Pharmacokinetics and therapeutic drug monitoring of antiretrovirals in pregnant women

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Highly active antiretroviral therapy is recommended for HIV-infected pregnant women to prevent mother-to-child transmission. The specific physiological background induced by pregnancy leads to significant changes in maternal pharmacokinetics, suggesting potential variability in plasma concentrations of antiretrovirals during gestation. Therapeutic drug monitoring (TDM) of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) is recommended in certain situations, including pregnancy, but its systematic use in HIV-infected pregnant women remains controversial. This review provides an update of the pharmacokinetic data available for PIs and NNRTIs in pregnant women and highlights the clinical interest of systematic TDM of certain antiretroviral drugs during pregnancy, including nevirapine, nelfinavir, saquinavir, indinavir and lopinavir.

Introduction

Mother-to-child transmission (MTCT) is the primary cause of HIV infection in children. According to the World Health Organization, about 2.3 million children are HIV-infected and 530 000 new infections were recorded in 2006. Of these, <1000 concerned North America and Europe together [1]. In the absence of antiretroviral therapy, the prevalence of MTCT is 20–50%, depending on the clinical status of the mother, and occurs during pregnancy or delivery, 33 and 66%, respectively [2]. Breast-feeding is also responsible for MTCT. Since the mid 1990s, highly active antiretroviral therapy (HAART) in pregnant women has helped to reduce MTCT drastically in high-income countries [3–5], whereas it remains dramatically high in resource-limited settings [6].

Since a low HIV viral load in pregnant women is a powerful predictive factor of low MTCT [7–10], the main goal of HAART during pregnancy is to maintain undetectable levels of HIV RNA in order to prevent MTCT. HAART usually associates two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI), or two NRTIs and one non-nucleoside reverse transcriptase inhibitor (NNRTI) [11–13].

Therapeutic drug monitoring (TDM) of NNRTIs and PIs is justified by the wide interindividual variability of their

plasma concentrations and the relationship observed between treatment efficacy or toxicity and plasma concentrations [14, 15]. Although its main limiting factor is the lack of studies demonstrating improvement in clinical outcomes, TDM may be useful in various recommended situations [16] such as treatment initiation, suspicion of poor compliance, clinically relevant drug–drug interactions, prevention of toxicity or dose-regimen changes [13, 17].

Pregnancy could be considered one of these situations, as it involves a specific physiological background with significant changes in maternal pharmacokinetics. Indeed, the increased progesterone level tends to affect absorption by reducing gastric emptying and small intestine motility. Drug absorption may be impaired by the higher gastric pH and the frequent nausea that occurs during pregnancy. Distribution is modified by elevated body water and fat, which increase the volume of distribution of both hydrophilic and lipophilic drugs, respectively. Plasma albumin and α -acid glycoprotein concentrations are also decreased during pregnancy (partly due to haemodilution), thus potentially affecting protein binding. However, the clinical consequence of the higher free drug fraction, which is the active form, remains to be determined. Indeed, a reduced protein-bound drug fraction may be compensated by increased distribution, metabolism and excretion

[18]. Pregnancy also affects drug metabolism. In particular, the expression of cytochrome P-450 (CYP) isoforms is highly variable during gestation [19], with potential consequences for the metabolism of many drugs, including NNRTIs and PIs. Finally, increased renal blood flow may enhance the clearance of some renally excreted drugs such as most of the NRTIs [20].

All these elements suggest significant variations of antiretroviral pharmacokinetics during pregnancy. This has been confirmed by numerous studies, previously reviewed [21, 22]. These data raise the question of systematic TDM in pregnant women. In the latest guidelines, the need for TDM during gestation is mentioned but not clearly defined [13, 17]. Here, we present an update of pharmacokinetic data to clarify the discussion of the clinical relevance of TDM of PIs and NNRTIs during pregnancy.

Pharmacokinetics of antiretrovirals during pregnancy

Among the antiretroviral drugs currently available, TDM is routinely recommended for NNRTIs and PIs, but not for NRTIs. Indeed, NRTIs require intracellular phosphorylation to become active, and their plasma concentrations are therefore poorly correlated to therapeutic response. Nevertheless, changes may occur in NRTI pharmacokinetics during pregnancy, as reviewed previously [21, 22]. Zidovudine is recommended to prevent MTCT, and its area under the curve (AUC) has been shown to be decreased during pregnancy [23, 24]. However, correlation between the plasma and the intracellular concentrations is difficult to demonstrate [21]. More recent data showed that pregnancy does not affect abacavir exposure [25]. Tenofovir AUC, minimal ($C_{\min}$) and maximal ($C_{\max}$) concentrations were decreased during the third trimester compared with post partum [26]. Emtricitabine exposure is only slightly decreased during pregnancy, and dose adjustments may not be necessary [27, 28]. Although there is scant data concerning enfuvirtide pharmacokinetics in pregnant woman, in an *ex vivo* model it does not seem to cross the placental barrier [29, 30]. In this review we will focus on the clinical relevance of TDM during pregnancy, and will therefore detail the pharmacokinetic data of NNRTIs and PIs in pregnant women.

Non-nucleoside reverse transcriptase inhibitors

The pharmacokinetics of NNRTIs is characterized by a long elimination half-life and CYP 2B6 and CYP 3A4 induction [31]. Their plasma concentrations are highly variable among patients, justifying TDM [14].

Efavirenz The use of efavirenz (EFV) during pregnancy has revealed malformations in animals. Cases of neural tube defects and other birth defects have been reported in humans [32, 33]. Thus, EFV belongs to the Food and Drug Administration (FDA) pregnancy class D, and its use during

pregnancy is not recommended [13, 34]. Consequently, there is no pharmacokinetic study of EFV in pregnant women.

Nevirapine In contrast to efavirenz, nevirapine (NVP) is extensively used in HIV-infected pregnant women. It is available as 200-mg tablets, and the recommended $C_{\min}$ is 4000–8000 ng ml⁻¹ [13]. NVP therapy is recommended in pregnancy provided it was well-tolerated before pregnancy. However, as for all patients, NVP initiation should be avoided in pregnant women with high CD4 counts, due to its potential to induce hepatotoxicity [13, 34]. Indeed, continuous NVP treatment could expose women to serious adverse events when started during pregnancy [35]. Single-dose NVP regimens are widely used to prevent MTCT, especially in resource-poor countries. Short exposure to NVP is well tolerated during pregnancy [36], but it can also increase drug resistance for both mothers and infants [37]. This leads to high virological failure of NVP-based treatment started in the 6 months following birth [38]. It is classified as FDA pregnancy category C [34].

