

# Pharmacologic and nonpharmacologic options for the management of HIV infection during pregnancy

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**Abstract:** Over the past decade, significant advances have been made in the treatment of HIV-1 infection using both pharmacologic and nonpharmacologic strategies to prevent mother-to-child transmission (MTCT). Optimal prevention of the MTCT of HIV requires antiretroviral drugs (ARV) during pregnancy, during labor, and to the infant. ARVs reduce viral replication, lowering maternal plasma viral load and thus the likelihood of MTCT. Postexposure prophylaxis of ARV agents in newborns protect against infection following potential exposure to maternal HIV during birth. In general, the choice of an ARV for treatment of HIV-infected women during pregnancy is complicated by the need to consider the effectiveness of the therapy for the maternal disease as well as the teratogenic or teratotoxic potential of these drugs. Clinicians managing HIV in pregnancy need to discuss the potential risks and benefits of available therapy options so that mothers can make informed decisions in choosing the best treatment regimen for themselves and for their children.

**Keywords:** HIV, pregnancy, acquired immunodeficiency syndrome, antiretroviral agents

## Introduction

According to the World Health Organization (WHO), an estimated 15.7 million women and 2.1 million children under the age of 15 years were living with AIDS as of December 2008.<sup>1</sup> One of the great success stories has been the influence of perinatal interventions on the reduction of mother-to-child transmission (MTCT) worldwide. This has been more evident in developed countries where interventions are more complex and effective but costly.

Without interventions, the risk of such vertical transmission of HIV has been estimated to be 15% to 35% worldwide.<sup>2</sup> In some developing countries, for example, Botswana, Zimbabwe, and Swaziland, the HIV epidemic has reversed the gains in infant survival made prior to 1999.<sup>3,4</sup> Attempts to eradicate perinatal transmission of the disease have led numerous national and international health agencies to institute guidelines for the management of the woman and her infant during the antepartum, intrapartum, and postpartum periods.

In contrast with general guidelines for the management of adults with HIV infection, the consensus for the management of pregnant women with HIV infection is that antiretroviral (ARV) therapy should be initiated and continued for the duration of the pregnancy regardless of viral load and CD4 cell count in order to reduce MTCT;<sup>5-7</sup> for women who are receiving antiretroviral drugs solely for prevention of perinatal transmission, however, delaying initiation of prophylaxis until after the first trimester can be considered.<sup>5</sup> In developed countries, the use of highly active antiretroviral therapy

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(HAART; which includes 2 nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs] with a protease inhibitor [PI]), ARV prophylaxis for the mother and fetus and then the infant, elective cesarean delivery, and infant formula rather than breastfeeding have reduced the incidence of MTCT from between 15% to 25% to less than 2%.<sup>8</sup> In less developed areas, simpler and more affordable ARV regimens are being offered to treatment-naïve pregnant women and their newborns; these involve combinatorial ARV approaches, where possible, or single agent treatment, most notably the use of the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (NVP), where lack of resources is a limiting factor.<sup>9</sup> The reductions in the rate of perinatal HIV transmission have been evident worldwide (including the Caribbean) due to the diverse interventions and programs supported by a variety of international funding agencies.<sup>10,11</sup>

## Perinatal transmission

One major achievement in the reduction of the MTCT of HIV was the Pediatric AIDS Clinical Trials Group Protocol 076 (PACTG 076)<sup>12</sup> regimen involving zidovudine (AZT), which in 1994 was shown to reduce the risk of MTCT by nearly 70%. The implementation of PACTG 076 coupled with increased antenatal HIV counseling and rapid testing in the United States and other countries with higher level resources<sup>13,14</sup> have substantially decreased the perinatal MTCT of HIV. In general, although the risk of MTCT is related to maternal viral load, studies have shown a continued risk of MTCT even at low maternal plasma HIV RNA levels (<1000 copies/mL);<sup>15,16</sup> in addition, the protective effect of antenatal ARV therapy increases with its complexity and duration and results in a decline in the rate of MTCT to around 3%.<sup>17–19</sup>

