Protecting the Fetus Against HIV Infection: A Systematic Review of Placental Transfer of Antiretrovirals

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Abstract

Background—Maternal-fetal transfer of antiretroviral drugs contributes to prevention of vertical transmission of HIV.

Objective—This systematic review discusses published studies containing data pertaining to the pharmacokinetics of placental transfer in humans, including paired cord and maternal plasma samples collected at the time of delivery as well as *ex vivo* placental perfusion models.

Methods—Articles pertaining to placental transfer of antiretrovirals were identified from PubMed, from references of included articles, and from U.S. Department of Health and Human Services Panel on Treatment of HIV-infected Pregnant Women and Prevention of Perinatal Transmission guidelines. Articles from non-human animal models or that had no original maternal-fetal transfer data were excluded. PRISMA guidelines were followed.

Results—A total of 103 published studies were identified. Data across studies appeared relatively consistent for the nucleoside reverse transcriptase inhibitors (NRTIs) and the non-nucleotide reverse transcriptase inhibitors (NNRTIs), with cord to maternal ratios approaching 1 for many of these agents. The protease inhibitors atazanavir and lopinavir exhibited consistent maternal-to-fetal transfer across studies, although the transfer may be influenced by variations in drug-binding proteins. The protease inhibitors indinavir, nelfinavir, and saquinavir exhibited unreliable placental transport, with cord blood concentrations that were frequently undetectable. Limited data, primarily from case reports, indicate that darunavir and raltegravir provide detectable placental transfer.

Conclusion—These findings appear consistent with current guidelines of using two NRTIs plus an NNRTI, atazanavir/ritonavir, or lopinavir/ritonavir to maximize placental transfer as well as to optimally suppress maternal viral load. Darunavir/ritonavir and raltegravir may reasonably serve as second-line agents.

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Introduction

The necessity of combination antiretroviral therapy (cART) for HIV-infected pregnant women has been well-established. Such regimens are important both for maternal wellbeing and to prevent perinatal transmission of HIV to the fetus. This decrease in perinatal transmission is thought to occur both by decreasing maternal viral load and by providing the infant with pre-exposure prophylaxis via placental transfer [1]. Cases have been reported, albeit rarely, of perinatal transmission from mothers on cART who had undetectable or very low levels of plasma HIV RNA [2, 3]. HIV viral shedding in the genital tract has been documented in women whose plasma HIV RNA was undetectable [4]. Such cases indicate that maternal HIV plasma RNA levels may not be fully indicative of transmission risk and that placental transfer of antiretroviral agents (ARVs) may be another necessary component in protecting the fetus from infection. Since even the most rigorous neonatal regimen cannot be expected to "cure" an infant already infected *in utero*, prevention of transmission should always be the highest priority.

The most recent, March 2014, United States Department of Health and Human Services (HHS) guidelines recommend that women already taking a cART regimen who have undetectable plasma HIV RNA viral load continue on their current regimens during pregnancy [1]. HHS recommends that treatment-naïve pregnant patients undergo resistance testing and then commence a cART regimen consistent with those recommended for non-pregnant adults [1]. That is, the regimen should contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a ritonavir-boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1]. Further, recognizing the importance of transplacental transfer of ARVs to the fetus, HHS guidelines recommend that at least one of the NRTIs selected has "high" placental transfer [1]. The HHS guidelines also suggest that certain ARVs be given in higher doses during the second and/or third trimesters of pregnancy in order to maintain adequate maternal concentrations [1]. While not specifically studied, it is reasonable to expect that these higher doses may also lead to higher absolute placental transfer.

Several types of studies address the issue of transplacental transfer, and each approach has its benefits and drawbacks. One approach is a measure of human cord blood and maternal plasma ARV concentrations at the time of delivery. This approach is relatively safe but only provides transfer information at a single time that is typically at or near term. Further, the time between the patient's last dose and delivery is variable. A recent variation of this approach is to include these data into a broader population pharmacokinetic model for the pregnant patient that contains a fetal compartment; this provides a more comprehensive (though theoretical) model of fetal exposure. Another approach utilizes *ex vivo* perfusion of recently-delivered human placentas; this enables collection of transfer data for known concentrations of ARVs but is typically limited to full or near-term placentas in non-infected women. A final approach involves animal studies of fetal transfer; this enables fetal transfer measurements *in vivo* at multiple time points, sometimes extended throughout gestation to include times preceding fetal viability. The largest downside to this approach is that it is unclear whether these findings can be extrapolated to humans due to various interspecies differences in the placenta composition as well as timing of the establishment of the

maternal-fetal circulation [5]. While non-human primate models appear more representative than mouse models [5], further work would still need to be completed prior to drawing conclusions based on any animal model. Given that animal models cannot be applied reliably to humans, they are not further addressed in this review.

The objective of this review is to present the available pharmacokinetic data regarding transplacental transfer of ARVs. When selecting an ARV regimen and dosing for a pregnant woman, clinicians must consider pharmacokinetic data both for this transplacental transfer and for treatment of the pregnant woman herself. While this review focuses only on the transplacental component, clinicians need to consider this information only in the context of the additional maternal pharmacokinetic and treatment components.

Methods

The aim was to include all studies containing pharmacokinetic data pertaining to placental transfer of ARVs. The search strategy was conducted according to PRISMA guidelines. The primary search was conducted in PubMed on March 29, 2014 and using the following search terms: (HIV AND (pregnancy OR placenta) AND (pharmacokinetics OR pharmacokinetic OR "placental transfer")). We kept the search terms broad enough to include any studies of pharmacokinetics of ARVs in pregnancy; many studies are focused on maternal pharmacokinetics but include a single paired cord blood and maternal plasma ARV concentration measurement at the time of delivery. This broader search strategy allowed us to capture such studies that contained placental transfer data despite not having an overall focus on placental transfer. Publication types designated as "review" were automatically excluded from the search. Articles were not restricted based on year of publication or language.

