**Pharmacokinetics, Placental and Breastmilk Transfer of Antiretroviral Drugs**

**in Pregnant and Lactating Women Living with HIV**

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# Abstract

**Background:** Remarkable progress has been achieved in the identification of HIV infection in pregnant women and prevention of vertical HIV transmission through maternal antiretroviral treatment (ART) and neonatal antiretroviral drug (ARV) prophylaxis in the last two decades. Millions of women globally are receiving combination ART throughout pregnancy and breastfeeding, periods associated with significant biological and physiological changes affecting the pharmacokinetics (PK) and pharmacodynamics (PD) of ARVs.

**Objective**: The objective of this review was to summarize currently available knowledge on the PK of ARVs during pregnancy and transport of maternal ARVs through the placenta and into the breastmilk.

**Methods:** We conducted a review of the pharmacological profiles of ARVs in pregnancy and during breastfeeding obtained from published clinical studies. Selected maternal PK studies used a relatively rich sampling approach at each ante- and postnatal sampling time point. For placental and breastmilk transport of ARVs we selected the studies that provided ratios of maternal to cord (M:C) plasma and breastmilk to maternal plasma (M:P) concentrations, respectively.

**Results:** We provide an overview of the physiological changes during pregnancy and their effect on the PK parameters of ARVs by drug class in pregnancy, which were gathered from 45 published studies. The PK changes during pregnancy affect dosing of several protease inhibitors during pregnancy and limit the use for several ARVs, including three single tablet regimens with integrase inhibitors or protease inhibitors co-formulated with cobicistat due to suboptimal exposures. We further analysed currently available data on the mechanism of the transport of ARVs from maternal plasma across the placenta and into the breastmilk and summarized the effect of pregnancy on placental and breastfeeding on mammal gland drug transporters, as well as physicochemical properties, C:M and M:P ratios of individual ARVs by drug class. Finally, we discussed the major safety issues of fetal and infant exposure to maternal ARVs.

**Conclusions:** Available pharmacological data provide evidence that physiological changes during pregnancy affect maternal and consequently fetal ARV exposure. Limited available data suggest that expression of drug transporters may vary throughout pregnancy and breastfeeding thereby possibly impacting the amount of ARV crossing the placenta and secreted into the breastmilk. The drug transporter role in the fetal/child exposure to maternal ARVs needs to be better understood. Our analysis underscores the need for more pharmacological studies with innovative study design, sparse PK sampling, improved study data reporting and PK modelling in pregnant and breastfeeding women living with HIV to optimize their treatment choices and maternal and child health outcomes.

# 1. Introduction

## Global maternal and perinatal HIV epidemic

Introduction of antiretroviral treatment (ART) as prevention of vertical HIV transmission combined with the scale up of efforts to identify HIV and increase access to antiretroviral drugs (ARVs) among pregnant women living with HIV have modified the trajectory of the perinatal HIV epidemic. In 2017, approximately 80% of pregnant women living with HIV (around 1.1 million women) globally received ARVs. Between 2000 and 2017, an estimated 2 million infections in children were prevented and with the addition of early infant diagnostics and pediatric ART there was a 62% reduction in AIDS-related deaths among young children aged 0-5 years globally [1]. By end 2017, in ten countries 95% of pregnant women received antenatal care, HIV testing, diagnostic and treatment services, and were able to achieve ≤50 new pediatric HIV infections per 100,000 live births and a transmission rate of either *<*5% in breastfeeding populations or *<*2% in non-breastfeeding populations, and were validated by the World Health Organization (WHO) for eliminating mother-to-child HIV transmission (MTCT) [1-3]. In resource-rich settings (namely the United States and Europe), with the implementation of universal prenatal HIV counseling and testing, universal maternal ART, scheduled Cesarean delivery for women with viral load >1,000 copies/mL near delivery, infant ARV prophylaxis, and avoidance of breastfeeding, the rate of perinatal HIV transmission has diminished to ≤2% [4, 5].

Despite this remarkable progress, challenges with HIV prevention, timely HIV identification and initiation of ART during pregnancy and the breastfeeding period in women remain and the target of eliminating pediatric HIV infection globally remains currently out of reach. An estimated 180,000 children <15 years of age, where vertical transmission represents the major route of infection, were diagnosed with HIV in 2017 [6]. New HIV infections among children have declined by only 8% since 2016 and 110,000 children died of AIDS-related illnesses in 2017 [6]. **Moreover,** there has been little progress in decreasing the rate of new HIV infections among **women** of childbearing potential, with an estimated 43% of the 4,400 new HIV infections which occur daily being in women >15 years of age [6]. With an estimated 18.2 million women >15 years living with HIV globally in 2017, the number of women initiating and receiving ART during pregnancy and breastfeeding will remain high in foreseeable future [6].

Even with timely identification and diagnosis of HIV, significant social and behavioral barriers such as stigma, fear of disclosure, and lack of social support continue to compromise the retention of women in care and on treatment during postpartum and breastfeeding periods [7]. In fact, the breastfeeding period appears to be now responsible for the majority of vertical HIV transmission globally [8]. In 2013, only 49% of women continued to take ARVs while breastfeeding, compared to 62% of women who took ARVs during pregnancy and delivery [8]. Younger age, initiation of ART on the same day as diagnosis, initiation of ART during pregnancy *versus* breastfeeding, and initiating late in the pregnancy have been associated with poor retention in care and on ART [7]. Significant programmatic investment, healthcare system strengthening and involvement of community resources will be required to achieve high rates of retention in care and treatment of women throughout their childbearing and maternity journeys.

## 1.2 Current approaches and recommendations to prevent perinatal transmission of HIV

The changes to maternal ART from short-term prophylactic to fully efficient lifelong treatment regimens played a major part in the impressive decline in vertical transmission rates described above. Since introduction of the first ARVs zidovudine (AZT, ZDV), lamivudine (3TC) and nevirapine (NVP) as therapeutic agents in the management of HIV in adults, these drugs promptly gained attention for their potential to serve as preventive agents for the vertical transmission of HIV. Due to the proactive role of the National Institutes of Health (NIH) in launching preventive PACTG076 clinical trial in mother/infant pairs, there was little delay in establishing the evidence that maternal and neonatal ARVs were effective in significantly decreasing perinatal HIV transmission and rolling out national and global recommendations for ARV prophylaxis in pregnancy and postpartum. In fact, the first global WHO guidance on using ARVs for mother-infant pairs was issued in 2001 [9], when the global adult ART guidelines were still under development . As new evidence was generated from clinical trials in pregnant and breastfeeding women and their infants, since 2001 regimens for preventive and therapeutic use of ARVs in mothers and children have evolved continuously. From 2001 through 2010, single dose (sd) NVP in mothers at labor in combination with a mono and dual nucleoside-reverse transcriptase inhibitor (NRTI) backbone of diverse durations was recommended until Option A (AZT for the mother and infant prophylaxis with either AZT or NVP for six weeks for non-breastfed infant or daily NVP until after one week following end of the breastfeeding) plus Option B (triple ARVs prophylactic regimen for the mother during pregnancy and throughout the breastfeeding and infant prophylaxis for six weeks after birth, whether or not breastfeeding) and subsequently Option B+ (triple ART for mother for life independent of CD4 count and infant prophylaxis for six weeks after birth, whether or not breastfeeding) were introduced by the WHO in their global guidelines in 2010 [10] and 2013 [11], respectively.

Until 2013, the majority of pregnant women living with HIV were provided with ARVs in late pregnancy and early breastfeeding with the main goal of preventing vertical transmission of the virus to the child. For women experiencing repeat pregnancies, this approach represented suboptimal virologic suppression, treatment interruptions and risk for the development of viral resistance. The 2013 WHO recommendation for Option B+, which entailed the lifelong ART for women diagnosed with HIV in pregnancy or breastfeeding, led to the rapid transition from preventive short-term ART to combination triple drug ART for women identified within MTCT services. In 2005, 93% of pregnant women on ARVs for prevention of MTCT in the 21 Global Plan priority countries were receiving sdNVP, only 1% were receiving ART and 6% were receiving other “effective regimens“ [12]. By 2015, this pattern was reversed with 92.8% of pregnant women receiving ART and 6.9% other “effective regimens” for prevention of vertical transmission only [12, 13].

Moreover, the rapidly accumulated evidence suggested that immediate initiation of lifelong ART for pregnant women diagnosed with HIV was more effective than the “on-again, off-again” approach, leading the WHO to recommended in 2015 that all pregnant women living with HIV be provided with Option B+ with the immediate initiation of lifelong triple drug combination ART to continue beyond pregnancy, delivery and breastfeeding regardless of immunologic and virologic criteria [14]. The simultaneous introduction of the “Test and Treat” approach by the WHO has further advanced universal initiation of all women of childbearing age on ART irrespective of pregnancy or breastfeeding status [15].

Since the introduction of Option B+ in 2013 [11], an increasing number of women of reproductive age living with HIV world-wide have been receiving combination ART with non-nucleoside reverse transcriptase inhibitors (NNRTI) efavirenz (EFV) combined with two NRTIs as a backbone [1]. Introduction of integrase strand transfer inhibitors (INSTIs) with their capacity to produce rapid virologic suppression led promptly to introduction of these ARVs, such as raltegravir (RAL) and dolutegravir (DTG), in pregnancy and postpartum for use off-label and in national, regional and global ART guidelines [15-17]. In light of recent safety concerns associated with DTG exposure during conception and early pregnancy, the 2018 WHO update on ART guidelines and national USA guidelines recommended limiting the use of DTG in combination with two NRTIs to the second and third trimesters of pregnancy [17, 18]. While evidence is being gathered about potential association of maternal DTG exposure with the neural tube defects in newborns, the use of alternative ARVs, EFV in global settings and RAL, EFV, NNRTI rilpivirine (RPV) and protease inhibitors (PIs) atazanavir/ritonavir (ATV/r) and darunavir/r (DRV/r) in the USA, has been recommended during conception and up to eight weeks of pregnancy, respectively [17, 18]. The European HIV treatment guidelines have also moved towards restricting the use of DTG and recommending the use of alternative ARVs, such as RAL, RPV, ATV/r and DRV/r in women planning to become pregnant while on ARVs and in pregnant women living with HIV [19].

With the millions of women on ART and obvious public health and individual health benefits of lifelong treatment to the mothers and their children, a major challenge is to account for the changes in the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of the ARVs throughout pregnancy and during breastfeeding. As with many other therapeutic agents, the Food and Drug Administration (FDA) approval and labeling information for use of ARVs in pregnant women is based on limited clinical data and nonclinical data with or without limited human safety data. Due to multiple logistical and ethical challenges limiting research opportunities for pregnant women living with HIV, the majority of the PK and PD information about ARV use in pregnancy has been collected in the postmarketing settings, using data from observational studies, registries, cohort studies and a limited number of clinical trials. The objective of this review was to summarize currently available knowledge on the PK of ARVs during pregnancy and on the transport of maternal ARVs through the placenta and into the breastmilk with regards to the fetal and child ARV exposures, respectively.