Projects to prevent MTCT in resource-limited settings have focused primarily on the provision of single-dose intrapartum and neonatal ARV as alternatives to more complex regimens. The first drug to be employed was the NRTI zidovudine (AZT; zidovudine); subsequently NVP became the preferred agent.<sup>12,19–21</sup> The most widely adopted regimen and that initially recommended by the WHO as an ‘absolute minimum,’ is a single dose of NVP given to the mother at the onset of labor and then a single dose given to the infant ≤72 hours postpartum.<sup>9</sup> Owing to the potential for development of resistance, however, the WHO has since modified this guideline to recommend combination ARV treatment as the preferred regimen for the mother where there is the capacity to do so.<sup>22,23</sup> Thus, while single agent treatments are effective in reducing MTCT, the development of affordable

regimens with superior efficacy and tolerability profiles remains an urgent global priority.

## Antiretroviral therapy: mechanism of action

Since high maternal viral load increases the likelihood of MTCT, one of the most effective mechanisms of action is simply the reduction of maternal HIV-1 RNA levels, which in turn lowers fetal prenatal and postnatal HIV exposure from maternal plasma, genital secretions,<sup>24</sup> and breast milk.<sup>25</sup>

Another possible mechanism of protection is pre-exposure of the infant to ARV agents that can cross the placenta which may protect the infant from exposure to a maternal genital tract virus during passage through the birth canal.<sup>26</sup> In addition, postexposure prophylaxis provided through drug administration to the infant after birth would protect against a cell-free or cell-associated virus that might have entered the fetal/infant system during labor through maternal-fetal transfusion during uterine contractions or by the infant swallowing genital tract secretions during passage through the birth canal.

## Antiretroviral therapy in pregnancy

This section reviews the potential toxicity of drugs that may cross the placenta, potential adverse effects that may be exacerbated during pregnancy, potential short- and long-term effects on the fetus and newborn child, and dosing changes that may be required owing to natural physiologic changes during pregnancy (eg, plasma volume expansion,<sup>27</sup> increase in the glomerular filtration rate,<sup>28</sup> and changes in CYP1A2, CYP3A4, and CYP2D6 activity – important enzymes involved in the xenobiotic metabolism).<sup>29,30</sup>

## Placental antiretroviral drug transfer

In mammals, the placenta separates the maternal and fetal circulation systems while ensuring fetal growth and development by transferring oxygen, carbon dioxide, nutrients, and waste products. Transplacental transfer occurs via passive diffusion, facilitated diffusion, active transport, pinocytosis, phagocytosis, and filtration.<sup>31</sup> Of these, the most common mechanism for drug transfer is passive diffusion. Thus, the factors defining Fick’s law of diffusion (eg, membrane thickness, surface area, and the concentration gradient) determine the degree of placental drug transfer. The drug properties that govern the extent of this transfer include: molecular weight, pKa (the pH at which the drug is 50% ionized), lipid solubility, and the affinity of the substance to plasma proteins.<sup>31</sup> In general, compounds with a molecular weight of

less than 500 Da exhibit complete transfer across the human placenta. Nonionized compounds cross the placenta more readily than ionized compounds do and drugs with greater lipophilicity (ie, the ability of a compound to dissolve in lipids and nonpolar solvents). Since most drugs are weak acids or bases, changes in pH affect their ionization and, in turn, lipophilicity and membrane permeability.<sup>31</sup>

Currently, there are eight US Food and Drug Administration (FDA)-approved NRTIs: abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), tenofovir (TDF), zalcitabine (ddC), and AZT. All have molecular weights of around 250 Da, sufficiently small enough to pass through the placenta by simple diffusion. As expected, all have been shown to cross the placenta in the human, monkey, rabbit, rat, and mouse.<sup>32–39</sup> The four FDA-approved NNRTIs: delavirdine (DLV), efavirenz (EFV), etravirine (TMC125) and NVP have molecular weights of 553 Da, 316 Da, 316 Da, 435 Da, and 266 Da, respectively.<sup>40–43</sup> Transplacental transfer of EFV is strongly suspected in humans since case reports of central nervous system malformations in neonates born to women exposed to EFV have led the manufacturer to modify the “pregnancy risk” warning label on EFV.<sup>41,44–46</sup> It has also been reported to cause central nervous system abnormalities in infants born to cynomolgus monkeys.<sup>50</sup> With a molecular weight of 266 Da, transplacental transfer of NVP would be expected and indeed

has been confirmed in humans.<sup>47–49</sup> With a molecular weight of 553 Da, limited transplacental diffusion of DLV would be expected to occur. Table 1<sup>51–64</sup> lists the chemical and physical properties that govern the diffusion of compounds across the placenta of the remaining classes of HIV drugs: PIs, fusion inhibitors, entry inhibitors, and an integrase inhibitor. In addition, the pKa of these compounds indicates that they are weakly basic and thus slightly ionized at physiologic pH, thus further limiting transplacental diffusion.<sup>51–64</sup>