Some studies have assessed NVP pharmacokinetics in pregnant women. The Pediatric AIDS Clinical Trials Group (PACTG) protocol 250, performed after a single-dose of NVP just before labour in 17 pregnant women, showed an increased volume of distribution and a decreased $C_{\max}$ at delivery (1663 ng ml⁻¹ after a 200-mg single dose vs. ~2000 ng ml⁻¹ in nonpregnant adults). Clearance was also increased in peripartum women compared with nonpregnant adults (29.32 ml kg⁻¹ h⁻¹ vs. an average of 22.5 ml kg⁻¹ h⁻¹, respectively) [39]. In contrast, the results of the HIVNET 006 study did not reveal altered pharmacokinetic parameters after a 200-mg dose of NVP (median $C_{\max}$ and clearance were 2032 ng ml⁻¹ and 20.36 ml kg⁻¹ h⁻¹, respectively) [40]. These discrepancies may be due to the high interindividual variability of NVP pharmacokinetic parameters and the small study sizes (18 and 21 women included, respectively). During late pregnancy, single-dose NVP had a very similar pharmacokinetic profile to that in nonpregnant adults, suggesting the influence of delivery but not late pregnancy on the single-dose NVP pharmacokinetic profile [41].

In the PACTG 1022 trial, continuous NVP pharmacokinetics (200 mg once daily for 14 days, then 200 mg twice daily) was assessed in 12 HIV-infected pregnant women (second or third trimester of gestation). Mean AUC_{0–12} and $C_{\max}$ appeared to be similar in pregnant women and in nonpregnant adults [42]. However, a recent study has shown significantly lower AUC_{0–12} and $C_{\max}$ in pregnant women compared with nonpregnant women (44 579 ng h⁻¹ ml⁻¹ and 4505 ng ml⁻¹ vs. 57 045 ng h⁻¹ ml⁻¹ and 5871 ng ml⁻¹, respectively). Moreover, NVP clearance was increased and $C_{\min}$ tended to be lower (although not significantly so) in pregnant women than in nonpregnant women [43] and below the recommended target $C_{\min}$ of 4000 ng ml⁻¹ [13, 44].

The predictive value of NVP plasma concentration on virological outcome is not fully established [45]. In these studies, the variations in NVP pharmacokinetics do not seem to alter clinical efficacy. However, von Hentig *et al.* [43] have highlighted the risk of a sub-inhibitory NVP plasma exposure associated with a subsequent risk of viral resistance during pregnancy. Indeed, 25% of pregnant women had low steady-state $C_{\min}$ (between 1250 and 2345 ng ml⁻¹) in their cohort. Similar results were found by Gingelmaier *et al.*, with mean NVP $C_{\min}$ of 2600 ng ml⁻¹ in 10 women at delivery. However, the only virological failure reported was due to poor compliance, and no MTCT was observed [46].

The conflicting results regarding NVP plasma concentration changes during pregnancy might be due to the small population samples evaluated and high interindividual variability. Therefore, systematic TDM of NVP during late pregnancy should be considered in patients treated for several weeks to enable dose adjustment to be performed when necessary.

Other NNRTIs No adequate and well-controlled studies of the recently released NNRTI etravirine have been conducted in pregnant women. In addition, no pharmacokinetic studies have been conducted in such patients [47]. To our knowledge, there are no data about the rilpivirine. Therefore, at present, these agents cannot be recommended during pregnancy.

Protease inhibitors

Current guidelines recommend NRTI and PI-based antiretroviral therapy, when available, as first-line treatment during pregnancy [12, 13], as PIs present few adverse events during pregnancy. However, some studies have suggested a higher risk of premature delivery when mothers were receiving PIs [48, 49]. Although a larger study did not confirm these observations [50], the association between PIs during pregnancy and premature delivery or low birth weight remains unclear [4, 51, 52]. A recent meta-analysis revealed a trend towards an increased risk of prematurity with PI-containing regimens (odds ratio 1.24), but not statistically significant [53]. Other works have suggested an increased risk of glucose intolerance or insulin resistance among HIV-infected pregnant women treated with PIs [54], but this is also debated [55, 56]. Overall, PIs are well tolerated by infants, probably because of the limited transplacental passage [57].

Nelfinavir In nonpregnant adults, nelfinavir (NFV) has highly variable bioavailability (80% with food) and elevated protein binding (>98%). It was available as 250-mg and 625-mg tablets, and the recommended $C_{\min}$ is 1000–4000 ng ml⁻¹ [13]. However, NFV marketing has been suspended since July 2007 due to ethyl mesilate contamination. NFV is metabolized by cytochrome P450 2C19 (CYP2C19) to the active metabolite M8. Both M8 and NFV

are eliminated through cytochrome P450 3A4 (CYP3A4). Elimination $t_{1/2}$ is 3–5 h [58]. NFV has been widely used during pregnancy and is well tolerated [57], thus it has a role in the management of pregnant patients with HIV infection [59]. NFV is classified as FDA pregnancy category B [34].