### 2. METHODS

In our search of the studies describing the pharmacology of ARVs in pregnancy, we excluded *in vitro* and non-human *in vivo* data as well as data from physiologically based pharmacokinetic (PBPK) modelling. Selected maternal PK studies used a relatively rich sampling approach at each ante- and postnatal sampling time point and hence utilised non-compartmental analyses to determine the area under the concentration versus time curve (AUC), the maximum observed concentration (Cmax), and the concentration at end of dosing interval (Cτ). However, studies based on a sparse PK sampling approach with a compartmental, i.e. population PK, analysis were listed if they provided at least one of the secondary PK parameters (i.e. AUC, Cmax and/or Cτ) derived from the model. Studies initiating treatment at onset of labor were excluded as they do not provide information on the steady-state or a comparison with postpartum, except for a study on 3TC as this was the only data available [20]. Equally, studies using non-pregnant women and/or adults as comparators, e.g. from routine therapeutic drug monitoring (TDM) or PK studies in non-pregnant populations, were omitted as they do not provide information on inter-occasion variability. Except for elvitegravir (EVG) boosted with cobicistat (COBI) [21, 22], single-case studies were not included in the review and the summary table. Although abstracts and posters from most recent global conferences (Conference on Retrovirus and Opportunistic Infections [CROI] and International AIDS Conference [IAS] from 2018) were screened, they were only included in the analysis and summary tables if provided information was detailed enough to quantify ante-/postnatal ratios of AUC, Cmax and/or Cτ.

A similar approach was taken when gathering the data for the cord-to-maternal blood (C:M) ratios of ARVs. However, as the C:M ratio comprises a measurement at a single time point, there is less variability in sampling strategy, data analysis and reporting. However, it can be difficult to ascertain the time between the last maternal dose of drug and the collection of the specimens following delivery. *Ex vivo* perfusion models allow for a much stricter control of amount and duration of drug exposure and appear to yield similar results to those found *in vivo* [23]. Due to the single time point sampling, and the variation in time post-maternal dose, some studies reported large ranges of C:M ratios. Since it remains unclear whether placental transfer increases at Cmax in-line with *ex vivo* models [24], single case reports with C:M ratio many times greater than what was reported in larger studies were excluded from the analysis and relevant summary table.

Infant exposure to ARV via breastmilk was summarised by reviewing all studies reporting on paired samples of maternal blood and breastmilk whilst the mother had been on treatment for long enough to attain ‘steady state’, allowing derivation of the milk to plasma (M:P) ratio. Studies reporting on breastmilk concentrations following sdNVP and those without paired plasma concentrations to derive M:P ratios were not included. Given the paucity of data for breastmilk exposure to DTG, a single case report was included.

**3. PHARMACOKINETICS OF ANTIRTROVIRAL DRUGS DURING PREGNANCY**

## 3.1 Effect of pregnancy on drug pharmacokinetics

The absorption, distribution, metabolism and elimination of almost all drugs are different in pregnant women as compared to non-pregnant women due to physiological changes occurring during pregnancy [25, 26]. These changes include increased levels of progesterone leading to decrease in intestinal mobility and therefore altered drug absorption. Pregnancy also translates in major hemodynamic changes such as plasma volume expansion leading to larger volume of distribution and higher dilution of plasma proteins. In parallel, steroid and placental hormones occupy protein binding sites thus resulting in increased free drug concentrations during pregnancy. Higher availability of free drug for biotransformation and elimination leads to lower total drug concentrations whereas the free concentrations (unbound pharmacologically active) remain unaltered for low hepatic extraction drugs thereby complicating the interpretation of total drug measurements. Furthermore, the increased hepatic and renal blood flow during pregnancy result in faster elimination of high hepatic extraction drugs and renally excreted drugs, respectively. Importantly, the activity of several drug metabolizing enzymes is also induced during pregnancy through activation of nuclear receptors by progesterone, which leads to suboptimal drug exposure of certain drugs [21, 27, 28]. A summary of the physiological changes during pregnancy and their impact on drug disposition is presented in **Table 1**.

**Table 1: Physiological changes during pregnancy and impact on drug disposition [25, 26].**

|  |  |
| --- | --- |
| **Physiological change** | **Pharmacokinetic effect** |
| *Drug absorption* |  |
| * Prolonged gastric emptying due to ↑ progesterone
 | ↓ Maximal drug concentration |
| * Increased gastric pH due to ↓ gastric secretion
 | ↓ Absorption of weak acid and base molecules |
| *Drug distribution* |  |
| * Increased total body water
* Expanded plasma volume (by 50%)
 | ↑ Volume of distribution of hydrophilic drugs |
| * Increased fat storage
 | ↑ Volume of distribution of lipophilic drugs |
| * Decreased maternal albumin
 | ↑ Free drug concentrations |
| * Albumin binding sites occupied by steroids and placental hormones
 | ↑ Free drug concentrations |
| *Drug metabolism* |  |
| * Increased cardiac output leading to ↑ hepatic blood flow
 | ↑ Elimination of high hepatic extraction drugs |
| * Enzyme induction or inhibition by progesterone and estrogen\*
 | ↑↓ Metabolism depending on main metabolic enzyme of a given drug |
| *Drug excretion* |  |
| * Increased renal blood flow
* Increased glomerular filtration rate
 | ↑ Elimination of renally eliminated drugs |

\* Induced enzymes during pregnancy: CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4, UGT; inhibited enzymes during pregnancy: CYP1A2, CYP2C19

## 3.1 Pharmacokinetics of ARVs by drug class

Understanding the changes of drug exposure during pregnancy and the extent of placental and breastmilk transfer is important to attain therapeutic ARV concentrations exceeding the susceptibility of the virus strain(s) of the mother, and at the same time to ensure the safety of ARVs in the mother and the fetus, newborn and breastfed child. From a PK perspective, the ante-/postpartum ratio of AUC, Cmax and Cτ are typically used to describe changes in maternal exposure over time. Based on these, a time- or concentration-dependent drug response can then be calculated. For ARVs the minimum plasma concentration is commonly used as the target measure for efficacy (virologic suppression) whereas AUC and Cmax are of more relevance to estimating drug exposure related toxicity [29-32]. There is, however, no gold standard threshold for reduction/increase in any of these parameters as it depends on drug class.

Inter- and intra-class comparisons of the extent to which ARV exposure changes antepartum and postpartum are complicated by the paucity of data and the lack of standardisation in the collection, analysis and reporting of the data. Below we summarize the PK characteristics of different classes of ARVs and provide detailed summaries of individual ARV PK data in **Table 2**.

### 3.1.1 Nucleotide reverse transcriptase inhibitors (NRTIs)

NRTIs (including nucleotide reverse transcriptase inhibitors, NtRTIs) remain the backbone of ART for pregnant women in the majority of global guidelines and clinical settings. Didanosine (ddI) and stavudine (d4T) are no longer used, nor are they recommended by international guidelines, and will not be discussed in this review.

In **Table 2** the data on NRTIs shows that in the third trimester of pregnancy AUC, Cmax and Cτ of NRTIs are reduced by ~20% compared to postpartum, although data on Cτ was missing from several studies. This moderate decrease in FTC, 3TC and TFV PK parameters can be explained by increased renal blood flow and glomerular filtration rate observed in pregnancy which contribute to a higher renal clearance of this predominantly renally excreted drugs [33]. Abacavir (ABC), in contrast, is metabolized by alcohol dehydrogenase and glucuronyl transferase and the AUC in the third trimester of pregnancy is equal to that observed postpartum. The influence of a larger plasma volume appears to be minor for NRTIs which show low plasma protein binding (**Table 3**).

The NtRTI TFV is highly hydrophilic (**Table 3**), requiring administration as a prodrug, either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), to achieve better oral absorption. TAF has enhanced stability and an improved safety profile compared to TDF. The only PK study in pregnant women with TAF [34] found that exposure during pregnancy and postpartum were within the range of those typically observed in non-pregnant adults for both TAF 25 mg (without PK booster) and TAF 10 mg (with COBI as PK booster). Furthermore, the lower exposure of TAF 25 mg during pregnancy compared to postpartum seems to be attributed to a higher than anticipated AUC postpartum. Importantly, pregnancy did not seem to alter the intestinal boosting effect of COBI when administered with 10 mg TAF.

Most of the PK data for AZT originated in the era before Option B was introduced and there are no PK studies of continuous AZT use from ante- to postpartum that compared exposure at steady-state. However, the efficacy of AZT is related to its triphosphorylated intracellular concentrations, which persist even after serum AZT concentrations have become undetectable [33]. Hence changes in exposure might not be appropriate surrogate markers for virologic suppression with AZT.

Overall, authors of the studies listed in **Table 2** generally concluded that Cτ remained above the concentration of the drug required to suppress viral replication [35, 36] or drug exposure was still within the therapeutic AUC target in non-pregnant adults [20, 34, 37]. Therefore, dose adjustments in pregnancy are generally not warranted for NRTIs and the clinical data supports the sustained virologic suppression with the standard dosing.

### 3.1.2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTI in combination with two NRTIs remain the drug of first choice (EFV in global resource limited settings) and as alternative choice (EFV and RPV in resource-rich settings) in newly diagnosed women of childbearing potential and pregnant women (at conception and up to eight weeks after conception) [15-18].

EFV has been the most widely used NNRTI in pregnancy and, since a recent study showed non-inferiority of EFV 400 mg once daily over 600 mg once daily in adults [38], 2016 WHO treatment guidelines have recommended using the reduced dose of EFV within the fixed dose TLE 400 (TDF300/3TC300/EFV400) combination in non-pregnant adults due to better tolerability with decreased risk of central nervous toxicity associated with plasma EFV exposure and reduced cost [39].Indeed, most of the EFV PK data in pregnancy has been gathered using the standard 600 mg EFV daily dose (**Table 2**). Whilst two studies with 600 mg EFV daily dose found no major differences in AUC, Cmax and Cτ in the third trimester of pregnancy compared to postpartum [40, 41], a larger study by Dooley et al. [42] reported >30% reduction in model-predicted EFV plasma Cτ trough concentrations with the same dose. However, the Dooley et al. study included a considerable proportion of extensive CYP2B6 metabolizers which were of higher risk of subtherapeutic EFV plasma trough levels (i.e. <1 μg/mL). Cytochrome P450 (CYP) CYP2B6 is responsible for over 90% of EFV metabolism [43]. Several single nucleotide polymorphisms (SNPs) in the CYP2B6 gene have been associated with variability in EFV pharmacokinetics. Of interest, genetic variants associated with loss-of-function in CYP2B6 have been shown to be more prevalent in black African populations thus putting them at lower risk of sub-optimal EFV exposure [43]. A recent study using EFV 400 mg daily in pregnant Ugandan women [44] also reported a nearly 30% decrease in Cτ in the third trimester of pregnancy, but values were in a similar range to that measured for EFV 600 mg and all women maintained virologic suppression, suggesting that EFV 400 mg can be used safely and effectively in pregnancy.