Lipophilicity, which is measured as a partition coefficient or a distribution coefficient ratio, is one of the most important characteristics governing the transfer of drugs through cellular membranes.<sup>31</sup> Generally, the cellular permeability of a compound is directly proportional to its lipophilicity. However, a compound with too high a partition/distribution coefficient is sequestered in the cell membrane (a lipid bilayer), thus reducing its diffusion into the cell. Therefore, highly lipophilic drugs have essentially the same problem as hydrophilic drugs; they have difficulty diffusing through multiple aqueous membrane interfaces necessary to enter the fetal circulation. The ideal partition coefficient for membrane diffusion from studies of the blood-brain barrier is between  $-0.2$  to  $1.3$  (log P, partition coefficient).<sup>62,65</sup> The partition coefficients for the protease, fusion, and integrase inhibitors listed in Table 1 are all outside this range, indicating that these drugs are highly lipophilic and should be trapped within

**Table 1** Chemical and physical properties of HIV protease, fusion, and integrase inhibitors

	Molecular weight (Da)	Partition/distribution coefficients	pKa <sup>1</sup>	Water solubility, pH 7.4	Pregnancy category <sup>2</sup>
<b>Protease inhibitors</b>					
Amprenavir mesylate <sup>3</sup>	505 <sup>54</sup>	3.30 or 4.20 <sup>60</sup>	NR	Low: $\sim 0.06$ g/L <sup>60</sup>	C
Indinavir sulfate	712 <sup>55</sup>	2.90 <sup>63</sup>	5.50 <sup>62</sup>	Low: 0.07 g/L <sup>60</sup>	C
Lopinavir	629 <sup>56</sup>	5.09 <sup>62</sup>	Nonionized <sup>62</sup>	Practically insoluble <sup>62</sup>	C
Nelfinavir mesylate	664 <sup>57</sup>	4.00 <sup>60</sup>	pKa <sub>1</sub> = 6.00 <sup>61</sup> pKa <sub>2</sub> = 11.10 <sup>61</sup>	Very low <sup>61,62</sup>	B
Ritonavir	721 <sup>58</sup>	5.20 <sup>60</sup> 3.99 <sup>62</sup>	pKa <sub>1</sub> = 1.76 <sup>62</sup> pKa <sub>2</sub> = 2.56 <sup>62</sup>	Low: 0.005 g/L <sup>60</sup>	B
Saquinavir mesylate	671 <sup>59</sup>	4.10 <sup>60</sup>	7.00 or 5.50 <sup>60</sup>	Low: 0.004 g/L <sup>60</sup>	B
<b>Fusion/entry inhibitors</b>					
Enfuvirtide	4492 <sup>53</sup>	$-0.875^{53}$	4.6 <sup>64</sup>	Low <sup>53</sup>	B
Maraviroc	514 <sup>52</sup>	NR	pKa <sub>1</sub> = 3.30 <sup>52</sup> pKa <sub>2</sub> = 2.56 <sup>52</sup>	High <sup>52</sup>	B
<b>Integrase inhibitor</b>					
Raltegravir	483 <sup>51</sup>	NR	NR	High <sup>51</sup>	C

<sup>1</sup>pKa, pH at which 50% of the agent is ionized. <sup>2</sup>Category B: drugs that, in animal reproduction studies, fail to demonstrate a risk to the fetus; however, well-controlled studies of pregnant woman have not been conducted. Category C: drugs where safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted. <sup>3</sup>Amprenavir mesylate is no longer commercially available and has been replaced with fosamprenavir calcium, a prodrug of amprenavir.