Articles identified by the PubMed search were further screened manually by review of the abstract and, frequently, the full article text. Articles were then only deemed eligible if they included *original* data pertaining to transfer of ARVs from mother to fetus in humans (e.g. review articles and consensus guidelines that were not excluded by PubMed were manually excluded at this point). Articles without readily-apparent transfer data, e.g. maternally-focused pharmacokinetic studies, were electronically searched using Adobe Acrobat's "Find" function. Specifically the article text was searched for the terms "cord," "amniotic," "placenta" (also detects the words "placental" and "transplacental"), "fet" (to detect "fetus" or "fetal"), and "neonat" (to detect "neonate" or "neonatal"). Occurrences of these terms were manually evaluated for presence of maternal-fetal ARV transfer data. If after this thorough process no transfer data were detected the article was excluded.

Finally, the references of included articles were reviewed for potentially relevant articles missed by the PubMed strategy above. Also, "Appendix B" of the HHS guidelines pertaining to ARVs in pregnancy [1], which contains a listing of studies for each available ARV, was reviewed for any other relevant studies not otherwise detected above.

Given the diversity of studies included, both in terms of ARVs and study designs, no summary measures of data were formally calculated (i.e. meta-analysis). For studies with

paired cord and maternal plasma ARV concentrations, ranges of transfer ratios and cord levels were presented for studies with similar results and any outlying results described separately. For other study designs each study's results are briefly described separately.

Results

1. Study Selection

The study selection process is displayed in Figure 1. In summary, the initial PubMed search yielded 282 articles for additional screening. Eighty-four articles were identified from the HHS guidelines Appendix B[1]. No additional eligible articles were discovered by reviewing the reference sections of the included articles. After removing duplicate records, 303 articles were screened. Based on the title or abstract, 95 records were excluded, leaving 208 full-text articles that were assessed for eligibility. Of those articles, 103 met our eligibility criteria and the remaining 105 were excluded either for being a non-human placental transfer study, for not containing maternal-fetal transfer data for ARVs in pregnancy, and/or for not containing original data (e.g. review articles and consensus guidelines).

This yielded 103 articles for inclusion. Their study designs can be stratified as follows: 71 paired maternal-fetal transfer studies in humans, 7 population pharmacokinetic models of maternal-fetal transfer (most were part of the same larger study), 19 *ex vivo* human placental perfusion models, and 8 studies with miscellaneous approaches including mechanistic transporter and protein binding studies and studies of cord or fetal cells for drug incorporation. Of note, the sum of the study design types is greater than 103 as two articles incorporated more than one approach.

2. Paired Maternal-Fetal Human Transfer Data

An overview of the paired maternal-fetal transfer data at the time of delivery is shown in Table 1.

2.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)—The reported average (median or mean, as specified in each study) cord to maternal plasma concentration ratios at the time of delivery were approximately 1 for abacavir, lamivudine, and stavudine [6-12]. The observed ratio was lower for didanosine, at 0.38, but only included a single study with 10 patients [7]. Of the three emtricitabine studies, the geometric mean ratio of cord to maternal plasma concentration was 1.2 in one study (n = 11); for this study the median time between dosing and delivery was 19 hours [13]. For the other emtricitabine study (n = 10), the median cord to maternal ratio was 1.6 but the median time between dosing and delivery was 8.5 hours [14]. For an emtricitabine case report (n = 1) the ratio was 1.7 at 13 hours after dosing [15].

The five included records for tenofovir varied in study design. Two studies and a case report all included patients at steady-state, yet the median cord to maternal plasma concentration ratio varied from 0.82 (range 0.64-1.1, n=14) [14] in one study to 6.0 (range 3.5-7.2, n =3) [10] for the other; the case report (n = 1) was in between with a ratio of 1.1 [15]. Data for differences in time elapsed post-dose were not available for comparison. The third study

included patients administered tenofovir at the onset of labor, excluding any patients who had previously received tenofovir. Patients received a dose of either 600mg (n = 63) or 900mg (n = 36); for both groups the median cord to maternal plasma concentration ratio was 0.6 [16].

The final tenofovir study included 16 patients administered a single dose of vaginal tenofovir 1% gel (containing 40mg tenofovir). While the cord blood concentrations were lower than in the oral single-dose tenofovir study (Table 1), the median cord to maternal plasma concentration ratio was similar at 0.5 (interquartile range (IQR) of 0.5 to 0.6) [17].

Zidovudine has been studied the most frequently, with 10 total included records from studies at the time of viable delivery. The average cord to maternal plasma concentration ratios were evenly dispersed from 0.81 to 1.6 [7, 8, 10, 18-24]. While for all of these studies patients were taking zidovudine throughout pregnancy, the dose was frequently increased and/or switched to an intravenous formulation during labor. The studies varied widely in these dosing protocols, so a wide range of cord concentrations was expected; further, since maternal levels were likely drawn at various points in time before, during, or after the zidovudine infusion and not necessarily at the immediate time of delivery a wide range in the cord to maternal ratios is not surprising.

Zidovudine placental transfer was studied in three additional studies in earlier-stage pregnancies, prior to elective termination. A study of 26 HIV-negative pregnant women in their first trimester (median 11 weeks), given 400mg of zidovudine, found a median ratio of zidovudine in fetal tissue to maternal serum of 0.92 (IQR 0.40-1.36) [25]. The second study included six HIV-positive patients given 1000mg zidovudine each (divided into five doses) prior to elective termination at 14-26 weeks (mean 18 weeks); it was not stated whether any of these patients were taking zidovudine prior to the study. Maternal zidovudine was not detected in 1 patient; for the remaining five patients, based on the raw data provided in the article, the median concentration ratio for fetal tissue to maternal serum was 1.3 (range 0.95 – 3.2) [26]. The third early placental transfer study included two HIV-positive women at 18 and 21 weeks of gestation prior to elective termination; they were administered zidovudine over three days (total 3200mg) prior to sampling of umbilical venous blood *in utero* under ultrasound guidance. One patient had a cord to maternal concentration ratio of 1.1 with umbilical vein concentration of 0.62 mg/L while the other had a ratio of 6.0 but with a lower cord concentration of 0.12 mg/L [27].