The two studies comparing etravirine (ETV) exposure in the second and third trimester with post-partum period (**Table 2**) reported total ETV exposure was generally higher during both, the second and third trimester, with no difference between the trimesters. CYP2C19 plays an important role in ETV metabolism (**Table 1**). Contrary to CYP3A4, CYP2C19 is inhibited during pregnancy thus likely explaining the observed increased exposure [45].

NVP demonstrated ~20% reduction of AUC, Cmax and Cτ in the second and third trimester of pregnancy (**Table 2**). NVP is predominantly metabolised by CYP3A4 and CYP2B6. Both CYP enzymes are induced in late pregnancy (**Table 1**) and single nucleotide polymorphisms of the genes encoding for these enzymes have been associated with altered NVP PK, placing mothers with CYP2B6 extensive metabolizer genotype at higher risk of having plasma trough concentrations below the recommended minimum concentration (Cmin) target during pregnancy and postpartum [46].

The absorption of RPV is dependent on low gastric pH. Furthermore, RPV is a substrate of CYP3A4 and exposure is therefore expected to decrease in late pregnancy due to increased enzymatic clearance. **Table 2** shows that AUC of total and unbound RPV is reduced by ~20-30% in the second and third trimester of pregnancy [47, 48], and in one study by as much as by 45% [49]; however, the differences are minor between trimesters. Despite the also markedly lowered Cτ in most of the studies, virologic suppression was maintained in the majority of them and no mother-to-child transmission has been reported in association with PK in pregnancy.

Similar to NRTIs, studies listed in **Table 2** generally concluded dose adjustments for NNRTIs in pregnancy are not justified as drug exposure was either increased without safety concerns [45, 50], unaltered [51], adequate to suppress viral replication [41, 42, 47-49, 52] or within the range observed in non-pregnant adults [40, 44].

### 3.1.3 Protease inhibitors (PIs)

PIs, which are no longer used or recommended, i.e. fosamprenavir (FPV), indinavir (IDV), nelfinavir (NFV), saquinavir (SQV) and tipranavir (TPV) will not be discussed here. PIs are predominantly metabolized by CYP3A4 and can inhibit but also induce CYP enzymes thereby causing drug-drug interactions [53]. This interaction potential is exploited in the case of the PI ritonavir (RTV or r) and the PK enhancer COBI, both potent CYP3A4 inhibitors, used in low doses as boosters in combination with ATV, DRV and lopinavir (LPV) to increase their plasma concentrations. However, use of COBI with PIs in pregnancy has been challenged by recent data on reduced DRV AUC and Cτ when boosted with COBI compared to RTV which led to the change in the product label advising against use of DRV/COBI in pregnant women [54]. Similarly, boosting of EVG by COBI results in very low EVG Cτ (see 3.1.4) due to pregnancy related induction of CYP3A4 which increases COBI metabolic clearance and thereby shortens the boosting effect. COBI has indeed been shown to be less robust than RTV boosting in presence of inducers [55]. Based on these observations and in the absence of PK data, boosting with RTV should be preferred to COBI when treating pregnant women with ATV.

PIs are more than 90% protein bound (**Table 3**) and hence their pharmacological activity depends on unbound drug entering the HIV-infected cells. It is notable that most PK and TDM studies only measure total drug concentrations [56], meaning that the impact of changes in protein binding during advancing pregnancy may not be fully appreciated with existing data. This is because estimating unbound drug concentrations in human plasma can be highly method dependent [56], is labour intensive, and is therefore not routinely performed (**Table 2**).

Changes in total drug AUC, Cmax and Cτ in pregnancy have been well characterised for the PIs (**Table 2**). Total ATV AUC, Cmax and Cτ can be reduced by approximately half compared to postpartum PK parameters, likely explained by the reduced gastric pH-dependent absorption, increased clearance by CYP3A4 and reduced protein binding in late pregnancy (**Table 1**). Studies specifically evaluating the effect of co-administration with TDF [57, 58], found that total ATV exposure can be further reduced with this combination of ARVs. This effect has equally been reported in non-pregnant adults, however, the exact mechanism of the drug-drug interaction between PIs and TDF remains unclear [59]. Whilst total ATV exposure was either sufficient to achieve virologic suppression [60, 61], similar to the one observed in the non-pregnant period [62], or sufficient to maintain intracellular concentrations similar to non-pregnant adults [63], two studies recommended a dose increase based on total concentrations measurements only [57, 58].

A dose increase from standard ATV/r 300/100 mg to 400/100 mg once daily in the second and third trimester of pregnancy have been suggested to ensure Cτ remains above the target Cmin concentration, especially in women also receiving TDF as part of their ART. DRV boosted with RTV showed ~30% reduction in total DRV AUC, Cmax and Cτ in late pregnancy. Whilst in some studies once daily dosing with 800/100 mg DRV/r achieved total DRV exposure sufficient to prevent MTCT [64] or reached adequate therapeutic drug levels [65], and both, 600/100 mg DRV/r twice daily regimen [66] and 800/100 mg DRV/r once daily regimen [67], showed no clinically relevant change in unbound (active) DRV during pregnancy, two studies concluded that an increase to 600/100 mg DRV/r twice daily should be recommended for all [68] or at least for patients who are ARV-experienced, poorly adherent or taking co-medications that could decrease exposure [64] in order to achieve total DRV plasma concentrations equivalent to those seen in non-pregnant adults. One study also specifically emphasized the importance of TDM in case the dose is not increased [65].

Similarly, total LPV AUC, Cmax and Cτ boosted with RTV are decreased by ~15% in the first and ~30% in the second and third trimesters of pregnancy compared to postpartum as a result of enzyme induction and decreased protein binding. In some studies 400/100 mg LPV/r twice daily achieved adequate total LPV concentrations [69-71] or virologic suppression in the majority of women [72, 73]. The studies using an increase dose later in pregnancy, e.g. 533/133 or 600/150 mg LPV/r, reported exposure similar to the average AUC in non-pregnant adults taking 400/100 mg twice daily and hence recommended a higher dose should be used during the second and third trimesters of pregnancy [74, 75]. However, as for DRV, studies measuring unbound LPV concentrations suggested that the observed decrease in unbound concentration did not warrant dose adjustments from the 400/100 mg twice daily dosing [70, 76, 77] and that it might be more important to perform close TDM, especially in women with poor adherence [70] or who harbor PI resistance mutations [71].

Although the booster RTV is not considered to contribute to the pharmacological effect, it is noteworthy that it consistently shows a greater reduction in AUC, Cmax and Cτ than the respective main-PI across the studies (**Table 2**).

### 3.1.4 Integrase strand transfer inhibitors (INSTIs)

Integrase strand transfer inhibitors (INSTIs) are the most recently introduced class of ARVs, are known for their capacity to reduce viral load particularly rapidly and are therefore ideal for prevention of perinatal transmission of HIV, particularly in those women who are diagnosed with HIV in late pregnancy (i.e. during third trimester). To date, no PK information is available on the use of most novel INSTIs, bictegravir (BIC) and cabotegravir (CAB) in pregnancy. RAL and DTG have only minimal metabolism by CYP but are metabolised by progesterone-induced UDP-glucuronosyltransferases (UGT) 1A1 found in the liver, lungs, intestine mucosa, brain, uterus and placenta [78], resulting in a net increase in their metabolism in late pregnancy and lower plasma exposures (**Table 2**). Studies found that despite the reduced total DTG Cτ in late pregnancy, Cτ in most women was well above the reported dolutegravir in vitro protein-adjusted 90% effective concentrations [78-80]. Similarly, the decrease in RAL exposure was not deemed of clinical importance [81] and achieved virologic suppression [82]. The only INSTI primarily metabolised via CYP3A4 is EVG which requires PK boosting with COBI to achieve therapeutic systemic exposures with a once-daily fixed formulation dosing regimen. PK data in pregnancy for EVG/COBI has shown significantly lower total EVG exposure and through concentrations during pregnancy due to induction of EVG and COBI metabolism (>60%) [21, 22, 83, 84] which was also associated with a decrease in the unbound active fraction in the single case for which data is available [21]. This led to the recommendation not to use EVG/COBI based ART during pregnancy in treatment-naïve women and close monitoring with TDM in treatment-experienced women who continue the EVG-based ART throughout the pregnancy [16, 17].

### 2.4.6 Fusion/entry inhibitors

The fusion inhibitor enfuvirtide (T-20) is currently not recommended in pregnancy and will not be discussed in this review. The entry inhibitor C-C chemokine receptor 5 antagonist (CCR5) maraviroc (MVC) has very limited PK data in pregnancy (one PK study, see **Table 2**) which suggests that even though MVC exposure is lower in pregnancy (AUC ~30% reduced compared to postpartum), Cτ achieved with standard adult regimens seem sufficient, and no dose adjustments are required [85].