**Abbreviations:** HIV, human immunodeficiency virus; NR, not reported.

cellular membranes and would be expected to exhibit very limited cross-placental transfer.

The placenta also plays an important role in the synthesis of hormones, steroids, and peptides and facilitates the transfer of nutrients and other physiologic substances via specific transporters necessary for a successful pregnancy.<sup>66</sup> The specificity of these transporters is not strictly limited to physiologic substrates. Xenobiotics (including environmental pollutants, toxins, and therapeutic and nontherapeutic agents) that bear structural similarity to physiologic substrates are also recognized by placental transporters. Thus, although placental transporters can protect the fetus from potential adverse effects of xenobiotics, they also play a crucial role in the transfer of therapeutic agents across the maternal-fetal interface.<sup>66,67</sup>

The placental transporters that carry the widest variety of xenobiotics belong to the adenosine triphosphate-binding cassette (ABC) superfamily of active membrane transporters.<sup>68,69</sup> These include P-glycoprotein (P-gp; eg, multidrug resistant [MDR]1, ABC1), breast cancer-resistant protein (eg, ABCG2), and several members of the multidrug-resistant protein (MRP; eg, ABCC) subfamily, such as MRP1, MRP2, and MRP5 (eg, ABCC1, ABCC2, and ABCC3).<sup>68–71</sup> In the placenta, they prohibit the maternal-fetal transfer of potentially toxic compounds.<sup>68</sup> Of these transporters, P-gp extrudes the widest range of chemically diverse substrates, hydrophobic or slightly charged with average molecular weights of approximately 800 Da for neutral molecules.<sup>72–74</sup> MDR1/P-gp expression in the human placenta has been demonstrated at the protein level,<sup>75</sup> and is located at the apical surface of the syncytiotrophoblast membrane, where it transports substrate from the trophoblast into the maternal plasma and away from the fetal circulation.<sup>68,76</sup>

The substrates of P-gp include anticancer drugs (eg, vincristine, vinblastine, the anthracyclines, etoposide, taxol, and mithramycin), cytotoxic agents (eg, colchicine and emetine), and HIV PIs (eg, nelfinavir [NFV], saquinavir [SQV], indinavir, and ritonavir).<sup>77,78</sup> Chappuy and colleagues<sup>79</sup> confirmed that P-gp plays a major role in limiting penetration of PIs into the fetus. This could be advantageous at early stages of embryonic and fetal development since it reduces exposure to potentially teratogenic drugs at a time when the MTCT of HIV rarely occurs.<sup>80</sup>

Preloading of the infant before birth with an effective anti-HIV drug requires choosing drugs such as AZT that cross the placenta readily.<sup>5,81,82</sup> Placental P-gp is an important factor that limits PI penetration, making PIs unsuitable as

a prophylactic agent.<sup>83,84</sup> Interestingly, according to the product package insert,<sup>52</sup> the fusion inhibitor maraviroc is a substrate for the with an affinity of 35  $\mu$ M (Ki) and, thus is also probably of limited use as a prophylactic to limit the MTCT of HIV. Still, these properties could allow MVC to be effective in reducing maternal HIV viral load while protecting the fetus from exposure to a drug.

## Nucleoside/nucleotide reverse transcriptase inhibitors

Nucleoside/nucleotide reverse transcriptase inhibitors have a small molecular size (~250 Da), can cross the placenta by simple diffusion, and can cause toxic damage to both mother and infant.<sup>85</sup> The most serious side effects associated with this class of drugs are anemia and, when used in combination therapy, lactic acidosis. However, based on pregnancies documented in the Antiretroviral Pregnancy Registry (2008),<sup>86</sup> the most frequently used nucleoside analogs – AZT, 3TC, and d4T – do not increase teratogenicity by more than 2-fold compared to controls. Follow-up of more than 20,000 children who had received AZT prophylaxis did not show any serious adverse effects.<sup>87</sup> An analysis of the causes of death in 223 children who died, within the first 5 years of life, ruled out drug-related causes.<sup>87</sup> In contrast, in a prospective study of 2644 children without infection who had been exposed to HAART,<sup>88</sup> neurologic symptoms with persistent mitochondrial dysfunction were reported in 0.26% versus 0.01% in the general population. Nonspecific changes in cerebral magnetic resonance imaging scans in children perinatally exposed to AZT (plus 3TC)<sup>89</sup> have been interpreted as a sign of neurotoxicity. Twenty-four weeks after combined nucleoside exposure, raised lactate values as well as impairment of hematopoiesis were noted in children.<sup>90</sup> Mitochondriopathies have been observed at least twice in pregnant women taking a combination of d4T/ddI plus NFV or NVP.<sup>91</sup> For these reasons, the combination d4T/ddI therapy is not recommended for use in pregnancy.<sup>5</sup> Hepatic toxicity with hyperbilirubinemia was described in one pregnant woman who died of sudden acute liver failure following the administration of AZT/3TC/NFV.<sup>92</sup>

