*. This post-marketing surveillance should be supported and monitored more closely from a regulatory perspective (see the module on pharmacovigilance).

3.3 Clinical pharmacology studies of ARV drugs among pregnant women

In clinical studies with ARV drugs that include pregnant women, the following data should be collected:

- viral loads during pregnancy and postpartum;
- maternal safety during pregnancy;
- birth outcome: gestational age, birth weight, congenital abnormalities and HIV infection status;
- full pharmacokinetic profiles in the second and third trimesters and postpartum;
- if protein binding is substantial, unbound plasma concentrations should be determined;
- additional single time-point plasma samples can be taken throughout the course of pregnancy (such as at every visit) to identify temporal changes during pregnancy;
- cord and maternal blood sample at delivery, ideally for all included subjects; and
- washout samples of ARV drugs from infants following delivery (see the module on pharmacokinetic modelling).

Although pharmacodynamics are monitored and should be reported (such as viral load or toxicity), absolute differences are usually small, and detecting such effects would require more sophisticated trial design and including much larger numbers of pregnant subjects. Hence, pharmacodynamics as the primary endpoint in such studies is generally unfeasible. For this reason, the primary endpoints of clinical pharmacology studies of ARV drugs among pregnant women are typically pharmacokinetic under the assumption that pharmacokinetic parameters such as total drug exposure are informative and predictive for ARV drug efficacy and safety.

As such, these studies should be powered to detect relevant differences in the primary pharmacokinetic endpoints of interest. These typically include total drug exposure, maximum concentration over a dosing interval and/or concentration at the end of the dosing interval and depend on what parameter correlated best with the pharmacodynamics in previous pharmacokinetic and pharmacodynamic studies involving non-pregnant adults. These pharmacokinetic parameters can be estimated by non-compartmental analysis and, if needed, also by population pharmacokinetic modelling, with the major advantage that such an approach enables interpolation when the dose being investigated is deemed inadequate during pregnancy.

This is in accordance with the FDA guidance on designing pharmacokinetic studies in pregnancy, in which they recommend that "the dose should [be adjusted to] produce a comparable range of unbound plasma concentrations of drug or active metabolites in both controls and pregnant patients" *(5)*. Pregnancy effects can be determined by the comparability of exposure of non-pregnant (control) and pregnant people by means of no-effect boundaries for the ratio of a pharmacokinetic parameter, an approach sometimes referred to as the bioequivalence method. For this approach, the null hypothesis is that pregnancy has a clinically relevant effect on the pharmacokinetic parameter of interest. If the 90% confidence interval for the ratio falls within the no effect boundaries (typically 80–125%), the null hypothesis can be rejected, and it is reasonable to conclude that pregnancy has no clinically relevant effect and no dose adjustment is needed.

The no-effect boundaries are preferably set based on well established pharmacokinetic and pharmacodynamic relationships for efficacy and safety. However, these relationships are

not always readily available, and setting these boundaries can therefore be challenging. Since pregnancy is a temporary condition, boundaries somewhat wider than the conservative bioequivalence boundaries can be acceptable (such as 70–143% or wider), especially if the therapeutic window is relatively wide and variability is large. Prespecifying these boundaries for the primary pharmacokinetic endpoint and powering the study accordingly are crucial. Further guidance on setting the no-effect boundaries and ensuring the inclusion of sufficient subjects for adequate statistical power is provided elsewhere *(30)*.

3.4 Placental transfer and infant washout

To assess fetal exposure, cord blood samples and maternal samples should be taken at delivery (ideally for all included subjects). In addition, for compounds with substantial anticipated fetal exposure based on preclinical data, it is recommended to collect serial washout samples after birth from neonates exposed to the ARV drugs in utero. This sampling is especially important for compounds metabolized by enzymes that are known to be immature in neonates (see the module on pharmacokinetic modelling). Depending on the half-life of the compound, serial neonatal plasma samples should be collected, with the duration of sampling based on an estimate of likely half-life among newborns. Because many neonate enzyme systems are immature, half-life might be substantially prolonged *(31)*.