The PACTG 353 study compared two NFV regimens during pregnancy and post partum: 750 mg t.i.d. (cohort 1) and 1250 mg b.i.d. (cohort 2). In these small samples, cohort 2 showed a better exposure to NFV, as 16/21 women (76%) met the target AUC (10 µg h⁻¹ ml⁻¹) during gestation, than cohort 1, in which only 3/9 (33%) did. Six weeks after delivery, AUC_{0–12} increased by 35% in cohort 2, but AUC_{0–8} remained unchanged in cohort 1 [60, 61]. Similarly, two case reports have shown significantly decreased AUC_{0–12}, $C_{\min}$ and $t_{1/2}$ associated with virological breakthroughs with NFV 1250 mg b.i.d. during late pregnancy [62, 63]. These results have been confirmed by other pharmacokinetic studies. With the same dose regimen, Villani *et al.* found significantly lower median AUC_{0–12}, $C_{\min}$ and elimination $t_{1/2}$ in third-trimester pregnant women than in matched nonpregnant women (25.76 vs. 32.49 µg h⁻¹ ml⁻¹, 0.8 vs. 1.8 µg ml⁻¹ and 3.7 vs. 5.2 h, respectively) [64]. In a prospective study, NFV plasma clearance was increased by 33% during pregnancy (49.6 vs. 37.3 l h⁻¹ ante and post partum, respectively). NFV AUC_{0–12}, $C_{\max}$ (both not significant) and C_{12} (0.54 vs. 1.40 µg ml⁻¹; $P=0.04$) were lower during pregnancy. The patient with the lowest C_{12} during pregnancy showed a virological breakthrough (1316 HIV-1 RNA copies ml⁻¹), whereas her viral load was undetectable at inclusion and returned to 119 copies ml⁻¹ after delivery [65]. This is consistent with another study showing NFV $C_{\min}$ during pregnancy below the recommended level of 1 µg ml⁻¹ in 45% of the women. Although not significant, there was a trend towards a lower decline in viral load in patients with low NFV $C_{\min}$ [66]. A retrospective study has given similar conclusions comparing NFV concentration ratios (CR) between 27 pregnant and 48 time-matched nonpregnant women. After adjusting potentially confounding factors, mean CR was 34% lower during pregnancy. This decrease was more pronounced in the third trimester. However, none of the children was infected and all but one woman with low CR (<90) had an undetectable viral load at delivery [67]. However, undetectable viral load at delivery was not always correlated with NFV exposure during pregnancy [68], which is contradictory to previous findings in nonpregnant adults [69]. In contrast, similar exposure to NFV ante compared with post partum has been shown by another group [70].

All these studies concern small study populations, which could explain the high variability in the pharmacokinetic parameters and the poor correlation between pharmacokinetic and virological data. A NFV population pharmacokinetic study has been recently completed describing NFV and M8 concentrations in pregnant (second or third trimester and day of delivery) and nonpregnant women. According to this model, NFV plasma

clearance was increased by 25% during pregnancy [71], confirming previous results by van Heeswijk [65]. The mean C_{min} obtained with Bayesian estimates in pregnant women was lower than in nonpregnant women (1.5 vs. 2.5 mg l⁻¹, respectively), but above the concentration target of 1 mg l⁻¹. However, it was only 0.6 mg l⁻¹ on the day of delivery. These findings suggest that the dosage does not have to be changed during pregnancy, but should be doubled on the day of delivery. As previously shown in nonpregnant adults [72], the drug regimen (b.i.d. or t.i.d.) did not influence the effect of pregnancy on NFV clearance [71]. The discordant results raised by Bryson *et al.* concerning the 750-mg t.i.d. regimen are probably due to the small size of the study population [60]. Of interest, decreased exposure to NFV during third trimester compared with post partum has also been shown with the new 625-mg tablet formulation [73].

Concentrations of M8 may also be affected during pregnancy, as AUC_{0-12} , C_{max} and C_{12} were about threefold lower ante than post partum [65]. M8 elimination was further increased by concomitant administration of NNRTIs [71].

In conclusion, NFV clearance is significantly increased during late pregnancy. Some groups have reported virological breakthroughs or suboptimal C_{min} during pregnancy. However, the clinical impact of pregnancy-induced NFV sub-exposure remains unclear. In a recent study, genotypic resistance tests were performed in 19 pregnant women exposed to NFV for prevention of MTCT who discontinued NFV at labour. The tests were performed before or during NFV therapy and after discontinuation. All infants were uninfected in spite of poor virological suppression, but five women showed new NFV-associated mutations after discontinuation [74]. This may be due to low NFV exposure during late pregnancy, but the lack of pharmacokinetic data makes the interpretation of these results difficult.

There is a clear decrease in NFV exposure in pregnant women, especially during the third trimester of gestation. The high interindividual variability and the risk of HIV mutations may justify TDM to indicate dosage adjustment when needed.

Saquinavir Saquinavir (SQV) is a lipophilic PI with low bioavailability and high protein binding (approximately 98%), mostly metabolized by CYP3A4. It is available as 200-mg hard-gelatine capsules (SQV-HGC) and 500-mg tablets [75]. The soft-gelatine capsule formulation was discontinued a few years ago (SQV-SGC) [76]. SQV recommended C_{min} is 200–4000 ng ml⁻¹ [13]. SQV is classified as FDA pregnancy category B [34].

Available data describe subtherapeutic exposure to SQV-SGC (1200 mg t.i.d.) during pregnancy [77], although no virological breakthrough or MTCT have been reported [78]. These small study populations, however, did not permit an estimate to be made of the clinical conse-

quences of such a low SQV plasma exposure. Furthermore, SQV-SGC is no longer used.

SQV is now commonly used in combination with low-dose ritonavir (r) as a booster. In 13 women receiving SQV-HGC/r 800/100 mg b.i.d. the mean AUC_{0-12} during pregnancy, labour and delivery and post partum were not significantly different (29.3, 26.2 and 35.4 µg h⁻¹ ml⁻¹, respectively). The C_{min} were also comparable between the three evaluation periods and always above 0.2 µg ml⁻¹ [79]. In the same way, 10 of 11 pregnant women taking SQV-HGC/r 1000/100 mg b.i.d. reached the 100 ng ml⁻¹ target C_{min} (between 96 and 2238 ng ml⁻¹) with no MTCT [80]. Similar conclusions have been drawn with the newer 500-mg tablet formulation [81, 82].

Another study assessed the efficacy and tolerability of SQV/r (1200/100 mg) once daily with a TDM strategy during pregnancy. Pharmacokinetic data showed that 43 of 46 (93%) pregnant women reached target C_{min} (100 ng ml⁻¹) despite a median C_{min} about three-times lower in all trimesters of gestation. The 24-h pharmacokinetic profile obtained for seven patients showed significantly reduced AUC_{0-24} , C_{max} and C_{min} in pregnant compared with nonpregnant women receiving the same dosage, but above the target thresholds [83]. The authors suggest that once-daily SQV/r would be an appropriate option for PI-naïve or limited PI-experienced pregnant women, but that TDM is advisable.