**Table 2: PK of antiretroviral drugs in pregnancy compared to ante- and postpartum.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Antiretroviral drug** | **Dose** | **Pregnancy trimester (weeks); n** | **Weeks postpartum; n** | **Ante-/postpartum exposure ratio** | **Ref.** |
|  |  |  |  | **Total** | **Unbound** |  |
|  |  |  |  | AUC | Cmax | Cτ | AUC | Cmax | Cτ |  |
| ***Nucleotide reverse transcriptase inhibitors (NRTIs)*** |
| Abacavir (ABC) | 300 mg BD | T3 (30–36); 25 | 6–12; 17  | 1.04  | 0.79 | BLQ | N/A | N/A | N/A | [37] |
| Emtricitabine (FTC) | 200 mg OD | T3 (31–37.9); 26 | 3.9–21.4; 22 | 0.82 | 0.97 | 0.68 | N/A | N/A | N/A | [35] |
|  |  | T3 (28–38); 27 | 3–9; 24 | 0.75 | 0.87 | 0.77 | N/A | N/A | N/A | [36] |
| Lamivudine (3TC) | 150 mg BD | T3 (≥38); 10 | 1; 10 | 0.97§,† | 1.09§,† | N/A | N/A | N/A | N/A | [20] |
|  | 300 mg BD | T3 (≥38); 10 | 1; 10 | 1.02§,† | 1.03§,† | N/A | N/A | N/A | N/A | [20] |
| Tenofovir (TFV) | 300 mg OD TDF | T3 (28–38); 34 | 3–9; 27 | 0.77 | 0.81 | 0.79 | N/A | N/A | N/A | [36] |
| Tenofovir alafenamide (TAF) | 25 mg OD TAF, no COBI  | T2 (21.1–27.4); 14  | 6.0–14.4  | 0.57 | N/A | N/A | N/A | N/A | N/A | [34] |
|  |  | T3 (30.0–37.6); 25 |  | 0.66 | N/A | N/A | N/A | N/A | N/A |  |
|  | 10 mg OD TAF + COBI  | T2 (20.4–27.1); 14 | 4.4–20.6  | 0.79 | N/A | N/A | N/A | N/A | N/A |  |
|  |  | T3 (30.0–36.4); 22 |  | 0.86 | N/A | N/A | N/A | N/A | N/A |  |
| Zidovudine (AZT, ZDV) | 300 mg BD | T3 (≥38); 10 | 1; 10 | 0.61§,† | $\~1$§,† | N/A | N/A | N/A | N/A | [20] |
| ***Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*** |
| Efavirenz (EFV) | 400 mg OD | T3; 22 | Not stated; 22 | 0.84 | 0.93 | 0.73 | N/A | N/A | N/A | [44] |
|  | 600 mg OD | T3 (30.1–38.7); 25 | 2.0–14.1; 25 | 0.97 | 1.11 | 1.03 | N/A | N/A | N/A | [40] |
|  |  | T3 (37); 73 | 6; 75 | N/A | N/A | 0.67§ | N/A | N/A | N/A | [42] |
|  |  | T2 (21–26); 10 | 2–9; 23  | 0.96 | 1.04 | 1.02 | N/A | N/A | N/A | [41] |
|  |  | T3 (28–37); 29 |  | 0.96 | 1.04 | 1.12 | N/A | N/A | N/A |  |
| Etravirine (ETV) | 200 mg BD | T2 (20–28); 5 | 3–12; 8 | 0.84§ | 1.11§ | 0.60§ | N/A | N/A | N/A | [45] |
|  |  | T3 (30–38); 13 |  | 1.34 | 1.34 | 2.03 | N/A | N/A | N/A |  |
|  |  | T2 (24–28); 13/12 | 6–12; 10/10 | 1.42 | 1.35 | 1.16 | 1.17 | 1.09 | 0.95 | [50] |
|  |  | T3 (34–38); 10/10 |  | 1.23 | 1.35 | 1.11 | 0.97 | 1.07 | 0.92 |  |
| Nevirapine (NVP) | 200 mg BD | T2–T3 (16–36); 26 | 4–12; 26  | 0.90 | N/A | N/A | N/A | N/A | N/A | [51] |
|  |  | T2 (20–24); 4 | 6; 15 | 0.76 | 0.77 | 0.87 | N/A | N/A | N/A | [52] |
|  |  | T3 (32–36); 15 |  | 0.80 | 0.80 | 0.79 | N/A | N/A | N/A |  |
| Rilpivirine (RPV) | 25 mg OD | T3 (30–37); 16 | 3–14; 15 | 0.55 | 0.65 | 0.51 | N/A | N/A | N/A | [49] |
|  |  | T2; 18  | 6.1–12.4; 28 | 0.77 | 0.84 | 0.91 | N/A | N/A | N/A | [47] |
|  |  | T3; 30 |  | 0.80 | 0.83 | 0.94 | N/A | N/A | N/A |  |
|  |  | T2 (24–28); 15/15 | 6–12; 11/11 | 0.71 | 0.79 | 0.65 | 0.74 | 0.85 | 0.68 | [48] |
|  |  | T3 (34–38); 13/13 |  | 0.69 | 0.80 | 0.58 | 0.78 | 0.90 | 0.64 |  |
| ***Protease inhibitors (PIs)*** |
| Atazanavir/ ritonavir(ATV/r) | 300/100 mg OD | T1 (8–14); 31 | <8; 45 | N/A | N/A | ATV: 0.65§r: 1.38§ | N/A | N/A | N/A | [60] |
|  |  | T2 (20–25); 74 |  | N/A | N/A | ATV: 0.69§r: 0.86§ | N/A | N/A | N/A |  |
|  |  | T3 (31–36); 83 |  | N/A | N/A | ATV: 0.72§r: 1.00§ | N/A | N/A | N/A |  |
|  |  | T3; 17 | 4–17; 17 | ATV: 0.94 | ATV: 0.94 | ATV: 0.96 | N/A | N/A | N/A | [62] |
|  |  | T1 (1–13.1); 10 | 12; 19 | N/A | N/A | ATV: 0.53§r: 0.43§ | N/A | N/A | N/A | [63] |
|  |  | T2 (13.2–26.2); 17 |  | N/A | N/A | ATV: 0.85§r: 0.35§ | N/A | N/A | N/A |  |
|  |  | T3 (26.3–40); 18 |  | N/A | N/A | ATV: 0.66§r: 0.25§ | N/A | N/A | N/A |  |
|  | 300/100 mg OD, no TDF | T2 (20–27); 14 | 1.7–5.7; 34 | ATV: 0.63§r: 0.34§ | ATV: 0.69§r: 0.38§ | ATV: 0.73§r: 0.71§ | N/A | N/A | N/A | [57] |
|  | 300/100 mg OD + TDF | T2 (20–27); 17 |  | ATV: 0.45§r: 0.46§ | ATV: 0.50§r: 0.49§ | ATV: 0.40§r: 0.50§ | N/A | N/A | N/A |  |
|  | 300/100 mg OD, no TDF | T3 (30–36); 13 | 6–12; 13 | ATV: 0.70 | ATV: 0.86 | ATV: 0.33 | N/A | N/A | N/A | [58] |
|  | 300/100 mg OD + TDF | T3 (30–36); 19 | 6–12; 19 | ATV: 0.66 | ATV: 0.69 | ATV: 0.61 | N/A | N/A | N/A |  |
|  | 300 or 400/100 mg OD | T3 (36–42); 29 | 3–10; 25 | ATV: 0.66r: 0.45 | ATV: 0.70r: 0.42 | ATV: 0.59r: 0.47 | N/A | N/A | N/A | [61] |
|  | 400/100 mg OD, no TDF | T3 (31–37); 37 | 1.7–5.7; 34 | ATV: 0.93§r: 0.45§ | ATV: 1.00§r: 0.47§ | ATV: 1.05§r: 0.71§ | N/A | N/A | N/A | [57] |
|  | 400/100 mg OD + TDF | T3 (31–37); 32 |  | ATV: 0.64§r: 0.46§ | ATV: 0.66§r: 0.44§ | ATV: 0.47§r: 0.50§ | N/A | N/A | N/A |  |
| Darunavir/ ritonavir(DRV/r)  | 800/100 mg OD | T3 (32–37); 16 | 4–13; 8 | DRV: 0.67r: 0.59 | DRV: 0.78r: 0.59 | DRV: 0.77r: 0.72 | N/A | N/A | N/A | [64] |
|  |  | T2 (20.7–27.3); 15 | 3.6–12.9; 23 | DRV: 0.62§ | DRV: 0.83§ | DRV: 0.36§ | N/A | N/A | N/A | [68] |
|  |  | T3 (30.0–37.1); 30 |  | DRV: 0.61§ | DRV: 0.71§ | DRV: 0.42§ | N/A | N/A | N/A |  |
|  |  | T1; 1 | Not stated; 14 | N/A | N/A | DRV: 1.63§ | N/A | N/A | N/A | [65] |
|  |  | T2; 9 |  | N/A | N/A | DRV: 0.55§ | N/A | N/A | N/A |  |
|  |  | T3; 18 |  | N/A | N/A | DRV: 0.47§ | N/A | N/A | N/A |  |
|  |  | T2 (24–28); 16/14 | 6–12;15/15 | DRV: 0.66r: 0.54 | DRV: 0.66r: 0.54 | DRV: 0.68r: 0.59 | DRV: 0.76 | DRV: 0.75 | DRV: 0.87 | [67] |
|  |  | T3 (34–38); 14/14 |  | DRV: 0.65r: 0.53 | DRV: 0.69r: 0.51 | D: 0.50r: 0.65 | DRV: 0.80 | DRV: 0.84 | DRV: 0.62 |  |
|  | 600/100 mg BD | T3 (31–36); 5 | 4–9; 5 | DRV: 0.78r: 0.74 | DRV: 0.76r: 0.63 | DRV: 0.82r: 0.72 |  |  |  | [64] |
|  |  | T2 (24–28); 11/6 | 6–12; 11/11 | DRV: 0.76r: 0.72 | DRV: 0.72r: 0.66 | DRV: 1.43r: 1.08 | DRV: 0.92 | DRV: 0.78 | DRV: 1.10 | [66] |
|  |  | T3 (34–38); 11/7 |  | DRV: 0.83r: 0.67 | DRV: 0.81r: 0.63 | DRV: 1.86r: 1.22 | DRV: 0.93 | DRV: 0.82 | DRV: 1.14 |  |
|  |  | T2 (20.3–26.7); 13 | 2.3–14.1; 27 | DRV: 0.74§ | DRV: 0.72§ | DRV: 0.84§ | N/A | N/A | N/A | [68] |
|  |  | T3 (27.4–41.0); 34 |  | DRV: 0.74§ | DRV: 0.71§ | DRV: 0.88§ | N/A | N/A | N/A |  |
| Lopinavir/ ritonavir(LPV/r)  | 400/100 mg BD | T2 (13–26); 11 | 2.6–8.9; 11 | LPV: 0.90§r: 0.59§ | LPV: 0.93§r: 0.64§ | LPV: 0.94§r: 0.77§ | LPV: 1.15§ | LPV: 1.02§ | LPV: 1.38§ | [69] |
|  |  | T3 (30–36.3); 11 |  | LPV: 0.65§r: 0.50§ | LPV: 0.76§r: 0.58§ | LPV: 0.59§r: 0.59§ | LPV: 0.76§ | LPV: 0.81§ | LPV: 0.82§ |  |
|  |  | T1 (≤14); 13 | 1.2–29.2; 30  | LPV: 0.88§ | N/A | LPV: 0.86§ | LPV: 1.10§ | N/A | LPV: 1.07§ | [76] |
|  |  | T2 (15–26); 29 |  | LPV: 0.73§ | N/A | LPV: 0.68§ | LPV: 0.85§ | N/A | LPV: 0.79§ |  |
|  |  | T3 (≥27); 36 |  | LPV: 0.74§ | N/A | LPV: 0.69§ | LPV: 0.84§ | N/A | LPV: 0.79§ |  |
|  |  | T1–T2 (8–29); 16 | 5–12; 12 | N/A | N/A | LPV: 0.69§r: 0.61§ | N/A | N/A | LPV: 0.76§ | [70] |
|  |  | T3 (26–40); 43 |  | N/A | N/A | LPV: 0.65§r: 0.53§ | N/A | N/A | LPV: 0.60§ |  |
|  |  | T3; 10 | 6 and 24; 10 | LPV: 0.60r: 0.36 | LPV: 0.57r: 0.36 | LPV: 0.60r: 0.33 | LPV: 0.57r: 0.34 | N/A | N/A | [72] |
|  |  | T3 (30–37); 17 | 5–13; 13  | LPV: 0.72r: 0.84 | LPV: 0.77r: 0.86 | LPV: 0.93r: 0.62 | N/A | N/A | N/A | [73] |
|  |  | T2 (21.7); 20 | 5.2; 20 | LPV: 0.72 §r: 0.57§  | LPV: 0.75§ r: 0.62§ | LPV: 0.74§ r: 0.47§  | N/A | N/A | N/A | [71] |
|  |  | T3 (31.1); 24 |  | LPV: 0.71§ r: 0.60§  | LPV: 0.76§ r: 0.59§  | LPV: 0.70§ r: 0.56§  | N/A | N/A | N/A |  |
|  |  | T2 (20–24); 12 | 8; 12 | LPV: 0.63§r: 0.48§ | LPV: 0.77§r: 0.56§ | LPV: 0.72§r: 0.43§ | LPV: 0.62§r: 0.80§ | LPV: 0.64§r: 0.75§ | LPV: 0.94§r: 0.67§ | [77] |
|  |  | T3 (30); 12 |  | LPV: 0.65§r: 0.44§ | LPV: 0.78§r: 0.48§ | LPV: 0.56§r: 0.43§ | LPV: 0.62§r: 0.60§ | LPV: 0.75§r: 0.63§ | LPV: 0.63§r: 0.67§ |  |
|  | 500/125 mg BD (T3) and 400/100 mg (PP) | T3 (32); 12 |  | LPV: 0.71§§r: 0.46§ | LPV: 0.85§r: 0.57§ | LPV: 0.68§r: 0.54§ | LPV: 0.69§r: 0.60§ | LPV: 0.86§r: 0.63§ | LPV: 0.75§r: 0.67§ |  |
|  | 400/100 mg BD (T2) and 533/133 mg BD (T3 and PP) | T2; 8 | 2; 23 | LPV: 0.38§r: 0.35§ | LPV: 0.53§r: 0.40§ | LPV: 0.25§r: 0.21§ | N/A | N/A | N/A | [74] |
|  |  | T3; 26 |  | LPV: 0.58§r: 0.59§ | LPV: 0.66§r: 0.60§ | LPV: 0.58§r: 0.90§ | N/A | N/A | N/A |  |
|  | 400/100 mg (T2 and PP), 600/150 mg BD (T3) | T2 (20.6–26.4); 11 | 1.9–3.7; 27 | LPV: 0.54§r: 0.61§ | LPV: 0.58§r: 0.53§ | LPV: 0.61§r: 0.73§ | N/A | N/A | N/A | [75] |
|  |  | T3 (30.3–37.4); 33 |  | LPV: 0.72§r: 0.71§ | LPV: 0.73§r: 0.71§ | LPV: 0.77§r: 0.67§ | N/A | N/A | N/A |  |
|  | 600/150 mg BD (T3) and 400/100 mg BD (PP)  | T2 (22.2); 16 | 4.7; 16 | LPV: 0.91§ r: 0.90  | LPV: 0.95§ r: 0.98  | LPV: 0.87§ r: 0.85  | N/A | N/A | N/A | [71] |
|  |  | T3 (31.2); 20 |  | LPV: 0.85§ r: 0.83 | LPV: 0.92§r: 1.01  | LPV: 0.76§ r: 0.76  | N/A | N/A | N/A |  |
| ***Integrase strand transfer inhibitors (INSTIs)*** |
| Dolutegravir (DTG) | 50 mg OD | T2 (20–26.4); 15 | 6–32; 22 | 0.63 | 0.74 | 0.49 | N/A | N/A | N/A | [78] |
|  |  | T3 (301–37.6); 28 |  | 0.71 | 0.75 | 0.66 | N/A | N/A | N/A |  |
|  |  | T3 (≈ 33); 8 | 4–6; 5 | 0.95 | 1.07 | 0.66 | N/A | N/A | N/A | [79] |
|  |  | T3;28 | 0.3–2.6; 27 | 0.95 | 0.91 | 0.93 | N/A | N/A | N/A | [80] |
| Elvitegravir/ cobicistat(EVG/COBI) | 150/150 mg OD | T3 (34); 1 | 6; 1 | EVG: 1.07§COBI: 0.56§ | EVG: 1.09§COBI: 0.52§ | EVG: 0.4§COBI: BLQ | N/A | N/A | N/A | [22] |
|  |  | T3 (33); 1 | 5; 1 | EVG: 0.93§COBI: 0.76§ | EVG: 0.94§COBI: 0.93§ | EVG: 0.30§COBI: 0.67§ | EVG: 1.28§COBI: 0.93§ | EVG: 1.45§COBI: 0.83§ | EVG: BLQCOBI: BLQ | [21] |
|  |  | T3; 7 | 5–7; 6  | EVG: 0.67 | EVG: 0.79 | EVG: 0.35 | N/A | N/A | N/A | [83] |
|  |  | T2 (20–26); 14 | 6–12; 14 | EVG: 0.76COBI: 0.56 | EVG: 0.92COBI: 0.72 | EVG: 0.19COBI: 0.40 | N/A | N/A | N/A | [84] |
|  |  | T3 (30–38); 24 | 6–12; 24 | EVG: 0.56COBI: 0.41 | EVG: 0.72COBI: 0.62 | EVG: 0.11COBI: 0.24 | N/A | N/A | N/A |  |
| Raltegravir(RAL) | 400 mg BD | T3 (32–35); 21 | 4–6; 18  | 0.71 | 0.82 | 0.64 | N/A | N/A | N/A | [81] |
|  |  | T2 (20–26); 16 | 3–14; 38 | 0.57§ | 0.74§ | 0.78§ | N/A | N/A | N/A | [82] |
|  |  | T3 (34–41); 41 |  | 0.47§ | 0.58§ | 0.80§ | N/A | N/A | N/A |  |
| ***Fusion/entry inhibitors*** |
| Maraviroc (MVC) | Various regimens | T3 (31–38); 18 | 4–15; 14 | 0.72 | 0.70 | 0.85 | N/A | N/A | N/A | [85] |