3.5 Disposition into breast-milk

When postpartum women included in clinical trials are breastfeeding, simultaneous maternal and infant plasma samples and breast-milk samples should be collected. In all samples, both viral load and concentrations of the ARV drug can be assessed. This sampling may be performed at standard postpartum visits, such as at 2, 6, 14 and 24 weeks postpartum. Preferably whole milk should be used for the analysis, since this is what the infant is ingesting.

3.6 Preclinical placental transfer

During the preclinical phases of drug development, parallel to or shortly after reproductive toxicology studies, the ex vivo human cotyledon perfusion model can be used to investigate the placental transfer of ARV drugs *(14)*. These experiments use term placentas obtained immediately following delivery and could be outsourced to institutes (typically academic medical centres) that have such models in place. The results of such studies can provide information about the fetal exposure to the ARV drug of interest, but such studies are limited to late pregnancy.

3.7 Modelling and simulation

Given the limited participation of pregnant women in clinical studies, leading to few data in pregnancy, modelling and simulation may facilitate understanding of pregnancy-related clinical pharmacology.

Population pharmacokinetic modelling can be helpful to quantify the sources of variability, handling sparse data, dealing with non-linearity, facilitating the pooling of data sets from studies with unbalanced design, trial simulation and interpolation (such as simulation of other dosing regimens in the target population). For this approach to be successful requires certain clinical data from the target population of pregnant women. These models can then be used for stochastic simulation to evaluate the drug exposure (or other secondary pharmacokinetic parameters of interest) during pregnancy, for example, to evaluate the frequency of individual drug exposure below a certain target.

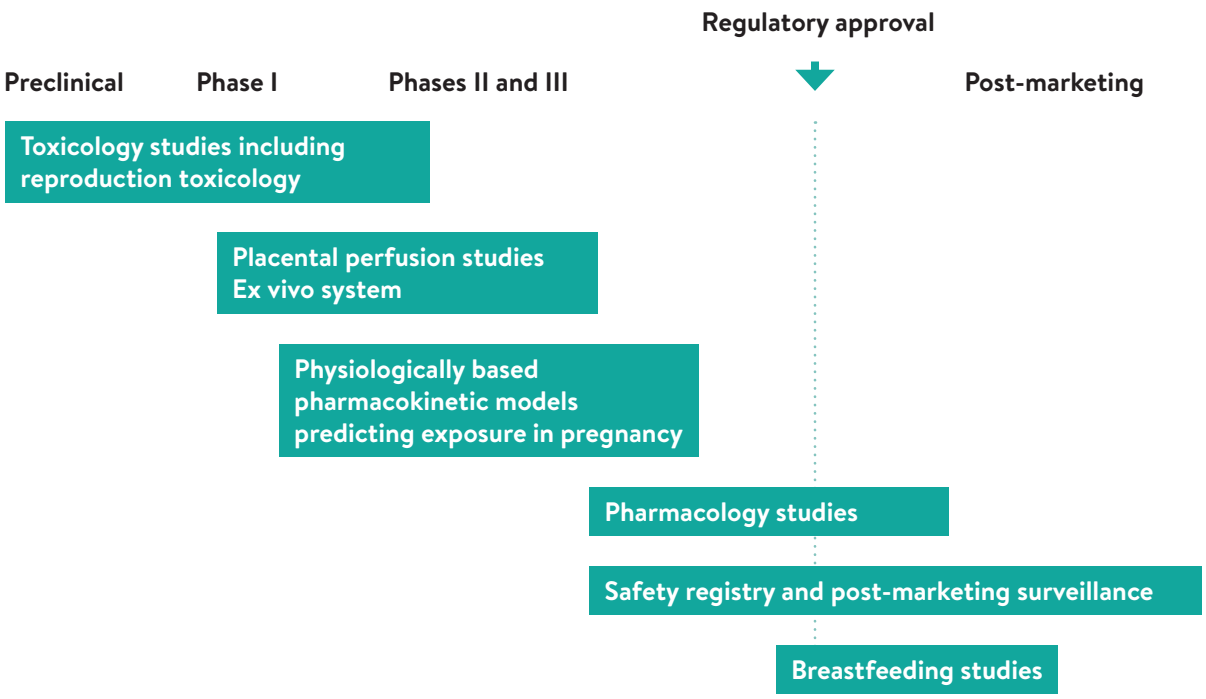
If the dose studied appears inadequate, the model can be used for simulating secondary pharmacokinetic parameters following alternative dosing regimens. This can inform