2.2 Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)—Only two placental transfer studies of efavirenz have been published. In one (n=23), the average cord to maternal ratio was 0.5 [28]; the other (n=56) used neonatal plasma with an estimated median ratio of 0.1 [29]. Three case reports of etravirine [30, 31] have been published, two (n=1 each) with cord to maternal plasma ratios of 0.3 [30] and 0.5 [15]; the other report did not include maternal plasma sampling [31] (see Table 1 for cord values). Nevirapine is the NNRTI that has been most studied in pregnancy, both throughout pregnancy and in patients presenting in labor. Average cord to maternal plasma concentration ratios were dispersed from 0.6 to 1.0 in patients on chronic nevirapine [10, 32- 37] and from 0.7 to 0.9 in patients starting nevirapine at labor onset [38-41]. Finally, cord and maternal plasma concentrations

of rilpivirine have been measured in just one case report [n = 1] with a cord to maternal ratio of 0.74 [42].

2.3 Protease Inhibitors—Ritonavir-boosted atazanavir and lopinavir are currently the first-line protease inhibitors in pregnancy [1] and they appear to have the highest reliable cord to maternal plasma concentration ratios in this drug class. In the seven included atazanavir studies, the average cord to maternal ratios ranged from 0.13 to 0.24 [35, 43-48].

In the ten lopinavir studies with a specified dosage (ranging from 400mg to 600mg twice daily) the average cord to maternal plasma concentration ratios for total lopinavir ranged from 0.16 to 0.23 [29, 33, 49-55] except for one study (n=6) with a median ratio of 0.57 [10]. In three other studies the dose was not specified: in one, the ratio was 0.24 [36] but in a small study [35] and in a case report [32] the cord concentrations were undetectable. Two studies of 400mg lopinavir additionally measured *free* cord and maternal lopinavir concentrations. The mean free lopinavir cord to maternal ratios were 0.43 (n = 16) [52] and 0.31 (n = 7) [51]. These ratios are higher than those for total lopinavir, consistent with the lower binding protein concentrations in the cord versus in maternal plasma. Accordingly, the mean α-1-acid glycoprotein (AAG) level was found to be 0.15 g/L in the cord and 0.47 g/L in the maternal plasma in one study (n = 16) [52].

Nelfinavir has also been well-studied in pregnancy, but is no longer recommended in patients able to tolerate other agents [1]. In the twelve included studies [10, 32, 33, 35, 36, 56-62], reported average cord to maternal concentration ratios fluctuated widely from 0.0 to 0.49; likewise, cord blood nelfinavir concentration averages varied from 0.0 to 0.27 mg/L. Concentrations of nelfinavir were frequently undetectable in both maternal and cord samples, and the studies that reported higher averages tended to exclude these undetectable concentrations from their summary measure. In cases of undetectable nelfinavir in maternal plasma this may be a result of either complete noncompliance or, more likely, poor bioavailability from failing to take the drug with a high-fat meal. Hence while in some patients the placental transfer appears similar to atazanavir and lopinavir, in others the nelfinavir is undetectable even in maternal plasma and thus does not reach the cord blood.

Indinavir [56, 57, 63] and saquinavir [32, 33, 56, 57, 64-66] both had low and unpredictable placental transfer ratios. Limited data for darunavir [31, 67-70], fosamprenavir [71], and tipranavir [72] reveal potential for moderate placental transfer (see Table 1 for details). In particular, darunavir has been studied in 5 case reports and 1 small (n = 9) study with cord to maternal plasma concentration ratios ranging from 0.11 to 0.32 [15, 31, 67, 68, 69, 70]

Finally, some of the studies of protease inhibitors included paired cord and maternal plasma sampling for the ritonavir booster. Most of these transfer ratios ranged from 0 to 0.2 [29, 33, 51, 53, 57, 70] although one smaller study reported a value of 0.55 [10]. It is not clear that placental transfer of ritonavir is necessary as its purpose is to increase the systemic exposure of its accompanying protease inhibitor, hence increasing the amount of those agents available for placental transfer.

2.4 Fusion/Entry Inhibitors—The fusion inhibitor enfuvirtide has been undetectable in all cord samples in a total of 11 patients observed to date [31, 72-74]. Placental transfer of the CCR5 receptor antagonist maraviroc has only been studied in one case report (n = 1) in which the cord to maternal plasma concentration ratio was 0.37 [15].

2.5 Integrase Inhibitor—Raltegravir is the only integrase inhibitor for which placental transfer data are published. These data are only from limited case reports for a total of five patients on raltegravir at steady-state and two not at steady-state. A case report of 1 patient reported a cord to maternal concentration ratio of 1.0 [50]. A report of 3 patients utilized neonatal plasma levels instead and reported high neonatal concentrations as well as high neonatal to maternal concentration ratios of 7.37, 9.5, and 15.5 [75]. The third set of cases focused on pre-term deliveries. One patient was at steady state prior to delivery at 33 + 2/7 weeks and had a neonatal plasma concentration of 3.8 mg/L with a neonatal to maternal ratio of 1.63 [76]. The other two patients in this report were not at steady-state, having started raltegravir only 14 to 23 hours prior to delivery. One of these patients delivered at 30 + 3/7 weeks with a neonatal concentration of 0.12 mg/L and a neonatal to maternal ratio of 1.9; the other delivered at 29 + 5/7 weeks with a neonatal concentration of 0.60 mg/L and a ratio of 2.0 [76].

3. Population Pharmacokinetic Models of Maternal-Fetal Transfer

A few studies of ARVs in pregnancy have utilized maternal, cord, and/or neonatal plasma ARV concentrations to construct a population-based model, describing the placental transfer process in the context of the maternal model. These models estimate a fetal to maternal exposure ratio, often expressed as a ratio of areas under the plasma concentration versus time curves (AUCs).

A population pharmacokinetic study of lamivudine in pregnancy included 228 total women receiving lamivudine throughout pregnancy, including 123 with cord samples at time of delivery [11]. The predicted fetal to maternal AUC ratio was 0.86 [11], slightly below the observed concentration ratios reported for the lamivudine studies in Table 1.