The use of SQV/r during pregnancy is effective and safe [84]. These data suggest that all the SQV/r regimens studied in pregnant women provide exposure above the target AUC_{0-24} , an $AUC_{0-24} > 10\,000$ ng h⁻¹ ml⁻¹ providing adequate virological response [85]. However, SQV plasma concentrations are lowered during pregnancy, and there is high interindividual variability (coefficients of variation for C_{min} , when available, range from 0.43 [81] to 1.13 [79]). Therefore, TDM of SQV/r should be considered during pregnancy. Nonboosted SQV should be avoided in pregnant women due to low plasma concentrations.

Lopinavir Lopinavir (LPV) is a widely-used PI available in combination with low-dose ritonavir. LPV/r capsules (133.3/33.3 mg) have recently been replaced by tablets (200/50 mg). The tablet formulation does not require refrigeration. It is not influenced by food intake and exhibits less interindividual variability [86]. It provides similar bioavailability to the capsule formulation [86]. In nonpregnant HIV-infected adults, LPV absorption is highly influenced by food intake. It is approximately 98–99% bound to plasma proteins. LPV is metabolized by CYP3A isoenzymes that are inhibited by low-dose ritonavir, in order to increase LPV exposure [87]. The recommended C_{min} for LPV is 3000–8000 ng ml⁻¹ [13]. LPV/r has recently been considered as a recommended PI during pregnancy [34]. It is classified as FDA pregnancy category B [34].

A pharmacokinetic study in 17 pregnant women receiving LPV/r capsules 400/100 mg b.i.d. has shown a

significantly decreased AUC_{0-12} during the third trimester of pregnancy compared with post partum (44.4 vs. 65.2 $\mu\text{g h}^{-1} \text{ml}^{-1}$, respectively). Only 18% of pregnant patients reached target AUC_{0-12} (as determined by the estimated 10th percentile AUC_{0-12} in nonpregnant adults), whereas 75% met the target post partum. None of the pregnant women reached the 50th percentile of AUC_{0-12} in nonpregnant adults (whereas 42% did post partum). In all but two patients LPV exposure increased from ante to post partum. C_{max} and C_{12} were also significantly decreased during pregnancy. The geometric mean ritonavir AUC was slightly lower during pregnancy, but not significantly. The authors reported one virological breakthrough in late pregnancy, whereas viral load remained undetectable until 35 weeks of gestation [88]. The same group showed that a LPV/r 533/133-mg b.i.d. regimen during the third trimester provided adequate LPV exposure (mean AUC_{0-12} was 85 $\mu\text{g h}^{-1} \text{ml}^{-1}$). These results suggest the need for a higher dose during late pregnancy. By 2 weeks post partum, standard doses were again appropriate [89].

However, many recent communications have presented different conclusions. In a population of 26 HIV-infected pregnant women, Lyons *et al.* found plasma LPV C_{12} close to that described in nonpregnant adults and above the target concentration (median C_{min} was 3660 ng ml^{-1} , range 250–9970) [90]. TDM was performed in two other observational studies of 16 and 21 pregnant women, respectively, receiving LPV/r (soft capsules) at different dosages. They showed highly variable C_{min} during pregnancy, from <30 to 9300 ng ml^{-1} [91] and from <250 to 17 486 ng ml^{-1} [92]. In one of these studies TDM also allowed dose adjustments to be made for three patients (from 266/66 to 400/100, from 400/100 to 400/200 and from 400/100 to 533/133 mg) [91]. Likewise, Khuong-Josses *et al.* have reported adequate plasma concentrations in 33 of 36 pregnant women receiving LPV/r 400/100 mg b.i.d. (mean LPV C_{min} were 6.13 and 5.10 mg l^{-1} in the second and the third trimester, respectively) [93]. Manavi *et al.*, however, showed low LPV trough concentrations in a population of 26 pregnant women treated with LPV/r (median C_{min} was 2964 ng ml^{-1}) [94]. In both reports, no correlation was found between C_{min} and reduction in plasma viral load.

Aweeka *et al.* compared LPV/r AUC_{0-6} (soft capsules) at 36 weeks of gestation and 6 weeks after delivery in 10 pregnant women. The geometric mean AUC_{0-6} were 26.5 and 41.9 $\mu\text{g h}^{-1} \text{ml}^{-1}$ ante and post partum, respectively. Although not statistically significant, they showed a trend towards decreased LPV exposure [within-subject geometric mean ratio (GMR) was 0.6] [70]. The largest cohort to date included 101 pregnant women (second and third trimester of pregnancy) receiving LPV/r 400/100 mg b.i.d. LPV C_{min} were 3806 and 3274 ng ml^{-1} at second and third trimester, respectively, and were significantly correlated to viral load at delivery. Among the subjects with undetectable viral load, C_{min} was statistically higher in matched nonpregnant adults than in pregnant women [95].

The use of LPV/r in pregnant women is effective and safe [90, 93, 96]. Some reports have shown reduced exposure to LPV during gestation compared with post partum or with nonpregnant adults. This decrease seems more pronounced in the third trimester of gestation. However, other groups have shown similar LPV trough plasma concentrations in pregnant women and in nonpregnant adults. This discrepancy suggests high variability between the populations of all the studies mentioned here. Moreover, the clinical significance of a reduced C_{min} during pregnancy remains unclear, as the correlation between C_{min} and reduction in plasma viral load is not obvious, contrary to the results observed in nonpregnant PI-experienced populations [97, 98]. In a recent LPV pharmacokinetic study, a 600/150-mg b.i.d. regimen during late pregnancy increased the probability of reaching the target C_{min} of PI-experienced patients (5.7 mg l^{-1}) from 21.1 to 55.3%, compared with a 400/100-mg b.i.d. regimen [99]. Considering these results, it may be wise to perform TDM and adjust the LPV/r dose when necessary. A 533/133-mg b.i.d. regimen (soft capsules) provided adequate LPV exposure during the third trimester of pregnancy [89]. This was confirmed with the new LPV/r tablet formulation, with a 600/150-mg b.i.d. regimen, which provided adequate LPV levels during the third trimester of pregnancy [28]. Finally, the lower interindividual variability found with the tablet formulation has been confirmed in pregnant women [100].