The doses were given once (OD) or twice (BD) daily. COBI: cobicistat; TAF: tenofovir alafenamide; TDF: tenofovir disproxil fumarate; TFV: tenofovir. T1: first trimester; T2: second trimester; T3: third trimester; PP: postpartum. n indicates the number of women sampled at the respective ante-/postpartum timepoint for total/unbound drug concentration. Ante-/postpartum exposure ratios are geometric mean or least squares mean ratio ante-/postpartum. If ratios were not provided (marked with §), the ratios were calculated based on the mean or median for each time point provided, rounded to the second decimal. One study reported data from samples that were not drawn at steady-state (marked with †). Area under the concentration versus time curve is indicated as “AUC”, maximum observed concentration as “Cmax”, concentration at end of dosing interval (concentration pre-dose or, if not provided, minimum concentration) as “Cτ”, below limit of quantitation as “BLQ”. N/A: Not applicable (as no data exist).

**4. PLACENTAL AND BREASTMILK TRANSFER OF MATERNAL ARVs**

## 4.1 Placental transfer of drugs

The ratio between the cord blood concentration in the newborn child to maternal plasma concentration, i.e. cord-to-mother (C:M) ratio, gives an indication of placental transfer of the ARVs, thereby providing important information on the efficacy and safety of ARV exposure *in utero* and during labor. Although the C:M ratio does not reflect intrauterine exposure for an entire duration of the pregnancy it is essentially the only practical means to obtain ratios of maternal/fetal/newborn ARV exposures.

The placenta is an organ that among other functions regulates the exchange of nutrients, gases and waste products between the mother and the fetus, while limiting the transfer of potentially toxic xenobiotics to the fetus. The placenta is composed of a rate-limiting layer of cells called syncytiotrophoblasts with a basal membrane facing the fetal side and a microvillous apical membrane directly connected with the maternal blood flow [86]. The transfer of nutrients and endogenous or exogenous compounds from the mother to the fetus requires translocation across both, the apical and basolateral, membranes of the syncytiotrophoblasts. Drugs predominantly cross the placenta by passive diffusion which depends on the concentration of the drug in the maternal plasma, the physicochemical properties of the drug, i.e. molecular weight (MW), degree of lipophilicity or log octanol-water partition coefficient at pH = 7.4 (log D) and pH at which the drug is 50% ionized (pKa), and plasma drug protein binding.

Low molecular weight drugs, and drugs that are lipophilic, predominantly unionized and unbound, such as most NRTIs, INSTIs or NVP are likely to cross passively the placental barrier (**Table 3**). Not surprisingly, the NRTI ZDV has become a first preferred ARV for prophylaxis of vertical HIV transmission when administered orally and intravenously to mothers in pregnancy and in labor, respectively [87, 88].Although NNRTIs are small, lipophilic molecules, their high plasma protein binding (with the exception of NVP) limit their passive diffusion (**Table 3**). This is reflected by C:M ratios, around 0.5 for EFV, ETV, and RPV.

In addition to passive diffusion, some endogenous molecules such as glucose are transported by facilitated diffusion, a carrier mediated but not energy-dependent process. Moreover, placental transfer can occur through an energy-dependent active transport mediated by efflux or uptake transporters and driven by energy from adenosine triphosphate (ATP) hydrolysis or the transmembrane electrochemical gradient provided by Na+, Cl- or H+ [89]. In recent years, several drug transporters have been localized on the apical brush border (maternal facing circulation) and on the basolateral (fetal facing circulation) membrane of the syncytiotrophoblast as illustrated in **Figure 1** [90-95]. Depending on their function and localization, syncytiotrophoblast transporters can either facilitate the entry of drugs in or removal from the fetal placental compartment.