Two articles from a single research study described placental transfer of emtricitabine on a population level. In both steps of this study patients previously on zidovudine monotherapy were given 400mg emtricitabine, 600mg tenofovir, and 200mg nevirapine at the onset of labor. The first step of the study included 38 HIV-infected pregnant women and described a median predicted cord level at delivery of 0.72 mg/L with a transfer ratio for cord to maternal plasma of 0.76 and an AUC ratio of 0.80 [77]. According to a figure provided in that article, the AUC ratio appears to peak at close to 1 for patients with 5 hours elapsed between the dose and delivery and gradually decreases to a plateau around 0.7 for patients delivering at 15-25 hours post-dose [77]. While the predicted cord concentrations were higher than those observed in the individual pharmacokinetic studies cited in Table 1, the predicted total placental transfer ratio (AUC ratio) appears a bit lower. The second article on this emtricitabine population pharmacokinetic study reported on the active, phosphorylated intracellular form of emtricitabine. It measured this metabolite in cord blood from 36 deliveries using liquid chromatography-tandem mass spectrometry and compared with

literature that described concentrations of this metabolite in non-pregnant adults [78]. From this study the median predicted exposure to the active intracellular phosphorylated emtricitabine was 5.9 times higher in the cord blood than in adults [78] despite the lower exposure to the parent drug reported in the first part of the study [77]. This is relevant clinically since it implies that measurement of the parent drug may underestimate the extent of placental transfer of active drug and hence measurement of the active form in future studies may provide more meaningful results.

The population pharmacokinetic study of emtricitabine also described tenofovir placental transfer in the same patients with the same study design as described above. In the first part of this study the median predicted cord concentration at delivery for tenofovir was 0.10 mg/L with a median predicted cord to maternal ratio of 0.71 and an AUC ratio of 0.60 [79]. From a figure provided the AUC ratio appears consistently around 0.6 beginning at 5 hours post-dose [79]. This ratio is consistent with the observed concentration ratio in the study of tenofovir given during labor [16] as shown in Table 1. The intracellular phosphorylation component of the study included 20 cord samples in which the intracellular metabolite was measured [80]. Unlike in the emtricitabine study, these levels were below the limit of detection in 6/20 of the subjects and below the limit of quantification in another 12/20 despite the parent drug being detectable in all of these samples [80]. The authors attributed this to possibly either low rates of cell transfer or a delay prior to phosphorylation in the fetus [80].

Two population pharmacokinetic studies described placental transfer for single-dose, 200mg, nevirapine at the onset of labor. The first study, involving the same 38 patients and design as the emtricitabine and tenofovir studies described above, predicted a median cord concentration at delivery of 1.35mg/L and a median fetal to maternal AUC ratio of 0.75 [41]. These values are consistent with the observed values reported for single-dose nevirapine in Table 1. A study of 113 patients predicted much lower transfer ratios of 0.11 to 0.25 despite having the same median time to delivery of around 5 hours [81]. This study, focused on neonatal dosing, provided these ratios without providing their actual observed or predicted cord concentrations for comparison.

No population pharmacokinetic studies calculated predictions for fetal to maternal AUCs of protease inhibitors. One population pharmacokinetic study modeled transplacental transfer of nelfinavir but provides predictions of inter-compartmental rate constants only; the fraction transferred was expressed only as observed, not predicted, values and hence included with the studies shown in Table 1 [60].

4. *Ex Vivo* Placental Perfusion Models

Ex vivo models of human placentas, immediately following delivery, have been utilized as another means of quantifying maternal-fetal transfer. Transplacental transfer results in the maternal-to-fetal direction are discussed below. Such results reflect the amount of the ARV transferred from the maternal side of the placenta to the fetal side relative to the transfer of antipyrine, a freely-diffusible molecule. These studies generally allowed recirculation of the ARV for up to 2 hours.

Earlier *ex vivo* models (1992-1998) measured maternal-to-fetal clearance indices for each ARV at low and high infused concentrations to reflect expected maternal trough and peak concentrations. Such indices were reported for abacavir [82], didanosine [83-85], lamivudine [86], stavudine [87], zidovudine [83], amprenavir [82], and ritonavir [88] and are summarized in Table 2. For most of the NRTIs the clearance indices did not appear to differ between the two concentration extremes whereas for the two protease inhibitors tested the transfer index was higher with higher plasma ARV concentrations. Two additional zidovudine models did not specifically calculate clearance indices. However, one of these models exposed the placenta to zidovudine over a longer period of time (14 hours) and showed that zidovudine equilibrated in the fetal compartment within 60 minutes of each of the three dosing exposures [89]. The other reported fetal and maternal concentrations at each time point in two placentas, without calculated AUCs; the ratios of each of these concentrations appeared to vary from 0.2 to 0.5 over 45 to 90 minutes [90].

Later *ex vivo* models often utilized a single perfusate concentration but additionally utilized these models to study influence of protein binding or transporters on placental perfusion in a manner not feasible *in vivo*. Two studies found a mean saquinavir maternal-to-fetal transfer index of 0.05 [91, 92]. One of these found that the amount crossing the placenta corresponded to the fraction not bound to serum albumin [91]. The other investigated two polymorphisms that affect P-glycoprotein expression, but this study had a small sample size (n = 15 across all genotypic permutations) and was unable to demonstrate an effect of genotype on transplacental transfer [92]. A third study found a mean clearance index of 0.04 ± 0.05 for saquinavir that increased to 0.14 ± 0.08 and 0.12 ± 0.04 with addition of P-glycoprotein inhibitors PSC833 and GG918 respectively [93]. These authors note that this indicates potential for increased teratogenicity when drugs that are P-glycoprotein substrates are administered with P-glycoprotein inhibitors during pregnancy [93]. A final saquinavir study found a mean maternal-to-fetal transfer index of 0.27 ± 0.1 in a control group, 0.23 ± 0.1 with MK-571 (an MRP1 transporter inhibitor), and 0.22 ± 0.2 with probenecid (an OAT transporter inhibitor) [94]. Based on these results the maternal-fetal transfer of saquinavir does not rely on MRP1 or OAT transporters. However, the authors also acknowledge that the results are questionable given that the transfer index for their control group is higher than the index of 0.05 in their previous study [92] despite using the same methods and experiencing similar rates of antipyrine transport [94].