Indinavir Indinavir (IDV) is an old PI, seldom prescribed today. Among PIs, IDV has the lowest plasma protein binding (60%), which may result in more substantial penetration into cerebrospinal and seminal fluids [101]. IDV is metabolized by CYP3A. It is licensed as 100-, 200- and 400-mg capsules, and the recommended C_{min} is 150–800 ng ml^{-1} [13]. IDV belongs to FDA pregnancy category C [34].

Few studies have investigated IDV pharmacokinetics during pregnancy. Nevertheless, a complete pharmacokinetic profile of IDV (800 mg t.i.d.) was recently performed in 11 women during pregnancy (third trimester) and 6 weeks after delivery [102]. It showed drastic decreases in AUC_{0-8} and C_{min} during pregnancy and three- to fourfold increased clearance. The pharmacokinetic parameters evaluated post partum were comparable to those in nonpregnant women. Two women did not achieve viral suppression at delivery, suggesting potential sub-inhibitory exposure during gestation [102]. These data confirmed the first case reports of HIV-infected pregnant women that showed a marked increase in IDV plasma clearance and decreased AUC_{0-8} (by 63 and 86%), C_{min} and C_{max} ante compared with post partum. One woman had a slightly increased HIV viral load in late pregnancy that returned to the initial value after delivery, without any dose adjustment [103].

Different results were found when IDV was combined with low-dose ritonavir during pregnancy. Indeed, the

IDV/r 800/200-mg b.i.d. regimen provided adequate IDV AUC_{0-12} in two women [68]. Similarly, another study enrolling 32 pregnant women has shown good efficacy and adequate trough concentrations in 28 women receiving an IDV/r 400/100-mg b.i.d. regimen (median C_{min} was 208 ng ml⁻¹). All viral loads >400 copies ml⁻¹ at delivery were related to poor compliance. None of the infants was infected using HIV RNA and DNA polymerase chain reaction measurements [104].

Overall, these results show variable changes of IDV plasma concentration in pregnant women, highly dependent on the adjunction of low-dose ritonavir as a booster. Indeed, exposure to IDV when used alone appears to be substantially lowered in late pregnancy, whereas exposure does not seem to be altered when boosted by ritonavir, suggesting compensatory inhibition of hepatic metabolism by ritonavir. However, the data are too limited to assert that TDM of IDV/r is unjustified.

Atazanavir Atazanavir (ATV) absorption is fast and highly dependent on gastric pH. It is 86% bound to serum proteins and extensively metabolized by CYP3A isoenzymes [105]. It is licensed as 150- and 200-mg capsules, and the recommended C_{min} is 200–1000 ng ml⁻¹ [13]. Few data are available on ATV use in pregnancy. It is classified as FDA pregnancy category B [34].

The first case report of ATV use in an HIV-infected pregnant woman showed adequate plasma concentrations. The authors reported mild hyperbilirubinaemia in the baby, who was clinically well [106]. The good efficacy and tolerability of ATV during pregnancy has been confirmed by a retrospective analysis of nine cases [107] and by the largest case series to date, which showed adequate plasma levels for all 19 women for whom TDM was practised during pregnancy [108].

The first pharmacokinetic study of ATV/r (300/100 mg day⁻¹) use in pregnancy ($n = 17$) showed similar values of the geometric mean AUC ante and post partum (28.5 vs. 30.5 $\mu\text{g h}^{-1} \text{ml}^{-1}$, respectively). ATV C_{min} did not differ, either (486 ante vs. 514 ng ml⁻¹ post partum) [109]. More recent data with the same regimen in 12 pregnant women (third trimester) showed comparable geometric mean AUC (26.6 $\mu\text{g h}^{-1} \text{ml}^{-1}$; % coefficient of variation 43) and C_{min} over the target of 150 ng ml⁻¹ for all women. However, the authors report that ATV AUC and C_{min} were approximately 40 and 21% lower, respectively, than historical data in HIV+ subjects [110]. This should be confirmed in further investigations.

When associated with acid suppressive therapy, the bioavailability of ATV can be reduced [105]. This could be a concern in pregnant women, as gestation leads to increased gastric pH [20]. However, all the women but two enrolled in these studies received ATV/r. When boosted with low-dose ritonavir, ATV absorption does not seem to be altered by antiacid therapy [111], which may explain

the adequate pharmacokinetic profile of ATV/r during pregnancy.

Other PIs Ritonavir (RTV) is a powerful CYP3A inhibitor used mostly in combination with other PIs as a low-dose booster. It belongs to FDA pregnancy category B [34]. In a small study, full-dose RTV exposure was decreased during pregnancy compared with post partum [112]. Due to limited experience in pregnant women and severe adverse effects, full-dose RTV is not recommended during pregnancy [34].

Finally, there are no pharmacokinetic data available for amprenavir/fosamprenavir, tipranavir or darunavir in pregnant woman. At present they cannot be recommended during pregnancy [34].

Do antiretrovirals need to be monitored during pregnancy?

The role of CYP3A4 on antiretroviral pharmacokinetics during pregnancy

Pharmacokinetic data have revealed low exposure to certain antiretrovirals (ARVs) during pregnancy, especially during the third trimester. It is of note that when associated with low-dose RTV, PI pharmacokinetics are usually not or only moderately affected by pregnancy, whereas most of the time, major changes are observed in non-enhanced PI pharmacokinetics (Table 1). However, Acosta *et al.* have shown increased RTV (used as a booster) mean AUC_{0-12} , C_{max} and C_{min} in post-partum compared with ante-partum values (GMRs were 1.57, 1.69 and 1.77, respectively), whereas SQV plasma concentrations were stable [79]. Burger *et al.* found similar values of RTV mean AUC_{12} , C_{max} and C_{min} during late pregnancy [81]. When combined with LPV, RTV exposure was also significantly lower during pregnancy compared with post partum (within-subject GMR for AUC was 0.36) [70]. Stek *et al.* showed significantly lowered RTV C_{min} (GMR = 0.62) and a trend to lower AUC during pregnancy (GMR = 0.84, not statistically significant) [88]. As RTV is a powerful CYP3A inhibitor, this supports the implication of cytochrome induction during gestation. Indeed, cytochrome P450 (CYP) activity is subject to major changes during pregnancy [18, 19], in particular through the potential induction of CYP3A isoenzymes, which are highly involved in PI metabolism.