Drug transporters are classified in two families: the ATP-binding cassette (ABC) transporter family and the solute carrier (SLC) transporter family. The ABC transporter family consist of efflux transporters such as P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) which act by removing drugs out of the apical placental membrane thus preventing the entry of potentially harmful drugs in the fetal circulation.[96] Members of the multidrug resistance-related protein (MRP) are expressed both on the apical and basolateral side of the syncytiotrophoblast. The expression of P-gp during pregnancy has been linked to fetal protection from pesticides in animal studies [97]. In human studies, the expression of P-gp has been shown to progressively decline with advancing gestation suggesting that the ability of the placenta to protect the fetus might be more efficient in early pregnancy compared to late pregnancy [98]. P-gp transports an extensive variety of drugs (e.g. anticancer drugs, antihypertensives, antiarrhythmics, glucocorticoids, directly acting anti-hepatitis C virus drugs, antibiotics, antimycotics, antidepressants, neuroleptics, antiepileptics) including HIV PIs, CCR5 inhibitor MVC and NRTI tenofovir prodrugs [99, 100],while BCRP predominantly transports anticancer drugs [100] .

The backwards transport of PIs and the CCR5 antagonist MVC by P-gp combined with their higher MW and the high protein binding for PI might explain their limited transfer across the placenta and lower C:M ratios (**Table 3**). Of interest, TAF, the prodrug of tenofovir and a substrate of P-gp and BCRP does not seem to cross the placenta as indicated by preliminary results from 15 mother-child pairs [34]. Importantly, several PIs and boosted INSTI EVG/COBI inhibit both P-gp and BCRP as summarized in **Table 4**, and consequently may increase the fetal exposure of co-administered substrate drugs [100].Similarly, some NNRTIs inhibit efflux transporters expressed at the level of the syncytiotrophoblats and therefore have the potential to modulate removal or entry into the fetal compartment of concomitantly administered drugs. On the other hand, ARV such as DTG and RAL are substrates of P-gp and BCRP, and therefore co-administered inhibitors of inducers of these transporters could modulate their placental transfer [101].

The SLC transporter family includes mainly uptake transporters. Members of the organic anion transporting polypeptide family (OATP), organic cation transporter (OCT), organic anion transporter (OAT), multidrug and toxin extrusion protein (MATE), organic cation/carnitine transporter (OCTN), concentrative nucleoside transporter (CNT), equilibrative nucleoside transporter (ENT) are involved in the placental transfer of endogenous compounds or drugs. Typical SLC substrates include amino acids, prostaglandins, carnitine, and drugs such as statins, methotrexate, metformin, tetracycline, verapamil, quinidine and NRTI ZDV [91-94, 96, 100]. The vectorial transport across the placenta may involve the coupled coordinated function of two SLC transporters such as for instance OCT3 (basolateral membrane) together with MATE1 (apical membrane) (**Figure 1**) [95]. Similarly to P-gp and BCRP, several HIV PIs inhibit OATP2B1 and therefore have the potential to limit the transfer of substrate drugs from the fetus into the maternal circulation [100].

**Table 3**: **Physicochemical properties [102, 103], cord-to-mother (C:M) ratio and milk-to-plasma (M:P) ratio of ARVs by drug class.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Antiretroviral drug** | **MW** | **log D** | **pKa** | **Protein binding (%)** | **Cord-to-mother (C:M) ratioa**  | **Milk-to-plasma (M:P) ratiob** |
| ***Nucleotide reverse transcriptase inhibitors (NRTIs)*** |
| Abacavir (ABC) | 286.3 | 1.7 | 5.8 | 49 | 1.03–1.06 | 0.85 |
| Emtricitabine (FTC) | 247.2 | -0.4 | 2.7 | < 4 | 0.76–1.66  | 0.63–3.01  |
| Lamivudine (3TC) | 229.3 | -0.9 | 4.3 | < 36 | 0.93–1.22  | 0.55–3.34  |
| Tenofovir (TFV) | 287.2 | -4.4 | 3.8 | < 0.7 | TAF: BLQ | No data |
| TFVc: 0.59–1.20  | TFVc: 0.015–0.07  |
| Zidovudine (AZT, ZDV) | 267.3 | 1.2 | 9.7 | 34-38 | 0.69–1.75  | 0.44–3.21  |
| ***Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*** |
| Efavirenz (EFV) | 315.7 | 5.1 | 10.2 | 99 | 0.49–0.81  | 0.54–1.23  |
| Etravirine (ETV) | 435.3 | 5.9 | 3.5 | 99.9 | 0.33–0.52  | 3.27 |
| Nevirapine (NVP) | 266.3 | 1.8 | 2.8 | 60 | 0.59–1.02  | 0.27–0.67  |
| Rilpivirine (RPV) | 366.4 | 5.8 | 5.6 | 99.7 | 0.50–0.55 | No data |
| ***Protease inhibitors (PIs)*** |
| Atazanavir (ATV) | 704.9 | 3.8 | 4.3 | 86 | 0.12–0.23  | No data |
| Darunavir (DRV) | 547.7 | 2.9 | 2.4 | 95 | 0.11–0.36  | No data |
| Lopinavir (LPV) | 628.8 | 5.0 | 4.7 | 98-99 | 0.16–0.57  | 0.07–0.19  |
| ***Integrase strand transfer inhibitors (INSTIs)*** |
| Dolutegravir (DTG) | 419.4 | 1.1 | 8.2 | 99 | 1.06–1.4  | 0.02–0.03  |
| Elvitegravir (EVG)  | 447.9 | 3.2 | 6.6 | 98-99 | 0.71–1.00  | No data |
| Raltegravir (RAL) | 442.4 | 0.5 | 6.7 | 83 | 1.00–1.50  | No data |
| ***Fusion/entry inhibitors*** |
| Maraviroc (MVC) | 513.7 | 2.1 | 7.3 | 76 | 0.33–0.37  | No data |

a Based on geometric mean or median. References: abacavir [37, 104, 105]; emtricitabine [35, 60, 106-109]; lamivudine [20, 104, 110-112]; tenofovir alafenamide (TAF) cord blood below limit of quantitation (BLQ) [34]; tenofovirdisoproxil fumarate (TDF)[60, 107-109, 113, 114]; zidovudine [20, 104, 110, 115-119]; efavirenz [40, 41]; etravirine [45, 109, 120]; nevirapine [51, 110, 121-127]; rilpivirine [47-49]; atazanavir boosted with ritonavir [60-62, 121, 128, 129]; darunavir boosted with ritonavir [64-68, 109, 130-133]; lopinavir boosted with ritonavir [71, 73-76, 110, 127, 134]; dolutegravir [79, 80, 108, 135]; elvitegravir boosted with cobicistat [22, 84, 108]; raltegravir [81, 133, 134]; maraviroc [85, 109].

b References: abacavir [136]; emtricitabine [137, 138]; lamivudine [136, 137, 139-144]; tenofovir disproxil fumarate [137, 138, 142]; zidovudine [139-141, 143, 144]; efavirenz [43, 142, 145]; etravirine [146]; nevirapine [136, 140, 141, 143, 144, 147]; lopinavir boosted with ritonavir [136, 139, 141]; dolutegravir [80, 148].

c tenofovir derived from TDF. Since TDF is rapidly converted to TFV in the gastro-intestinal tract, only the tenofovir entity is present thereafter to cross the placenta or be secreted in breastmilk.

**Table 4: The ARVs, substrate and/or inhibitory properties for drug transporters expressed in placental syncytiotrophoblasts and mammary gland epithelial cells.**a,b

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Antiretroviral drug** | **ENT2**  | **MATE1** | **OATP2B1** | **OAT4** | **P-gp** | **BCRP** | **MRP1** | **MRP2** | **MRP5** |
| ***Nucleotide reverse transcriptase inhibitors (NRTIs)*** |
| Abacavir (ABC) |  |  |  |  |  | X |  |  |  |
| Emtricitabine (FTC) |  |  |  |  |  |  | X | X |  |
| Lamivudine (3TC) |  |  |  |  |  |  |  |  |  |
| Tenofovir (TFV) |  |  |  |  |  |  |  |  |  |
| Zidovudine (AZT, ZDV) |  |  |  | X |  | X |  |  |  |
| ***Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*** |
| Efavirenz (EFV) |  |  |  |  |  | X | X | X |  |
| Etravirine (ETV) |  |  |  |  |  | X |  |  |  |
| Nevirapine (NVP) |  |  |  |  |  |  | X | X |  |
| Rilpivirine (RPV) |  |  |  |  |  |  |  |  |  |
| ***Protease inhibitors (PIs)*** |
| Atazanavir (ATV) |  |  | X |  | X | X | X | X |  |
| Darunavir (DRV) |  |  | X |  | X |  |  | X |  |
| Lopinavir (LPV) |  |  | X |  | X | X |  | X |  |
| Ritonavir (RTV) |  | X | X |  | X | X | X | X |  |
| ***Integrase strand transfer inhibitors (INSTIs)*** |
| Bictegravir (BIC) |  | X |  |  |  |  |  |  |  |
| Dolutegravir (DTG) |  |  |  |  |  |  |  |  |  |
| Elvitegravir/cobicistat (EVG/COBI) |  | X |  |  | X | X |  |  |  |
| Raltegravir (RAL) |  |  |  |  |  |  |  |  |  |
| ***Fusion/entry inhibitors*** |
| Maraviroc (MVC) |  |  |  |  |  |  |  |  |  |

a ENT1/3, CNT1/3, OATP4A1, OCT3, OCTN1/2 are not represented in the table as ARVs are not substrates or inhibitors of these transporters. This table compiles data obtained from *in vitro* transport/inhibition studies using human isoforms [99, 100, 102, 149-170].

b Substrates are annotated by grey squares and inhibitors by a cross.

**Figure 1: Localization of uptake and efflux transporters in syncytiotrophoblasts. [90-95]** The direction of the drug transfer is indicated by the arrows.



### 4.2 Infant exposure to ARV *in utero*

Information on the comparative safety of specific ART regimens used during pregnancy is sparse and the labels for most individual and combination ARVs are rather cautious [171]. *In utero* exposure to PIs, for instance, has been associated with an increased risk for preterm birth (e.g. [172-174]), possibly due to immune reconstitution syndrome [175], and data from the PROMISE study [176] raised concerns about the combination of LPV/r with TDF-FTC also causing premature birth compared with ART with LPV/r and ZDV-3TC. Maternal TDF use in pregnancy, for example, seems to lower infant bone mineral content and bone mineral density [177]; even though this effect was not statistically significant it needs further investigation.