One group published two reports of indinavir models; in the earlier study the mean ± standard deviation clearance index was 0.39 ± 0.09 (n=5) [95]. This is perhaps surprising given the poor transfer *in vivo* as shown in Table 1. However, these clearance indices may vary between placentas, as later models using the same methods reported indices of 0.25 ± 0.03 (n=7) and 0.34 ± 0.14 (n=5) for identically-treated subgroups [96]. In the subgroup with the initial mean clearance index of 0.25, upon addition of PSC833, a P-glycoprotein inhibitor, the clearance index significantly increased (p = 0.047) to 0.37 ± 0.14 [96]. In the subgroup with the initial mean clearance index of 0.34, addition of ritonavir did not significantly alter this index (p = 0.31) and resulted in a mean index of 0.39 ± 0.13 [96].

An *ex vivo* model of lopinavir transport revealed mean maternal-to-fetal clearance indices of 0.68 ± 0.12, 0.57 ± 0.07, and 0.10 ± 0.01 when infused with albumin concentrations of 2

g/L, 10 g/L, and 40 g/L respectively [97]. These results are consistent with the *in vivo* placental transport data in the presence of typical plasma albumin concentrations (e.g. 40 g/L). That is, at this higher, physiologic, albumin concentration the lopinavir is mostly bound and unable to cross the placenta as freely.

A model of nelfinavir transport revealed a mean clearance index of 0.085 ± 0.05 for maternal perfusate nelfinavir concentrations of less than 500 mcg/L (n = 3) and a mean index of 0.39 ± 0.1 for the remaining 10 placentas, with perfusate concentrations ranging from 1256 to 4436 mcg/L [98]. These results are consistent with the poor placental perfusion in the presence of lower maternal concentrations in *in vivo* models, as discussed above.

An *ex vivo* model of maraviroc transport had an overall mean maternal-to-fetal clearance index of 0.26 ± 0.07 [99]. No *in vivo* placental transfer studies have been published for comparison. This study found a significant inverse correlation between the clearance index and the gene expression levels of ABCC2, ABCC10, and ABCC11 transport proteins but not for the other ABC transport proteins tested, indicating that those 3 efflux transporters may hinder maternal-to-fetal transport of maraviroc [99].

Finally, enfuvirtide was studied in three *ex vivo* placentas with 18 serial samples each [100]. The mean concentration in the maternal perfusate was 12,400 mcg/L (2.5 times the goal maximum concentration *in vivo* of 5000 mcg/L) [100]. Consistent with *in vivo* data (Table 1), enfuvirtide was undetectable (< 50mcg/L) in all 54 fetal venous samples [100].

5. Miscellaneous Studies

The remaining ARV studies focused on mechanisms of the transplacental transport rather than the extent to which transport occurs. While these are not technically pharmacokinetic studies they are pertinent to the interpretation of the pharmacokinetic data. Four such studies focused on zidovudine. One *in vitro* study investigated zidovudine uptake by syncytiotrophoblasts, finding that the uptake affinity was increased in the presence of dehydroepiandrosterone sulfate (DHEA-S) although the actual transporter involved was not identified [101]. The rest of the studies looked at consequences of the zidovudine uptake. One found that trophoblast cells exposed to zidovudine did not convert it to the toxic catabolite 3′-amino-3′-deoxythymidine (AMT), and hence this was unlikely to be a mechanism of toxicity to the fetus [102]. A study of incorporation of zidovudine into cord blood leukocyte DNA discovered such incorporation in 70% of samples, although interindividual variability was high in the extent of this incorporation that did not appear correlated with the length of zidovudine treatment [103]. A karyotypic study of exposed cord blood cells was consistent with this finding of zidovudine-induced mutagenicity, finding a higher proportion ($p < 0.001$) of aneuploid cells in the exposed group (median 18.8%) versus controls (median 6.6%); these alterations were randomly distributed across all chromosomes [104]. However, the clinical ramifications of these alterations are unknown.

One study suggested a significantly higher, 3.3-fold ($p < 0.0009$) mean increase in the expression of the MDR1 gene in the placentas of HIV-infected versus uninfected women [105]. This gene encodes P-glycoprotein, which can result in efflux transport of many protease inhibitors [105]. The increased expression did not appear to be confounded by

protease inhibitor administration to the HIV-infected group, as a similar extent of increased expression was observed whether the women were treated with zidovudine alone or in combination with nelfinavir and lamivudine [105]. This finding may account in part for difficulty in transplacental transport of protease inhibitors in HIV-infected women.

An *in vitro* study of the ATP-binding cassette (ABC) efflux transporters revealed that the prodrug tenofovir disoproxil fumarate was actively effluxed from trophoblast cells by ABCB1 and ABCG2 transporters but not by ABCC2 [106]. However, tenofovir itself was not effluxed by these transporters [106].

Two protein binding studies were conducted involving protease inhibitors, which as a class are highly-bound to AAG. Both collected cord blood and maternal plasma from HIV negative women, subsequently spiking these samples with a protease inhibitor. The first study found the unbound fraction of both indinavir and saquinavir (p   0.001) to be significantly higher in cord samples than in maternal samples [107]. Accordingly, the cord samples were found to have significantly lower levels of AAG compared to maternal samples (p < 0.05) [107]. A similar study of lopinavir found that the unbound fraction actually did not differ significantly between cord and maternal samples; this was attributed to saturable binding at higher concentrations of lopinavir [108]. However, presence of ritonavir did not appear to interfere with the fraction of lopinavir that was protein-bound [108]. The measured fractions unbound are consistent with those discussed above from studies of total and free lopinavir concentrations in cord and maternal plasma of HIV-infected women who were chronically administered lopinavir *in vivo* [51, 52].

Discussion

The published pharmacokinetic data for maternal-fetal transfer of ARVs still leave many clinical questions unanswered. Vertical transmission outcomes cannot feasibly or ethically be studied in fetuses exposed to ARVs *in utero* in absence of maternal ARV exposure or vice versa. Hence, clinical outcomes due to transplacental transfer of ARVs cannot be rigorously studied separately from maternal administration of ARVs.

As discussed in the introduction, vertical transmission from mothers with low or undetectable viral loads, although rare, can occur [2, 3]. This provides reasonable evidence for administering ARVs that are transferred across the placenta as a form of prophylaxis for the fetus. This also raises the question of what cord to maternal ratio is needed to be considered adequate placental transfer. Alternatively, perhaps the ratio is not important but rather the absolute concentration of the ARV in the fetal circulation is the key factor. While most of the studies to date have measured ARV concentrations at the time of term or near-term delivery, the fetal concentrations earlier in pregnancy are unknown. Finally, studies have been unable to assess how many drugs that cross the placenta are necessary for fetal prophylaxis – for instance, in a patient on a three-drug regimen, must all three cross the placenta or would only one or two drugs crossing the placenta be sufficient?