CYP3A activity, assessed with 6 β -hydroxy-cortisol:cortisol ratios, has been studied in pregnant women receiving IDV or NFV. In this study, although the data are not conclusive for NFV due to conflicting pharmacokinetic results, available post-partum ratios ($n = 2$) suggest enzyme induction during late pregnancy [68].

Lower M8/NFV ratio is also consistent with increased CYP3A activity [65, 71, 113]. Indeed, NFV is mostly metabolized into the active derivate M8 by CYP2C19, which seems to be inhibited during pregnancy [114]. On the other hand,

Table 1

Summarized pharmacokinetic data of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) in pregnant women, related clinical events and TDM recommendations

Drug	FDA cat.* [34]	Recommendation for use in pregnancy [34]	Pharmacokinetic data (AUC, C _{min} , C _{max})	Related clinical events	TDM recommendations
NNRTIs					
Nevirapine Single-dose (200 mg)	C	Recommended	Conflicting results§ [39–41] and high interindividual variability. Median AUC (range) from 90.8 (36.2–119), n = 6 [39] to 163.3 (43.8–268.3), n = 20 [40]		TDM is not justified
Continuous 200 mg b.i.d.			Conflicting results [42, 43, 46] and high interindividual variability. Mean AUC† (± SD) comparable: 65.5 (± 17.9) vs. 71.6 (± 28.3), n = 5 [42], or significantly decreased: AUC (95% CI) 44.6 (36.6, 52.6), n = 16, vs. 57.1 (46, 68.1)‡, n = 13 [43]		Systematic TDM should be considered during late pregnancy
Efavirenz	D	Not recommended	No data are available		Insufficient data
Etravirine	B	Insufficient data	No data are available		Insufficient data
PIs					
Nelfinavir 1250 mg b.i.d.	B	Recommended	250-mg tablets: Decreased AUC [60–65, 71], CR‡ [67] and C _{min} [64, 66] Median AUC: 25.7 vs. 32.5‡ [64], 28.3 vs. 43.3† [113], 25.2 vs. 33.5† [65] Target C _{min} not reached in 45% pregnant women [66]; median (range) C _{min} : 0.8 (0–2.6) vs. 1.5 (0.5–4.9)‡ [64] Decreased M8†§ [65, 66, 71] 625-mg tablets: Decreased median (range) AUC: 18.7 (3.6–53.7) vs. 30.8 (18.5–52.6)† [73] Conflicting results†‡§ [60, 61, 71]	4 virological breakthroughs [62, 63, 65, 67] NFV-associated mutations [74]	Systematic TDM should be considered
750 mg t.i.d. Lopinavir/r 400/100 mg b.i.d.	C	Recommended	Capsules: Decreased AUC, C _{max} and C _{min} (GMRT: 0.72, 0.77 and 0.44, respectively) [88]; AUC GMR: 0.6 [70]; mean C _{min} : 3.3 vs. 5.1‡ correlated to viral load [95]; TDM allowed dose adjustment in 7/37 pts§ [91, 92] Other studies showed median C _{min} § (3.66, n = 26) and mean C _{min} § (5.1; n = 19) above the target [90, 93] Tablets: Mean C _{min} (range) comparable on capsules and tablets: 4.86 (0.7–8.67) and 4.57 mg l ⁻¹ (2.05–7.98), respectively [100]	1 virological breakthrough [88] Among subjects with undetectable viral load, C _{min} was higher in controls [95]	Systematic TDM should be considered, especially during late pregnancy (533/133 mg b.i.d. and 600/150 mg b.i.d. regimen seem to provide adequate LPV exposure)

Table 1
Continued

Drug	Recommendation for use in pregnancy [34]	Pharmacokinetic data (AUC, C _{min} , C _{max})	Related clinical events	TDM recommendations
533/133 mg b.i.d. (capsules) 600/150 mg b.i.d. (tablets)		Adequate AUC† (3rd trim.) [89] Adequate AUC and C _{min} † (97 and 6.7, respectively) (3rd trim.) [28] Probability of reaching the target C _{min} (5.7 mg l ⁻¹) from 21.1 to 55.3%¶ [97]		
Saquinavir (SQV) SQV/r (HGC) b.i.d.	B	Alternate 200-mg capsules: Comparable median AUC (29.7 vs. 30.4)† and decreased median C _{min} (0.3 vs. 0.6)† [79], but above 0.1 [79, 80] 500-mg tablets: Comparable mean (± SD) AUC, C _{max} and C _{min} §: 5.8 (2.5), 1.1 (0.5) and 0.4 (0.2), respectively [81]		TDM of SQV/r should be considered during pregnancy
Indinavir (IDV) 800 mg t.i.d.	C	Alternate Decreased AUC and C _{max} † [103] GM (95% CI) C _{min} : 25.5 (4.4, 149.1) vs. (13.8, 675.5)† [102] Adequate AUC§ (>34.5, n = 2) [68] Adequate median (range) C _{min} : 0.2 (0–10.7), n = 32§ [104] Adequate AUC, C _{max} and C _{min} § [106, 108]; mean (95% CI) AUC†: 28.5 (23.7, 34.2) vs. 30.5 (24.4, 38); C _{max} †: 2.6 (2.1, 3.2) vs. 2.9 (2.2, 3.8); C _{min} †: 0.5 (0.4, 0.6) vs. 0.5 (0.4, 0.7) [109]	1 virological breakthrough [103] Viral suppression not achieved at delivery [102]	Systematic TDM is recommended Despite adequate exposure, data are too limited TDM does not seem to be essential. This should be confirmed in further investigations
IDV/r 800/200 mg b.i.d. 400/100 mg b.i.d. Atazanavir/r	B	Insufficient data		
Fosamprenavir Tipranavir Darunavir	C C B	Insufficient data Insufficient data Insufficient data		Insufficient data Insufficient data Insufficient data

*Food and Drug Administration pregnancy categories: B, animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted. C, safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus. D, positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from use of the drug among pregnant women might be acceptable despite its potential risks.

†Between pregnancy and post partum.

‡Between pregnant women and matched nonpregnant women, respectively.

§Compared with pharmacokinetic data in nonpregnant adults.

¶Compared with a 400/100-mg b.i.d. regimen.

AUC, area under curve (μg h⁻¹ ml⁻¹); C_{max}, peak concentration (μg ml⁻¹); C_{min}, minimum concentration (μg ml⁻¹); CR, concentration ratio; GM, geometric mean; GMR, geometric mean ratio.