There is some concern about the effect of administering NRTIs, particularly AZT, during pregnancy. Lower levels of mitochondrial DNA have been found in the placenta and cord blood of HIV-infected women receiving AZT during their pregnancy compared to uninfected women.<sup>93</sup> In another study, infants born to HIV-infected women exposed to AZT during their pregnancy had lower levels of mitochondrial DNA in their peripheral blood leukocytes at one and two



years of age than those born to HIV-infected women who were not exposed to AZT; both had lower levels compared to infants born to uninfected women.<sup>94</sup> Preclinical studies in monkeys showed that offspring receiving perinatal (in utero and for six weeks after birth) exposure to AZT alone as well as double-NRTI combinations (AZT/3TC, AZT/ddI, or d4T/3TC) had skeletal muscle mitochondrial DNA depletion and other abnormalities that persisted for 1 year compared to offspring of monkeys not receiving perinatal drug exposure.<sup>95</sup> The long-term relevance of these findings is not known. Nevertheless, AZT is an important component of the combination therapies used to reduce MTCT.

In animal experiments, tenofovir was not found to have any maternal toxicity but fetal growth was lowered by 13% versus controls and was associated with a slight decrease in bone density.<sup>96</sup> Subsequently, it has been found that long-term use in adults may induce renal toxicity and osteomalacia in some patients.<sup>97</sup> In studies of TDF-containing regimens in pediatric patients, loss in bone mineral density was observed<sup>98</sup> but renal toxicity was not reported;<sup>99</sup> in a third study, renal toxicity was seen in a small number of children.<sup>100</sup> Studies of the use of TDF in regimens to reduce MTCT<sup>101,102</sup> have suggested that it may be helpful in preventing induction of resistance to NVP (reviewed by Foster and colleagues).<sup>103</sup> Currently, the US PHS Perinatal Guidelines recommend use of TDF as a component of combination regimens in pregnancy in the context of coinfection with hepatitis B virus, but otherwise only after consideration of other alternatives.<sup>5</sup>

## Nonnucleoside/nucleotide reverse transcriptase inhibitors

Nonnucleoside/nucleotide reverse transcriptase inhibitors block reverse transcriptase by binding at a different site on the enzyme than NRTIs.<sup>104</sup> The molecular sizes are similar to those of NRTIs and thus are expected to readily diffuse across the placenta. In the prevention of MTCT, NVP has been employed successfully, particularly in combination with AZT or 3TC.<sup>105,106</sup> However, owing to the enhanced risk of liver toxicity during the first 18 weeks of treatment in women with CD4+ T-cell counts of more than 250/ $\mu$ L, patients must be monitored closely, especially during dose escalation.<sup>5</sup> Treatment with NVP in pregnant women is only recommended following very careful assessment of the benefit:risk ratio.<sup>5</sup> Perinatal single- and 2-dose prophylaxis has resulted in the development of drug resistance.<sup>107,108</sup> If a mother gives birth less than 2 hours following the administration of NVP or has not received any prior NVP, the newborn should receive a dose immediately after birth and another