Of the various methods for determining the extent of placental transfer, paired cord to maternal ratios is most common and can conveniently be completed in the context of studies

of third trimester pharmacokinetics. However, this ratio only provides evidence of exposure at one point in time and can vary greatly depending on timing of the most recent maternal dose relative to time of delivery, missed doses at the time of delivery, and timing of the maternal plasma sample. *Ex vivo* perfusion models allow for strict control of the drug concentration to which the system is exposed as well as duration of this exposure and appear to yield similar results to those found *in vivo*. As new drugs enter the market, this method is unlikely to replace the *in vivo* methods since studies during pregnancy itself are necessary for determining the pharmacokinetics in that population; once such a study is underway it is fairly simple to then obtain the paired maternal and cord samples at delivery in these same patients. However, the *ex vivo* models have the advantage that they could be used for new drugs before any data for safety in pregnancy are available. For instance if a new drug is thought to have similar clinical efficacy to other drugs already on the market and the *ex vivo* model shows limited placental penetration perhaps researchers could decide to not pursue studying this drug in pregnancy and focus their efforts on drugs with higher placental transfer. In the future, perhaps placentas from pregnancy terminations could be used as a unique opportunity to study placental transfer of antiretrovirals from earlier in pregnancy. This could provide more information on second trimester placental transfer than can be achieved from *in vivo* studies.

In determining target ARV concentrations for the cord blood, comparison with each ARV's IC50 value for the wild-type HIV virus is a reasonable starting point. Data for these values from published studies [109, 110, 111], but converted to units of mg/L, are shown in Table 3. In comparing average cord ARV concentrations from Table 1 with the IC50 values in Table 3, all of the ranges of average cord concentrations for NRTIs except for zidovudine included values less than the IC50. The cord concentrations for nevirapine and efavirenz were more than 100 times greater than the IC50 and the cord concentration for raltegravir was fifty times the IC50. The cord concentrations for lopinavir and atazanavir were greater than the IC50, whereas the cord concentrations of nelfinavir, indinavir, and saquinavir were frequently undetectable and hence well below the IC50. This approach has clear drawbacks as achieving a concentration equal to the IC50 is only effectively suppressing half of the viral replication. Further, the cord concentrations measured in studies may be artificially low depending on time elapsed since the patient's last medication dose, which may often be unintentionally omitted during labor. The extent to which the target concentration should be increased above the IC50 is unclear. Further, fetuses may not require the same ARV concentrations as HIV-positive adult patients because 1) intent of ARV exposure in the fetus is prophylactic, 2) fetal circulation contains decreased levels of AAG so lower total concentrations of protein-bound drugs (e.g. protease inhibitors) are required to achieve similar free concentrations, and 3) fetuses at various times throughout pregnancy can be expected to have vastly different pharmacokinetic parameters from adults and even from neonates.

Limitations to this systematic review include the possibility of incomplete retrieval and inclusion of all identified research in these areas. These types of studies are observational and descriptive, often with small sample sizes, which could lead to challenges in obtaining acceptance for publication in biomedical journals. The descriptive results themselves, however, should not lead to reporting bias in either direction.

Overall, both the *in vivo* studies and *ex vivo* placental models mostly demonstrate a moderate (> 0.5) extent of maternal-fetal transfer for both the NRTIs and NNRTIs, although data are sparse for NNRTIs besides nevirapine. However, the maternal-to-fetal transfer is less for the protease inhibitors. It appears highest for ritonavir-boosted atazanavir and lopinavir based on many studies, as well as possibly for darunavir and tipranavir based on limited case reports. Placental transfer of indinavir and saquinavir is extremely limited (< 0.2) and transfer of nelfinavir is often extremely limited, though in many cases nelfinavir is not even entering the maternal plasma at a predictable level. Decreased levels of AAG in the fetal circulation relative to the maternal circulation may account for the lessened transfer of protease inhibitors that are highly protein-bound. Raltegravir provides substantial transfer and while it is not currently recommended as first-line in pregnancy due to limited data, perhaps it may be recommended in combination with two NRTIs in the future. Enfuvirtide appears to have absolutely no maternal-to-fetal transfer. Consistent with national guidelines, recommended treatment with two NRTIs plus an NNRTI or ritonavir-boosted atazanavir or lopinavir should provide consistent ARV transplacental transfer. The extent of transfer of these recommended agents across the placenta at term varies by individual ARV administered, and each is expected to contribute to fetal prophylaxis against wild-type HIV1 infection.

Acknowledgments

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Key Points

- Nucleoside reverse transcriptase inhibitors and non-nucleotide reverse transcriptase inhibitors have reliable maternal-to-fetal transfer across *in vivo* studies and *ex vivo* human placental studies.

- Protease inhibitors, except for atazanavir/ritonavir and lopinavir/ritonavir, appear to have inconsistent maternal-to-fetal transfer.

- The maternal-to-fetal transfer of protease inhibitors may be affected by differences in drug-binding proteins between the maternal and fetal circulations.

Records identified through
database searching
(n = 282)

Additional records identified
through other sources
(n = 84)

Records after duplicates removed
(n = 303)

Records screened
(n = 303)

Records excluded
(n = 95)

Full-text articles assessed
for eligibility
(n = 208)