M8 is metabolized by CYP3A into an inactive form. Therefore, CYP3A induction and CYP2C19 inhibition during pregnancy would contribute to decrease the M8/NFV ratio.

Dextromethorphan N-demethylation has also been used as a measure of CYP3A activity. The urinary dextromethorphan:3-hydroxymorphinan ratio in 25 pregnant women showed 35–38% increased CYP3A activity in all trimesters compared with post partum [115].

A mechanistic approach to NFV pharmacokinetics in pregnant mice showed that after oral, but not after i.v. administration, the plasma clearance of NFV was 134% higher and bioavailability decreased by 32% in pregnant compared to nonpregnant mice. This was not due to changes in plasma protein binding, but to significantly higher CYP3A4 liver expression [116]. However, data are not currently available to extrapolate these findings to humans.

CYP3A induction is regulated by 'orphan nuclear receptors', including pregnane X receptor (PXR) and constitutive androstane receptor [117]. Increased progesterone levels during pregnancy may be implicated in the augmented CYP3A activity by interacting with these receptors [19]. As activation of PXR and upregulation of other genes are major determinants of drug disposition, including ARVs, the potential of the PXR genotype to modify ARV therapy efficacy should be considered [118].

Another mechanism explaining the increased bioavailability of certain PIs when combined with low-dose RTV in pregnant women could be mediated through P-glycoprotein (P-gp). Indeed, PIs are substrates of P-gp and most of them may substantially inhibit P-gp, with various potencies [119]. However, studies on tissue cultures and in mice have shown that ritonavir is a relatively poor P-gp inhibitor. On the other hand, the wide distribution of P-gp in the human blood–placental barrier does not decrease maternal PIs plasma concentrations, but limits the transfer of PIs towards the fetal circulation [120]. This ability to protect the fetus from xenobiotics is more evident in early pregnancy than at term [121]. In conclusion, P-gp may not play a predominant role in ARV pharmacokinetic changes during pregnancy. Furthermore, the involvement of other transporters [such as multidrug resistance protein (MRP) 1, MRP2 or breast cancer resistance protein] in ARV pharmacokinetic changes during pregnancy remains to be determined.

Variations in the plasma protein binding of a drug, when elevated, may have a clinically significant effect in altering free drug concentrations. Furthermore, an increased free concentration of several drugs (e.g. anticonvulsants) has been observed during pregnancy [122]. All the PIs, except IDV, are highly bound to plasma proteins (>90%) [123]. Therefore, the apparent hypoalbuminaemia induced by pregnancy might be responsible for the variation in plasma concentration of PIs. Some studies have reported 24–28% decreased plasma albumin levels during pregnancy compared with post partum [65, 88]. The

increased plasma volume and changes in protein binding during pregnancy theoretically impact on the apparent volume of distribution (V_d), resulting in a possible variation of PI plasma concentrations [19]. This could account for part, but not all, of the increased PI clearance, as PIs are mainly bound to α -acid glycoprotein (AAG) [123]. The variation of AAG concentration during pregnancy has been shown to be moderately altered by pregnancy [124]. More recent data, however, have shown a twofold decrease in AAG during late pregnancy [125]. This may explain the increased clearance of highly bound PIs. Nonetheless, IDV is not highly bound to plasma proteins, and its clearance is also affected by pregnancy. Therefore, a larger free fraction is unlikely to be the only parameter involved in increased IDV clearance during pregnancy. Indeed, protein binding would have to be reduced to almost zero to produce the change in oral clearance observed by Unadkat *et al.* [102]. Finally, plasma protein binding does not explain the variation in PI exposure when RTV-boosted, since in nonpregnant adults the unbound fractions of IDV and SQV are similar with or without low-dose RTV [126]. Overall, this underscores the probably weak impact of protein binding in pharmacokinetic variations of PIs during pregnancy. As PIs are highly bound, TDM of their free concentration could be useful [122]. Else *et al.* have described decreased LPV concentration during the third compared with the second trimester of pregnancy, but there was no change in the unbound percentage [127]. At this point, however, free drug monitoring of PIs is at the preliminary stage, and more studies are needed to establish the influence of protein binding on the concentration variations of PIs during pregnancy.

Cytochrome induction during pregnancy is likely to be the main mechanism explaining increased PI clearance in pregnant women. This assumption is confirmed by low exposure of other drugs that are also highly metabolized by hepatic CYP during pregnancy, such as antiepileptics [128], corticosteroids [129] and antidepressive agents (e.g. fluoxetine) [130]. Systematic monitoring during pregnancy has recently been suggested for some of these drugs [128]. In the same way, the pharmacokinetic variations of certain antiretrovirals during gestation, mainly related to CYP induction, boost the argument for systematic TDM.

Pathophysiological variability

Beside pregnancy itself, other physiological or pathological factors may influence the pharmacokinetics of ARV in HIV-infected pregnant women. Indeed, body weight has been significantly related to lower LPV exposure in HIV-infected adults [131]. Increased body weight during pregnancy may explain, at least in part, the decreased exposure to ARVs observed in pharmacokinetic studies. Stek *et al.*, however, did not show any correlation between body weight and LPV concentrations [88]. Finally, pregnancy may have a particular effect on the HIV viral load, involving

plasma dilution and the positive effect of progesterone on HIV-1 infectability and synthesis [132].

Besides pregnancy, pharmacokinetic changes due to HIV disease itself have to be considered. However, most of the data available in the studies reviewed here concern HIV-infected patients as controls, or focus on ante compared with post partum, each woman being her own control. This lessens the effect of HIV disease on the pharmacokinetics of antiretrovirals, while it highlights the effect of pregnancy.

Clinical involvement

Many of the studies we have reviewed showed decreased exposure to ARVs during pregnancy, which could lead to therapeutic failure and virological mutations. On the other hand, none of them has revealed any MTCT, and few of them showed virological breakthroughs. This discrepancy may be due to the small size of the studies. Indeed, MTCT incidence is quite low in high-income countries (recent data report a MTCT rate of 1.3% [5]) and only larger populations would allow the correlation of plasma concentrations during pregnancy to clinical outcomes. However, clinical trials are difficult to perform in pregnant patients, and the use of other methods, such as population pharmacokinetics, could provide a valuable tool to ensure adequate power.