To date, Zash et al. provided the most comprehensive overview to date on adverse birth outcomes from a birth surveillance study of 47,027 pregnant women in Botswana [178]. Among the 10,592 HIV and ART exposed infants more than half had been ART exposed since conception. The most widely used ART in that cohort was EFV in combination with TDF and FTC. Historically, evidence for central nervous toxicity in animal models and single human subject cases reports initially lead regulators to add EFV on the “no-use” list for pregnancy in early 2000 and change in FDA rating from category C to category D in 2005 [179]. However, the drug had already been adopted for clinical use and was widely prescribed in resource-limited settings. A meta-analysis of observational cohort studies found no evidence of an increased risk of overall or central nervous system congenital anomalies associated with first-trimester exposure to EFV[180] , highlighting the challenges of extrapolating safety data from animal models into humans discussed below. A single, once daily, fixed dose combination (FDC) including EFV in combination with TDF/ FTC or TDF/3TC has since become the preferred WHO-recommended ART regimen used by most HIV-infected pregnant women worldwide [11, 15]. The review from the birth surveillance study extended prior findings on the safety of TDF/FTC/EFV started during pregnancy [178].

A systematic review confirmed that, compared to ZDV monotherapy, both NNRTI- and PI-based regimens had a consistent, harmful association with low birth weight, and that the harmful or protective effect of the ART depends also on the selection of the backbone, e.g. PI-based ART increases the risk for (very) preterm birth when paired with ZDV and 3TC, whereas EFV with TDF and FTC exhibits a protective effect against low birth weight [181]. The mechanism is not clear but immune reconstitution syndrome has been proposed as potential cause [171].

No research has been published on whether specific ARVs have the potential to interact for instance with fetal-maternal tolerance (protective immunity) of the placenta [182], placental blood flow, endothelial function or transporters responsible for the crossing of nutrients across the placental barrier to the fetus. Such interaction might impacton birth outcome such as small for gestational age and low birth weight. Furthermore, other complex systemic factors such as maternal immunologic, physiologic and hormonal changes associated with ART may also affect the fetal growth and maturation. Clearly, more research is required to evaluate potential mechanisms for the association between ART regimens and adverse birth outcomes.

Data from animal models, as illustrated by the EFV example above, are not always reliable, even though this is not a problem unique to ARVs. To satisfy regulatory requirements, developmental toxicity testing is typically conducted in two mammalian species, in rats and rabbits. But toxicokinetic differences and indirect maternal toxicity can lead to large inter-species differences [183] and the chosen animal species for testing might not always been the closest representation of the human system. Safety data from large birth surveillance studies such as the Botswana cohort and registries such as the Antiretroviral Pregnancy Registry [184]canprovide a crucial complimentary source of safety information, especially when it comes to detecting less common safety signals such as neural-tube defects (NTDs) recently reported with DTG exposure around the time of conception [185].

The development of birth defects depends on genetic and environmental factors, including exposure to drugs, and therefore their frequency depends greatly between populations. Acute maternal exposure to hazardous substances in the month before conception leads to the generation of new mutations during the formulation of the ovum cell and the first trimester of pregnancy, when organogenesis takes place, is the period of maximum risk to the developing fetus as exposure to hazardous chemicals can cause a variety of localized birth defects [186]. An important conclusion in the Botswana study was that infants exposed to ART from conception, irrespective of specific regimen, had worse birth outcomes than HIV-unexposed infants [178]. Similarly, a cohort study from Brazil found that first trimester *in utero* exposure to ARVs compared to exposure later in pregnancy was associated with lower weight-for-age z-scores at birth and lower length-for-age z-scores up to 2 years of life [187]. Several mechanisms were proposed to explain the reduced intrauterine and postnatal growth with early exposures such as reduced levels of insulin-like growth factor-1 or mitochondrial toxicity [187].

The potential effect of ART exposure during conception and early pregnancy on the pregnancy outcomes significantly complicates the development and implementation of global HIV treatment guidelines which are based on a public health approach. Treatment guidelines need not to account just for the risk-benefit ratio of ART exposure during the second and third trimesters of pregnancy, most relevant to the vertical transmission of HIV, but also for the risk-benefit ratio for ART exposure around conception and early pregnancy in women of reproductive age. Most recently, the current uncertainty about a potential for an increased risk of NTDs associated with DTG-exposure around conception in African women has slowed the highly anticipated global roll-out of DTG-based first-line ART and calls for the need for more robust pharmacovigilance systems to monitor safety of ART and other treatments in pregnancy, especially in resource limited settings. Evaluating birth outcomes in resource-limited settings, however, can be difficult for various reasons (e.g., birth at home or outside the public sector, lack of equipment and training on proper assessment and reporting), and birth surveillance studies, such as the one in Botswana, should be considered where feasible and could be potentially expanded to other therapeutic interventions commonly used during pregnancy, such as malaria and tuberculosis treatments.

Administering ART to a pregnant woman requires a delicate balancing act of treating and protecting the mother while preventing HIV and protecting the child [188]. However, it is important not to forget that HIV itself is a risk factor for adverse birth outcomes as noted by early systematic reviews [189] and confirmed by more recent data [190], and the benefits of ART during pregnancy for prevention of vertical HIV transmission remain unquestionable. Infants who were HIV exposed but not ART exposed in the Botswana study had the worst birth outcomes, even though baseline characteristics such as poorer access to healthcare of the mothers in general can be confounding factors. Ultimately, while we did not specifically analyse the pregnancy outcome data, the studies in this review with pregnancy outcome data available generally concluded that ARVs were safe and rates of adverse pregnancy outcomes were comparable to general populations. .

## 4.3 Transfer of ARVs into the breastmilk

The use of ART throughout breastfeeding aims to prevent perinatal transmission by supressing viral replication in mother and preventing passage of the HIV into the breastmilk. Thus, factors determining the transfer of ARVs into breastmilk and to the breastfed infant are important to understand their PD and to establish neonatal exposure safety profiles. The mammary gland comprises large interconnecting alveoli producing milk which is emptied into collecting ducts. The blood-milk barrier is constituted of a single layer of epithelial cells in the alveoli. Similarly to the placental transfer of drugs, passive diffusion of the ARVs in breastmilk depends on the physicochemical properties of the drug (see **Table 3**). Compared to plasma, the pH is slightly lower in the breastmilk (i.e. pH = 7.2) and the fat content is high resulting in weak bases to be trapped in milk and highly lipophilic drugs to be extensively partitioned into milk [191]. Another influencing factor relates to the presence of drug transporters in the mammary epithelial cells. Members of the OCT, OCTN, OATP, MRP, CNT, ENT, PEPT (peptide transporter) as well as P-gp and BCRP have been detected in human mammary cells [191, 192]. Among them, BCRP appears to play an important role in blood-to-milk drug transfer. BCRP localizes to the apical side of mammary epithelial cells indicating that the direction of transport is from the mammary epithelial cell to the milk. Of interest, the human mammary expression of BCRP was shown to be upregulated during lactation [193]. Thus, substrates of this transporter are actively transferred into the breastmilk thereby exposing breastfed infants to potentially harmful xenobiotics. This paradoxical finding from a toxicological standpoint led to the hypothesis that BCRP may also transfer nutrients critical for postnatal development of the infant [194]. Besides BCRP, other transporters including OCT1, OCTN1, CNT1, CNT3 and ENT3 were shown to be upregulated during lactation whereas OCTN2 and P-gp were shown to be downregulated [192]. The downregulation of P-gp during lactation may be an adaptive and protective response to reduce breastmilk levels of exogenous potentially toxic compounds. Of interest, ABC and SLC transporters have a temporal expression during lactation. Mdr1a, Mdr1b, Mrp1, Octn2, Ent2, Ent3 were shown to decrease throughout lactation in rat mammary glands while Octn1, Cnt2, Cnt3, Ent1, Pept1, Pept2 were shown to increase in early lactation [195]. Given the temporal change in transporter expression, the amount of drug substrates transferred in the breastmilk might vary throughout lactation; longitudinal assessment of lactating women at intervals postpartum to evaluate inter-individual change in transporter expression and correlation with PK parameters has not been undertaken. Furthermore, given their dual role in the transport of endogenous substances and drugs, transporters may influence not only their breastmilk concentrations, but become also a site for drug-drug interactions or drug-nutrient interactions. Importantly, some HIV PIs, and the NNRTIs EFV and ETV have been shown to inhibit BCRP, whereas NVP, RPV and the INSTIs DTG, RAL or BIC are not inhibitors, and NRTIs are only weak inhibitors of BCRP in the range of physiological concentrations [102, 166]. (**Table 4**) The physiological implication of BCRP inhibition by these ARVs is currently unknown however interactions with dietary components could theoretically occur and impact the supply of nutrients critical for the infant development.

It is worth emphasizing that the overall drug accumulation in the breastmilk and subsequent exposure to the breastfed infant is also dependent on maternal and infant factors. Maternal factors include maternal ARV dosing, drug PK and stage of lactation. Lower maternal dosing, drugs with shorter half-life or higher protein binding are likely to accumulate less in the milk, although exceptions occur. The stage of the lactation is also important as the protein content declines and the fat content increases with the transition from colostrum to mature milk shortly after birth. Infant factors important for drug exposure include suckling pattern (volume of milk consumed), frequency and timing relative to maternal concentrations [196].

## 4.4 Infant exposure to maternal ARVs through breastmilk

As detailed above, drugs administered to the mother can enter the breastmilk through both active transport mechanisms and by passive diffusion and therefore be ingested by the breastfeeding infant. The FDA has long recommended clinical lactation studies to be conducted pre-licensing or in the early phase after licensing in drugs that are anticipated to be widely used in women of childbearing age [197]. However, this has not been the case for women living with HIV and ARVs. Until very recent changes in guidance [16, 17, 137], women living with HIV in resource-rich settings, where newly licensed ARVs have been promptly deployed, have been universally advised to completely abstain from breastfeeding irrespective of whether virologically suppressed or not. In contrast, in low-resource settings, WHO guidance has been for exclusive breastfeeding, but until 2013 [11], ART recommendations were for short maternal ARV courses around the time of delivery, making it challenging to study the breastmilk transfer of ARVs when both mother and infant have reached steady state.

Many studies seek to estimate ARV exposure of the breastfed infant by conducting nested PK components within the large preventive trials which ultimately informed policy for lifelong ART for women diagnosed with HIV during pregnancy or postpartum. For this reason, questions surrounding changes in penetration of drug into breast milk at different stages of lactation from colostrum through to mature milk, and regarding infant factors which may influence PK, have not been rigorously evaluated.

A wide range of breastmilk penetration of each drug, expressed as the median milk to plasma (M:P) ratio, have been reported for several ARVs (**Table 3**). Studies which have explored the concentration of ARVs in both maternal blood and breastmilk at intervals throughout the dosing interval [137, 139, 141, 198] have indicated that the maximum concentration in breastmilk tends to occur an hour or two later than the maximum concentration in maternal blood. Furthermore, the clearance of drug from the breastmilk is often slower than from the maternal blood [137, 143]. Together, this means that for some drugs, particularly those with short plasma half-lives such as the NRTI, the total exposure as measured by AUC may be higher in the breastmilk as compared to maternal blood, but this difference may be missed if few time points are sampled. Whilst collection of paired blood and breastmilk samples is ideal to calculate M:P ratios [199], it is important to have prior knowledge of when the maximum concentrations are likely to be seen in order to choose the best sampling time points for a sparse strategy.