follow-up studies investigating dose adjustments during pregnancy *(32)*. Further, this approach can be used for optimizing design and clinical trial simulation. This enables optimization of sampling schedule throughout the course of pregnancy, which could provide information about the temporal change of pharmacokinetics during pregnancy *(33)*. Further, it could guide the plan of analysis for a clinical study, inform the choice of primary outcome measures and determine the number of women that should be included for adequate statistical power.

Full bottom-up approaches, such as physiologically based pharmacokinetic modelling, use mechanistic information, including system-related parameters (such as organ volumes, blood flows and tissue composition) and drug-related parameters (such as intrinsic metabolic clearance or drug ligand affinity). These parameters are combined in systems of differential equations that are based on a pragmatic compartmental structure describing the anatomy, physiology and biochemistry of the pregnant women. This approach enables the way the body processes a drug to be simulated in a mechanistic manner, taking molecular processes as a starting-point. Consequently, it provides comprehensive and integrated understanding of the pharmacokinetics and pharmacodynamics of a drug and can be completed even in the complete absence of clinical data in the target population (by extrapolation).

For example, fetal exposure can be quantitatively predicted by physiologically based pharmacokinetic modelling *(21,22)*. Placental transfer can be parameterized using an in vitro-to-in vivo extrapolation approach based on clearance values or rate constants from ex vivo human cotyledon perfusion experiments. These parameters can then be integrated in fetal-maternal whole-body physiologically based pharmacokinetic models to predict fetal exposure. Following such an approach, recent studies successfully predicted fetal exposure based on human placental transfer *(20,33,34)*. Later, this can be verified with cord blood and matched maternal blood samples collected at birth in clinical studies (Fig. 3.3).

Fig. 3.3. Studies involving pregnant women in developing drugs



4. CASE STUDIES

Currently, most pharmacokinetic studies among pregnant women living with HIV are conducted by two clinical trial networks: 1) the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Network protocol P1026s and 2) Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women (PANNA) network *(8,9)*. These studies follow an opportunistic design and perform intensive pharmacokinetic sampling during pregnancy and postpartum. Together they have conducted intensive pharmacokinetic sampling on more than 1000 pregnant and postpartum women receiving more than 25 ARV drugs. Most recently, these networks reported the pharmacokinetics of rilpivirine and dolutegravir among pregnant women living with HIV *(35,36)*. Pharmaceutical companies sometimes conduct and publish similar studies *(37)*. Such studies routinely conduct cord blood sampling. Less frequently, washout data from infants is collected. Several neonate washout studies have been performed, especially in case of in utero exposure to drugs metabolized by UGT. Examples are studies performed by the IMPAACT Network with raltegravir, dolutegravir and elvitegravir *(31,36,38)*.

Although not yet standard practice, the design of these studies would also be ideal for assessing breast-milk disposition (when national guidelines allow for breastfeeding). Waitt et al. *(26)* systematically reviewed the pharmacokinetic studies investigating the transfer of ARV drugs to breast-milk and subsequently to the infant.

The ARIA study (NCT01910402) is a progressive example of how to manage women enrolled in Phase II trials who become pregnant. In this study, sponsored by the pharmaceutical industry, women who become pregnant during the study are allowed to continue study drugs with informed consent and are included as a separate arm in the study (NCT02075593). This demonstrates the growing awareness, implementation and future opportunities for (pre-marketing) clinical research that includes pregnant women.