Another reason for this discrepancy could be the increased unbound fraction of PIs, the active form, whereas the total concentration is lowered. This would result in an apparent decrease in PI concentration, but would not affect the activity, with the result that this apparent sub-exposure to ARVs during pregnancy would not have any clinical involvement. Thus, in pregnant women TDM of total drug concentration may be less relevant than TDM of the unbound fraction. As previously suggested, it may be more informative to determine unbound fraction of PIs during pregnancy [122].

Virological breakthroughs have been observed during pregnancy, sometimes associated with low plasma concentrations of NFV, LPV or IDV [62, 63, 65, 67, 74, 88, 102, 103]. Moreover, several studies have described the onset of resistance mutations in both ARV-naïve and experienced pregnant women. Indeed, reverse transcriptase mutations conferring resistance to NNRTIs have been identified in women receiving a continuous NVP-based regimen during pregnancy who discontinued it post partum [133, 134] or a single dose of NVP [135]. In another study, Duran *et al.* identified that resistance mutations occurred in 16.1% of pregnant women, which is a similar rate to that reported in nonpregnant populations with newly diagnosed HIV-1 infection [136]. The occurrence of these mutations was not associated with a particular ARV. Finally, Kakehasi *et al.* have shown new mutations in five out of 19 women (26.1%) post partum compared with ante partum, after NFV-based therapy during pregnancy [74]. However, pharmacokinetic data are lacking in all these studies to assess

the correlation between sub-exposure to ARVs and the onset of virological mutations. On the other hand, the discontinuation of ARV therapy post partum is a major concern raised by some of these groups. Indeed, the onset of these mutations may be due to MTCT prophylaxis withdrawal after delivery. However, a recent 12-month follow-up study has shown no difference between ARV-naïve women who stopped ARV therapy after delivery and those who continued it, in terms of CD4 count, CD4% and viral load over 1 year post partum [137]. The sample size of this study ($n = 206$), although derived from a cohort of >3200 pregnant women, might limit its power to detect differences between the two groups. Another study has shown that the mean duration to suppression was 20 days longer in ARV-experienced patients, suggesting the need for resistance testing in this population [138].

Further evaluation is required to investigate the reasons for failure of viral suppression in pregnant women. Decreased exposure to ARV therapy during gestation could be one of them. However, the link between the lower ARV plasma concentrations during pregnancy and treatment failure has not yet been demonstrated. More data are needed, especially follow-up studies combining TDM and genotyping and/or disease progression markers in pregnant women.

Methodological issues

The conclusions of all these pharmacokinetic studies taken together must be interpreted with caution. Indeed, the wide heterogeneity of study designs makes it difficult to compare them properly. Assessment of treatment adherence illustrates this heterogeneity. Whereas many studies did not consider adherence in their methods, some groups assumed that adherence rates are usually higher during pregnancy or did not observe anything suggesting poor adherence [65, 67]. Indeed, as assessed by self report and behavioural information or pill counting, adherence to ARVs seems better ante than post partum [139] and better in pregnant than in nonpregnant HIV-infected women [140]. Even during pregnancy, however, adherence is lower than what it should be for optimal viral control, especially for PI-based regimens [139]. Adherence assessment according to CD4 count and viral load variations during pregnancy is less conclusive, as it does not allow one to discriminate between the reasons of treatment failures [141]. Therefore, adherence assessment with standardized methods may be a useful tool to harmonize pharmacokinetic studies during pregnancy.

Besides the issue of adherence, the pharmacokinetic parameters used to monitor antiretrovirals in pregnant women change between studies, and the most suitable has yet to be determined. However, the general consensus is to use the concentration at trough. The way of expressing the results, especially the mean, when study populations are small and variability is high, is also questionable.

Furthermore, there is huge interindividual variability in TDM results for NNRTIs and PIs [142] due to the high variability of their bioavailability, partly depending on parameters such as food intake, which are usually poorly controlled in pharmacokinetic studies. Of interest, Villani *et al.* have shown lower plasma NFV concentrations during the drug elimination phase than those during the absorption phase. Neither NFV concentration close to the known value of peak concentration ($t_{\max} = 3$ h) nor k_a was changed during pregnancy. This suggests increased drug elimination in pregnant women, partially compensated for by greater bioavailability. According to the authors, it could mask the rise of systemic clearance in several patients [64].

Another issue that needs to be addressed when comparing concentrations and parameter values across studies is the quantification method. Although most laboratories use high-performance liquid chromatography ultraviolet spectrometry (HPLC-UV) or high-performance liquid chromatography tandem with mass spectrometry (HPLC-MS/MS), results can differ, making cross-study comparisons more difficult. Again, this issue should be put into perspective, as comparisons between pregnant and nonpregnant women are done in the same analysis conditions.

In conclusion, several factors lead to substantial variability between the different studies and represent a severe limit to cross-study comparisons. Future pharmacokinetic studies in pregnant women should address the methodological issues discussed above, especially the assessment of treatment adherence and the choice of adequate pharmacokinetic parameters. Moreover, follow-up studies, including disease progression markers and genotyping, should assess the relevance of TDM in pregnant women and establish optimal cut-offs in such patients.

Conclusion

Pharmacokinetic studies have shown that pregnancy significantly affects exposure to certain antiretrovirals. Sub-exposure to these drugs is more evident in the third trimester and is likely to be due mostly to a cytochrome induction. However, the clinical consequences of low exposure to antiretroviral drugs during pregnancy are not clear. Moreover, pharmacokinetic data in pregnant women must be interpreted with caution. The high interindividual variability, the small population sizes of most studies and the heterogeneity in methods are limiting factors to addressing the question. Further evaluation is required to clarify the clinical impact of reduced exposure to some ARVs during pregnancy, in particular follow-up studies combining TDM, genotyping and disease progression markers in pregnant women. Meanwhile, pharmacokinetic data suggest that TDM of nevirapine, nelfinavir, saquinavir, indinavir and ritonavir-boosted lopinavir during late pregnancy is advisable. Atazanavir monitoring should be further investigated. Finally, pharmacokinetic studies of

newer ARVs (i.e. fosamprenavir, darunavir, tipranavir and etravirine) in pregnant women are needed.

Competing interests

None to declare.

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