dose after 48 to 72 hours.<sup>47,109,110</sup> Data indicate that there may be clinically significant levels of NVP in plasma for more than two weeks after stopping chronic therapy as well as after a single dose of NVP.<sup>111</sup> Resistance mutations have been identified postpartum in women who received single-dose intrapartum NVP prophylaxis as well as in women who had stopped NVP-containing combination regimens taken during pregnancy for the prevention of MTCT.<sup>112,113</sup> In the latter study,<sup>113</sup> NVP resistance was seen in 13% of women despite the staggered discontinuance of ARV drugs (in which the nucleoside backbone was continued for five days after stopping NVP). Furthermore, in the Perinatal HIV Prevention Trial, women who received a single dose of NVP intrapartum were less likely to achieve virologic suppression at six months, compared with women not receiving intrapartum NVP, suggesting that their responses to subsequent NNRTI therapy were compromised; those that had NVP resistance mutations had an even poorer response.<sup>114</sup> Preliminary data from a South African study<sup>115</sup> suggest that administration of a single dose of NVP combined with AZT/3TC and given intrapartum and then for three or seven days postpartum, may reduce the development of resistance compared with the administration of single-dose NVP.

To our knowledge, there are no published studies reporting on the use (either pharmacokinetics or efficacy) of efavirenz (TMC125), a recently approved drug, during pregnancy. Efavirenz has been reported to cause embryonic toxicity in rhesus monkeys and neural tube defects in humans after first trimester exposure.<sup>45,86,116</sup> Thus, EFV is not used during the first trimester and is used only after the second trimester when there is no alternative treatment option and provided that reliable contraception is then practiced after delivery.<sup>5</sup>

## Protease inhibitors

Protease inhibitors prevent HIV replication by inhibiting the activity of HIV-1 protease, an enzyme used by the viruses to cleave nascent proteins for final assembly of new virions.<sup>117</sup> The transplacental diffusion of agents of this class is partly limited by their molecular weight (Table 1) but most importantly by their affinity for the placental P-gp transporter.<sup>77,79</sup> The use of PIs in combination therapy has been suspected to contribute to increased rates of premature births and malformations.<sup>118</sup> However, this is unlikely owing to the minimal placental transfer of PIs,<sup>119</sup> and any link has not been confirmed by other studies.<sup>120,121</sup> Increases in the incidence of premature births were reported by Thorne and colleagues<sup>122</sup> whereas no increases were reported by Mandelbrot and colleagues<sup>18</sup>

or Tuomala and colleagues.<sup>120,121</sup> In addition, in a study of 233 pregnancies, multiple regression analysis revealed no association between prematurity rate and the individual PIs used or the week of gestation that these drugs were initiated.<sup>123</sup> Nevertheless, owing to possible maternal diabetogenic effects and hepatic toxicity, the use of PIs in pregnancy should be monitored carefully, especially in the later stages.<sup>5,124</sup>

There are two characteristics of PIs that are particularly relevant to their efficacy and tolerability in pregnancy. First, large patient variability in plasma concentrations is a common feature of PIs and second, considerable data indicate that there is a significant association between PI concentration and the virologic response and/or toxicity. Thus, the physiologic changes that occur in pregnancy may lower PI plasma levels below the therapeutic minimum.<sup>125,126</sup> In one clinical study of lopinavir (LPV),<sup>127</sup> exposure in pregnant women resulted in LPV concentrations of about half that measured in nonpregnant adults receiving standard dosing. Further, only 18% of the women studied during the third trimester of pregnancy had LPV area under the curve (AUC) above the 10th percentile for nonpregnant adults and none exceeded the 50th percentile.<sup>126</sup> All but one of the women were fully suppressed at delivery, however, suggesting that the plasma levels of LPV may be superior to anticipated efficacy.<sup>127</sup> Since approximately 99% of LPV is bound to serum proteins,<sup>128</sup> pregnancy-related decreases in this fraction could yield better viral suppression than would be anticipated from total plasma measurements.

Similar results for plasma pharmacokinetics have been reported for NFV.<sup>129</sup> For example, during the third trimester of pregnancy, the mean difference in plasma levels, AUC, and trough concentration in NFV-treated participants was significantly ( $P < 0.01$ ) lower in pregnant compared with nonpregnant women.<sup>129</sup> In contrast, pharmacokinetic studies of SQV in HIV-infected pregnant women reported SQV exposures in excess of the AUC, and AUC did not change significantly during gestation, labor, and delivery.<sup>130</sup> Similar findings were reported from a recent study using the new Invirase® formulation of SQV (Roche Pharmaceuticals, Nutley, NJ).<sup>131</sup> Together these findings suggest that SQV is a strong PI candidate when considering treatment options for pregnant HIV-1-infected patients.