Ex vivo human cotyledon perfusion experiments have also been conducted, and the literature has been reviewed *(14)*. The placental transfer of the HIV integrase inhibitor dolutegravir was evaluated in an ex vivo human cotyledon perfusion model *(39)*. ARV drug placental transfer has been integrated into physiologically based pharmacokinetic models and fetal exposure has also been predicted *(20,33,34)*.

The major database for collecting safety information for ARV drugs during pregnancy is the Antiretroviral Pregnancy Registry, where pregnancy exposures and outcomes are reported on a voluntary basis.

5. SUMMARY

Pregnant and breastfeeding women are mainly excluded from clinical research, resulting in the use of "untested" ARV drugs by pregnant and breastfeeding women and their infants. Including pregnant and breastfeeding women in clinical research is critical, and the period between FDA approval and the first clinical pregnancy and lactation data should be minimized or eliminated.

The recommendations provided here will assist in effectively evaluating all aspects of clinical pharmacology that are required for safe and effective treatment of women living with HIV and their children and to optimize pharmacotherapy during pregnancy. This will facilitate more timely and quantitative information on safe treatment strategies for pregnant and breastfeeding women living with HIV.

6. KEY CONSIDERATIONS

- Placental transfer should be studied during the preclinical phases of drug development using techniques such as the ex vivo human cotyledon perfusion model.
- Regulatory authorities and ethical committees should require and support the inclusion of pregnant women in pre-marketing clinical trials. At the very least, women enrolled in Phase II or III clinical trials should not be removed from the study drug if they become pregnant during the trial.
- Clinical pharmacology studies of ARV drugs among pregnant and lactating women should be executed according to the high standards and requirements stated in this toolkit.
- Modelling and simulation should be used to facilitate understanding pregnancy-related clinical pharmacology and to inform clinical studies involving pregnant women.
- Cord blood samples and maternal samples should be taken at delivery to assess fetal exposure, and washout samples in neonates should be taken to assess neonatal elimination.
- Postpartum lactating women should be included in clinical trials, and breast-milk transfer from mother to infant should be assessed.
- The safety of ART and pregnancy outcomes should be closely monitored during pharmacokinetic studies that include pregnant women and by post-marketing surveillance studies.

7. USEFUL RESOURCES

FDA and EMA guidance for industry

EMA

- The exposure to medicinal products during pregnancy: need for post-authorisation data http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf

FDA

- Establishing pregnancy exposure registries https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071639.pdf
- Pharmacokinetics in pregnancy – study design, data analysis, and impact on dosing and labelling https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072133.pdf)
- Clinical lactation studies – study design, data analysis, and recommendations for labelling https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072097.pdf

Perinatal guidelines for treating women living with HIV

- Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States https://aidsinfo.nih.gov/guidelines/html/3/perinatal/0
- BHIVA guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review) http://www.bhiva.org/pregnancy-guidelines.aspx
- European guidelines for treatment of HIV-positive adults in Europe http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

WHO guidelines

- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1

Other

- Antiretroviral Pregnancy Registry http://www.apregistry.com
- International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Network protocol P1026s https://clinicaltrials.gov/ct2/show/NCT00042289
- Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women (PANNA) network www.pannastudy.com and https://clinicaltrials.gov/ct2/show/NCT00825929
- European Placental Perfusion Network https://www.facebook.com/EuropeanPlacentalPerfusionGroup
- ARIA study at clinicaltrials.gov https://clinicaltrials.gov/ct2/show/NCT02075593; pregnancy substudy https://clinicaltrials.gov/ct2/show/NCT01910402
- Guidance for industry: establishing pregnancy exposure registries http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071639.pdf

Key publications with open access

- Pregnancy-associated changes in pharmacokinetics: a systematic review http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002160

8. ACKNOWLEDGEMENTS

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