An example of the different results which may be obtained from sampling at different time points can be seen when contrasting the M:P ratios for FTC between a study which sampled pre-dose and at 1-2 hours post dose and obtained a time-averaged M:P ratio of between 0.63 and 2.1 [138] with a study that compared the ratio of AUC between 0 and 12 hours post-dose and obtained a median M:P ratio of 3.01[137]. The maximum FTC breastmilk concentration is reached at an average of 4 hours post-maternal dose, and therefore the maximum exposure to the breastfed infant will have been missed by the former study design. As a principle, when a drug has not been previously studied in breastfeeding mothers, it is ideal to generate intensive PK profiles in at least a small number of women (~5-10) in order to design sparse sampling strategies which can capture the most informative time points.

The exposure of the breastfed infant to maternal ARVs through the breastmilk is difficult to estimate precisely. It has proven impossible to determine with accuracy the exact volume of milk ingested by a breastfed infant, and therefore most authors have relied on the standard assumption that an infant ingests 150 mL/Kg of milk per day [43]. Furthermore, where PK sampling has been at a single time point, it can be difficult to calculate the total exposure of drug within the breastmilk; as explained in the case of FTC, it may be possible to significantly under or overestimate the overall exposure of drug over the full dosing interval if data are not available to compute the AUC. Notwithstanding these limitations, a 2015 meta-analysis of all existing data drawn from breastfeeding mother-infant pairs indicated that for most ARVs, the breastfed infant would be exposed to less than 10% of the weight-adjusted pediatric ARV dose which would be given to an infant of that weight should they require the drug for their own treatment. The exceptions were for NVP and 3TC, where ‘doses’ exceeding the 10% threshold may be delivered to the infant [137, 200]. Olagunju *et al.* considered the exposure of breastfed infants to EFV according to maternal CYP2B6 genotype, and demonstrated that a significantly ‘higher’ dose was delivered to the infants of mothers homozygous for loss-of-function alleles [198]. However, whilst an exposure index of no more than 10% of the weight-adjusted therapeutic pediatric dose has been proposed as a safety threshold for infant exposure to maternal drugs from breastmilk [201], this figure is somewhat arbitrary; it does not necessarily correlate with clinical significance. Initial reports of detectable concentrations of 3TC in the plasma of breastfed infants whose mothers were receiving this drug as part of combination ART suggested this was of unlikely clinical significance; however, further analysis of infants who became HIV-infected despite maternal ART in the Kisumu Breastfeeding and PEPI-Malawi [202] studies indicated high rates of NRTI mutants, likely emerging as a consequence of the selection pressure exerted by these low concentrations of drug. The concentration of drug measurable in infant plasma may not correlate with the ‘dose’ to which the infant is exposed through breastmilk. Furthermore, as illustrated by the case of DTG, a relatively low infant ‘dose’ via breastmilk may result in appreciable infant plasma concentrations where infant drug metabolising enzymes (in this example, UGT1A1) are immature [80]. Therefore, the individual PK and PD factors involved in the drug transfer from breastfeeding mother to infant, and the clinical significance thereof warrant further evaluation.

**6. DISCUSSION**

Pregnant women and breastfeeding women are generally excluded from drug development clinical trials for ethical and logistical reasons [188, 203]. The recent attention to safety concerns relating to DTG highlights the fact that clinical trials of this novel, effective and well tolerated ARV have in fact excluded pregnant women, and discontinued participation of women who inadvertently became pregnant during trials [188]. It is not uncommon to observe a lag time of several years between the initial ARV approval and the time when the first PK data during pregnancy become available. Thus, in absence of data on the PK of investigational agents during pregnancy, ARVs are typically prescribed off label and at the dose recommended for non-pregnant adults.

Available pharmacological data provide evidence that physiological and possibly drug transporter changes during pregnancy influence maternal and fetal ARV exposures. Specifically, it is PK changes during pregnancy that have limited the use for several ARVs, including three single tablet regimens with EVG/COBI (2) and DRV/COBI (1), and affected the dosing of several PIs in late pregnancy. Furthermore, limited available data suggest that expression of drug transporters may vary throughout pregnancy and breastfeeding thereby possibly impacting the amount of ARV crossing the placenta and secreted into the breastmilk. The drug transporter role in the fetal/child exposure to maternal ARVs is currently understudied and needs to be better understood.

Our analysis of PK data in pregnant women highlights the paucity of data and limited numbers of participants in published studies. The reported PK parameters have not always been standardized; comparisons across studies can be difficult for instance if AUC is not measured for the entire dosing interval, The data on free (unbound) drug concentrations during pregnancy and postpartum have not been systematically included, and this is particularly important for drugs highly bound to proteins to better evaluate the necessity to adjust dosage. The postpartum PK data in the analyzed studies were obtained during variable time windows ranging from 1-24 weeks after delivery, with the majority being conducted at ≤12 weeks postpartum. However, it has been demonstrated that the timing of the postpartum curve in PK studies in pregnancy is very important as pregnancy-related changes in PK require several weeks to be reverted [204]. In order to give a true reflection of the PK parameters in the non-pregnant state, the timing of the postpartum sample needs to be scheduled no earlier than 3 weeks postpartum. Equally, for the studies on the transplacental transport of ARVs, the timing between the last maternal dose and the blood collection at delivery is important whereas in existing studies this is frequently unknown or unreported. In *ex vivo* perfusion models it was shown that the timing of sampling for the paired maternal and cord blood matters as placental transfer is increased during maternal peak concentrations [24]. More information about the elapsed time interval would help to assess whether the findings from the perfusion models translate into humans, and if so to correct for changes in transfer rate when reporting C:M ratios. Future studies should prioritise the development of logistics to enable this data to be captured with greater precision.

The majority of studies on the penetration of maternal ARVs into breastmilk use single or very sparse sampling for the M:P ratio within a narrow period of time and, therefore, fail to evaluate the changes in the PK throughout different stages of lactation and child growth and development which may influence drug transport and child’s exposure. Multiple changes in maternal health such as use of oral and injectable contraceptives and other drugs, changes in nutritional status and co-morbidities could possibly also modify the PK and PD of ARVs during breastfeeding. Finally, the role of drug transporters in the transfer of ARVs into breastmilk is poorly understood and requires further investigation.

Collaborative networks combining the data and resources have proven an effective strategy for conducting clinical trials in pregnant and breastfeeding women. Two large maternal and maternal/pediatric HIV networks, namely European-based PANNA (<http://pannastudy.com/network>) and USA-based IMPAACT (<https://impaactnetwork.org/>), have been successfully working in generating quality ARV PK pregnancy data through multi-country collaborations using standardized multi-ARV protocols such as the IMPAACT1026s protocol. Additionally, given the physiological and social complexity of women during this phase of life, innovative methods should be considered to enable the best, most efficient study designs together with maximizing the interpretation of the resulting data. For example, optimized study design can be particularly informative for sparse PK sampling to be used in population PK analyses which explore the sources of variability in drug concentrations between women, together with investigation of the clinical relevance of such variability. Standardisation of PK data reporting and mechanisms for sharing complete data sets should maximise the use of sparse data across populations.

Physiologically based PK (PBPK) modelling, in particular, constitutes an attractive approach to simulate both the ARV PK during pregnancy and to predict drug exposure in breastmilk and breastfed infant. PBPK modelling allows to simulate the PK of drugs using *in vitro* data (e.g. physicochemical characteristics, intrinsic clearance, permeability) through a mathematical description of the absorption, distribution, metabolism and elimination (ADME) of a drug. This approach also integrates the mathematical description of physiological parameters reflecting a population of interest such as pregnancy in order to predict realistically drug PK in special populations. PBPK modeling has proved to be useful to quantify drug exposure changes during pregnancy for ARVs with renal elimination such as TFV, FTC and 3TC [205] and those metabolized in the liver such as DRV/r [206]. For example, DRV/r placental transfer data obtained from *ex-vivo* cotyledon perfusion model, were implemented in the latter PBPK model to simulate DRV/r fetal exposure at term. The simulations predicted DRV fetal plasma trough levels higher or around the half-maximal effective DRV concentration for a resistant strain of virus suggesting that oral maternal DRV/r dosing of 600/100 mg twice daily may provide benefits for the prevention of  *in utero* transmission of HIV [207]. These promising data suggest that PBPK may not only become a useful tool to quantify changes in the PK of drugs during pregnancy, but can also be used to simulate clinical trials *in silico* in order to optimize the design of PK studies in pregnant women including, for instance, dose selection. Furthermore, PBPK feto-maternal modelling has the potential to help define most appropriate dosing and target exposures for both pregnant women and their unborn children.

**7. CONCLUSIONS**

The majority of clinical trials of ARV in pregnant and breastfeeding women have been focused primarily on PD targets of preventing perinatal HIV transmission, with sparse data available on the PK of ARV during pregnancy and breastfeeding. Moreover, postmarketing surveillance for the use of ARTs during the childbearing period remains critically underdeveloped. Our analysis of ARV studies in pregnancy and postpartum summarized the available PK data on ARVs during pregnancy and breastfeeding and identified knowledge gaps to be addressed. There is currently an unmet need for a stronger research agenda advocating for pharmacological studies in pregnant and breastfeeding women living with HIV to optimize mother/child pair health outcomes. While acknowledging the need for careful consideration of ethical considerations, benefits and risks, logistical facilitators and limitations, shift needs to happen from exclusion of pregnant and breastfeeding women living with HIV into clinical trials including PK studies [188, 203, 208, 209].

As the Best Pharmaceuticals for Children Act (BPCA) has advanced the research in the relevant therapeutic areas for infants and children, the introduction of similar regulatory requirements such as, for example, the *“Best Pharmaceuticals for Pregnant and Breastfeeding Women Act”* (<https://bpca.nichd.nih.gov/about/Pages/default.aspx>) could play catalytic role in encouraging the pharmaceutical industry to perform pregnancy and breastfeeding studies, improve labeling for drug products used in women, prioritize therapeutic areas such as HIV and sponsor clinical trials and other research about on- and off-patent drug products in pregnant and breastfeeding women, including women living with HIV. Finally, advancing the ARV pharmacology research agenda in pregnancy and breastfeeding is not possible without meaningful involvement of women living with HIV, their advocacy and support.

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