Finally, there have been several case reports, all involving pregnant HIV patients showing multi-drug resistance, of the incorporation of other protease inhibitors in ARV regimens to prevent MTCT. Three of these involved ritonavir-boosted darunavir,<sup>132–134</sup> the other included ritonavir-boosted tipranavir.<sup>135</sup> All births were by cesarean delivery; in none of the cases was there transmission of HIV to the newborn.

Because of their potency and limited transplacental passage protease inhibitors are ideal to be used as strategies for the prevention of MTCT. Providers need to be aware of the different pharmacokinetic issues with the diverse drugs and should choose those with proven efficacy and adequate maternal drug levels.

## Fusion/entry inhibitors

The US Food and Drug Administration has designed a drug toxicity classification system.<sup>136</sup> This system classifies drugs from A to D based on the potential risks to a fetus during pregnancy. Both enfuvirtide (ENF) and MVC are in category B (ie, drugs that, in animal reproduction studies, fail to demonstrate a risk to the fetus; however, well-controlled studies of pregnant woman have not been conducted).<sup>5</sup> What is the likelihood that these drugs will cross the placenta? The molecular weight of ENF is 4492 Da and therefore is too large a molecule to diffuse across the placenta. Still, MVC, with a molecular weight of 514 Da, is likely to exhibit limited transplacental diffusion. Since MVC is a substrate for the efflux transporter P-gp, this limited diffusion should be reduced further to the extent that placental transfer would be minimal.<sup>52</sup> The chemokine coreceptor 5 inhibitor still under development, vicriviroc, has a molecular weight of 557 Da, similar to that of MVC but it has been reported in at least in vitro studies not to be a substrate for P-gp. Thus, vicriviroc should exhibit limited transplacental diffusion.<sup>137–139</sup>

## Integrase inhibitors

Raltegravir (RAL) is the first integrase inhibitor to receive FDA approval. Raltegravir limits the preparatory step that inserts the viral DNA into the exposed regions of the DNA of the host cell. With a molecular weight of 483 Da (Table 1), RAL is likely to partially pass through the placenta, assuming a low affinity for the P-gp transporter.<sup>51</sup> In preliminary animal studies, the drug was found to readily cross the placenta in rats and to a limited extent in rabbits,<sup>5</sup> and it is classified as FDA pregnancy category C (ie, drugs for which safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted). Similarly, the integrase inhibitor elvitegravir, currently under development, has a molecular weight of 448 Da and like RAL should partially pass through the placental, assuming a low affinity for the P-gp transporter.<sup>140,141</sup>

## Nonpharmacologic strategies

A major nonpharmacologic strategy to reduce the MTCT of HIV is elective cesarean delivery before the onset of

labor.<sup>142,143</sup> The effectiveness of elective cesarean delivery probably resides in decreasing the exposure of the fetal circulation to maternal circulation that normally occurs during labor by disruption of the placental barrier. It also avoids direct neonate contact with potentially infected maternal secretions during passage through the birth canal. This is true even if the patient was or was not receiving AZT therapy.<sup>142–145</sup>