Full-text articles excluded, non-
human animal model, or
No maternal/fetal transfer data, or
No original data (e.g. review)
(n = 105)
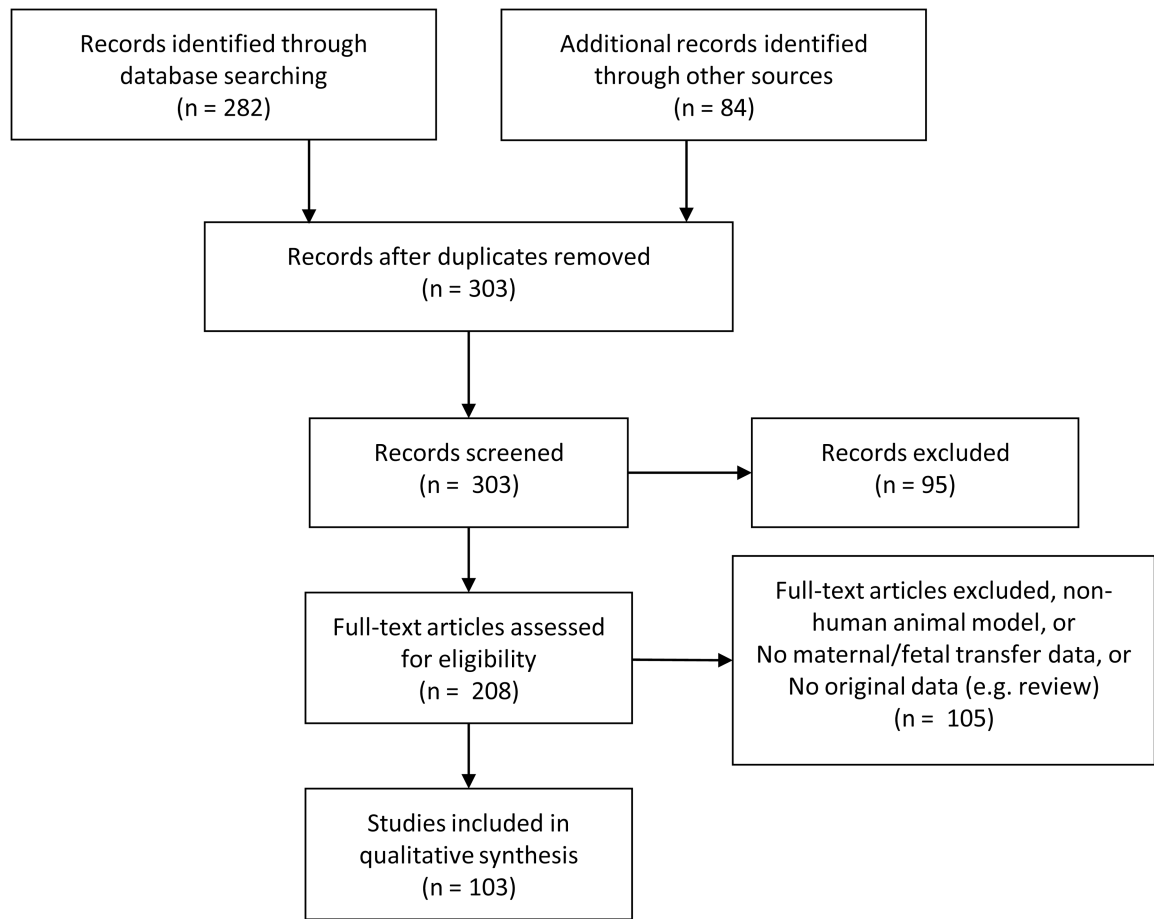
Studies included in
qualitative synthesis
(n = 103)

Figure 1. Overview of search strategy and included studies

Table 1

Summary of paired human maternal-fetal transfer data at time of delivery

The range of average cord (or neonatal) ARV levels and average cord (or neonatal) to maternal ARV plasma ratios are included for each ARV. The "averages" reported from each article are typically medians but also include means. All ARVs were assumed to have reached steady-state prior to measurement unless otherwise noted.

ARV	Number of Studies*	Total Number Paired Samples**	Range of Average§ Cord Levels (mg/L)	Range of Average§ C:M	Comments
NRTIs					
Abacavir [6, 7]	2	14	0.26 - 0.83	1.03-1.06	
Didanosine [7]	1	10	< 0.05	0.38	14 additional excluded from C:M as maternal plasma levels were < LOQ
Emtricitabine [13-15]	3	22	0.25 – 0.26	1.2 – 1.7	
Lamivudine [7-11]	5	258	0.22 – 0.4	0.93 – 1.22	
Stavudine [7, 12]	2	22	0.04 – 0.14	1.0 – 1.3	Median of 0.04 for n=32, but 20 of these were excluded from study's C:M (1.3) as maternal levels were <LOQ [7]
Tenofovir					
Steady-state [10, 14, 15]	3	18	0.03, 0.05 [10, 15]	0.82 (n=14) [14] 1.1 (n = 1) [15] 6.0 (n=3) [10]	
Labor only [16]	1	99	0.08 (600mg) 0.12 (900mg)	0.60	n=63 on 600mg, n=36 on 900mg
Vaginal [17]	1	16	0.002 (IQR 0.001 – 0.003)	0.5 (IQR 0.5-0.6)	Single dose of 1% vaginal gel (40mg tenofovir) 2 hours prior to scheduled Cesarean
Zidovudine [7, 8, 10, 18-24]	10	153	0.12 – 0.70 (9 studies)	0.81 – 1.6 (8 studies)	All studies assumed steady-state prior to labor but increased and/or switched to IV at start of labor
NNRTIs					
Efavirenz					
Cord data [28]	1	23	1.1 (0.47-4.5)	0.49 (0.37-0.74)	
Neonate plasma [29]	1	56	1.7 (0.05-7.9)	0.1	C:M median estimated from figure (average not reported)
Etravirine	3 case reports	Singleton cases [30, 15]:	0.11, 0.22	0.33, 0.51	
		Twin case [31]:	0.41 (twin 1), 0.35 (twin 2)	-	No maternal plasma levels at delivery; dizygotic

ARV	Number of Studies*	Total Number Paired Samples**	Range of Average§ Cord Levels (mg/L)	Range of Average§ C:M	Comments
Neviravine					
Steady-state [10, 32-37]	7	70	1.5-3.4 (for studies with n > 2, minimum = 2.4)	0.59-1.0	C:M values evenly dispersed across wide range
Labor only [38-41]	4	74	0.76 – 1.4	0.71-0.92 (3 studies)	In all 3 studies, average 4-5 hours from dose to delivery. Average of 0.92 as weighted mean from 3 subgroups reported in 1 study [38].
Rilpivirine [42]	1	1	0.016	0.74	
Protease Inhibitors					
Atazanavir [35, 43-48]	7	158	300mg: 0.13-0.22 400mg: 0.18-0.200	13 – 0.24	3 studies with 300mg daily [43-45], 1 with 400mg [47], 1 with both [46], 2 unspecified [35, 48]; all with 100mg RTV
Darunavir					
Study, 600mg BID [70]	1	9	0.38	0.15	All doses with 100mg RTV
Case Reports, 600mg BID [15, 31, 67, 69]	4	5	Single: 0.21-1.4 Twins: 0.58, 1.0	0.15 – 0.32 (excludes twins)	Includes 3 case reports (4 patients) of single gestation [15, 67, 69] and 1 case report of dizygotic twins (for which no paired maternal concentration provided) [31]
Case Report, 800mg once daily [68]	1	1	0.43	0.11	
Fosamprenavir [71]	1	7	0.11	0.27	For amprenavir active metabolite.
Indinavir	3	n = 21 [56] n = 4 [57] n = 19 [63]	All cords < LOQ 0.00 0.12	0.00 0.01 0.12	GMR of 0.12 excluded 7/26 cords with ARV < LOQ [63]
Lopinavir					
400mg (+ 100 RTV) BID [10, 33, 49-53]	7	63	0.45 – 0.70 (4 studies)	0.16 – 0.22 (6 studies)	One study did not provide cord levels. Two studies had outlying levels: 1) 1.3 mg/L (n=1) with C:M in range [50], 2) 0.08 mg/L and C:M 0.57 (n=6) [10]
533mg (+ 133 RTV) BID [54]	1	23	0.89 mg/L	0.23	
600mg (+150 RTV) BID [29, 53, 55]	3	83	0.88 - 1.0	0.16 – 0.20	One study [29] with neonate plasma instead of cord
Dose not specified [32, 35, 36]	3	54	0.00 - 0.96	0.00 - 0.24	Detectable in study with 42 patients [36]; not detectable in any cord samples in study with 11 patients [35] and case report [32]
Nelfinavir [10, 32, 33, 35, 36, 56-62]	12	217	0.00 – 0.27 (10 studies)	0 – 0.49	Many cord samples <LOQ; studies reporting higher values for cord and C:M typically excluded the LOQ samples. Median values for studies fairly evenly distributed throughout the ranges specified.

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ARV	Number of Studies*	Total Number *Paired* Samples**	Range of Average§ Cord Levels (mg/L)	Range of Average§ C:M	Comments
Saquinavir [32, 33, 56, 57, 64-66]	7	37	<LOQ in 5/6 reporting cord levels	0.00 – 0.04 (6 studies)	1 study with median 0.128 mg/L in cord (n = 7) but no ratio reported [66]
Tipranavir [72]	1	1	15.6	0.41	
Ritonavir (booster only, 100-150mg) [10, 29, 33, 51, 53, 57, 70]	7	132	0 – 35.8	0.00 – 0.55	1 study (n=6) with ratio 0.55 [10], otherwise highest ratio was 0.24 [53]
Other ARVs					
Enfuvirtide [31, 72-74]	4	11	Undetectable in all cord samples.		3 of these records are case reports (n 2)
Maraviroc [15]	1	1	0.069	0.37	
Raltegravir [50, 75, 76]	3	5	0.19 (cord) 0.21-3.8 (neonate)	C:M 1.00 N:M 1.63-15.5	All case reports. N:M concentrations evenly distributed throughout range reported.

*
Number of studies, ranging from case reports to large trials.

**
Sum of patients included in each study for the paired C:M reading; occasionally more patients were included in each study's report of average cord ARV level (unpaired).

§
Reported as median by most articles but reported by some as means.

Abbreviations in order of appearance: ARV = antiretroviral drug; C:M = cord to maternal plasma ARV ratio; N:M = neonatal to maternal plasma ARV ratio (prior to neonatal ARV dosing); NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; GM(R) = geometric mean (ratio); LOQ, limit of quantification of assay; IQR = interquartile range; RTV, ritonavir

Table 2
Maternal-to-fetal clearance indices from *ex vivo* placental perfusion models for antiretroviral agents infused at both expected trough and peak *in vivo* concentrations

Low (trough) concentrations were 0.2 to 2 mcg/mL and high (peak) concentrations were 6-15 mcg/mL, except where otherwise specified.

Antiretroviral Drug	Maternal-to-Fetal Clearance Index (Mean ± Standard Deviation)	
	Low ARV Concentration	High ARV Concentration
Abacavir [82]	0.47 ± 0.19	0.50 ± 0.07
Didanosine [83-85]	0.14 ± 0.03 to 0.35 ± 0.1	0.15 ± 0.04 to 0.39 ± 0.16[a]
Lamivudine [86]	0.23 ± 0.14	0.14 ± 0.06
Stavudine [87]	0.24 ± 0.07	0.24 ± 0.05
Zidovudine [83]	0.31 (n = 1)	0.29 ± 0.04
Amprenavir [82]	0.14 ± 0.08	0.39 ± 0.09
Ritonavir (with 10mcg/mL ZDV) [88]	0.085 ± 0.05[b]	0.30 ± 0.11[b]

[a] The index of 0.39 was from a study in which a high concentration, 118 μg/mL (500μM) didanosine was infused; however, this study used a low concentration of 0.24 μg/mL (1μM) with similar results [84].

[b] For ritonavir the "low" plasma concentration was 20 mcg/mL and the "high" concentration was 100 mcg/mL. Concentrations of 1-2 mcg/mL were also attempted but yielded undetectable ritonavir on the fetal side.

ARV = antiretroviral drug, ZDV = zidovudine

Table 3

IC50 values for wild-type HIV for select antiretroviral agents [109, 110, 111]

Converted from original molar concentrations to mg/L for ease of comparison with cord data.

Antiretroviral Drug	IC50 (mg/L) [109][*]	
Zidovudine		0.0053
Lamivudine		0.55
Didanosine		1.18
Stavudine		0.11
Abacavir		0.46
Tenofovir		0.20
Nevirapine		0.024
Efavirenz		0.00051
Indinavir		0.0037
Nelfinavir		0.0032
Saquinavir		0.0017
Lopinavir		0.0019
Atazanavir [110]	No AAG:	0.0049
	With AAG:	0.047
Raltegravir [111]		0.0036

[*] From this reference except where otherwise specified.

AAG = α-1-acid glycoprotein, a drug-binding protein