Whether scheduled cesarean delivery offers any benefit to women with low or undetectable viral loads is not clear. For women with HIV RNA < 1000 copies/mL, the data are insufficient to determine if MTCT rates would be further reduced by elective cesarean delivery. One retrospective chart review study of 2539 women receiving HAART found a MTCT rate of 1.3%. Women with HIV RNA levels of <1000 copies/mL were reported to have MTCT rates of 0.8% with scheduled cesarean delivery and 0.5% with all other delivery modes.<sup>146</sup> In another report from the European Collaborative Study of 4525 women receiving HAART,<sup>147</sup> the overall MTCT rate was 2.9%. In this study of a subset of 560 women with undetectable HIV RNA levels, scheduled cesarean delivery was associated with a significant reduction in MTCT in univariate analyses ( $P = 0.0004$ ).<sup>147</sup> However, after adjustment for ARV therapy (none versus any), the effect was no longer significant ( $P = 0.36$ ). Very similar results, suggesting the possibility of vaginal delivery in cases of adequate viral suppression, were reported in the study of the French Perinatal Cohort, where elected cesarean section was associated with a lower MCTC risk in the overall population but not among women delivering with viral loads less than 400 copies/mL. Among the 2856 women with viral loads <400 copies/mL, the MTCT rate was 0.6%, and among the 1338 mothers with viral loads <50 copies/mL, the rate was only 0.4%.<sup>148</sup> It should be noted, moreover, that cesarean deliveries carry an additional risk of postpartum morbidity. In a retrospective study of 401 HIV-infected women, the incidence of serious postpartum complications was 12% after emergency cesarean deliveries, 6.4% after elective cesarean deliveries, and 4% after vaginal deliveries.<sup>149</sup> A cohort study of 299 vaginal deliveries, 260 elective cesarean deliveries and 139 cesareans with ruptured membranes in Latin America and the Caribbean showed low morbidity associated to elective cesareans with an unadjusted OR of 1.16 (95% CI: 0.5, 2.7). Morbidity was higher (odds ratio (OR), 2.96; 95% CI: 1.3, 6.7) for those with ruptured membranes or procedures after labor.<sup>150</sup> Taken together, the data from these various reports are not sufficient to confirm or to rule out a benefit from scheduled cesarean

delivery among women with HIV RNA < 1000 copies/mL who are receiving HAART.<sup>147</sup>

The American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice and the Perinatal HIV Guidelines Working Group have issued guidelines for the best route of delivery for pregnant women with HIV infection.<sup>151</sup> For women with HIV RNA levels >1000 copies/mL and who are receiving ARVs, both panels recommend consideration of scheduled cesarean delivery for women near to the time of delivery.<sup>151</sup> For women with HIV RNA levels <1000 copies/mL, the decisions on the mode of delivery should be individualized. German-Austrian recommendations for HIV therapy in pregnancy closely reflect those of the ACOG and the Perinatal HIV Guidelines Working Group.<sup>152</sup> There may be other maternal reasons for the choice of an elective cesarean delivery. The ACOG recommends that patient's autonomy regarding their decision regarding route of delivery must be respected, and ultimately the decision must be individualized according to circumstances.<sup>151</sup>

If the decision is made to perform a scheduled cesarean delivery to prevent MTCT, ACOG recommends that it be done at 38 weeks' gestation as determined by the best clinical and sonographic estimates and to avoid amniocentesis.<sup>151</sup> Unfortunately, in many resource-constrained settings, elective cesarean delivery is seldom feasible.<sup>153</sup> Therefore, in these settings, the efforts to prevent HIV infection in infants are limited to reducing MTCT around the time of labor and delivery, which generally accounts for one-third to two-thirds of overall transmission (depending on whether the mother then breastfeeds).<sup>1</sup>

The other nonpharmacologic method that can reduce the MTCT of HIV is avoidance of breastfeeding. Breast milk, which can carry HIV, can increase the likelihood of MTCT.<sup>25</sup> The highest concentration of HIV per mL of breast milk is found in colostrum, or early milk.<sup>154</sup> It is not clear to what extent breastfeeding influences the efficacy of ARV therapy since only a few trials in breastfeeding populations (all conducted in Africa) report HIV transmission rates beyond 4 to 8 weeks and the results differ by study.<sup>9,155–159</sup> In the HIVNET 012 trial,<sup>157</sup> the initial reduction in perinatal transmission was maintained at 18 months in a breastfeeding population, a finding supported by those in the DITRAME (Diminution de la Transmission Mere-Enfant) trial.<sup>156–160</sup> In contrast, the PETRA (Perinatal Transmission) study<sup>159</sup> examined the efficacy of short-course treatment regimens with AZT and 3TC in a predominantly breastfeeding population and reported that early reductions in HIV infection

rates and HIV infection or mortality at 4 to 8 weeks declined and became statistically nonsignificant by 18 months. A prospective study following 236 infants from birth until 24 months of age born to HIV-positive mothers in Harare, Zimbabwe,<sup>161</sup> reported that breastfed infants had the greatest cumulative relative risk of MTCT of HIV-1, followed by mixed-fed infants, with the highest incidences occurring within the first 3 months. The guidelines established by the Perinatal HIV Guidelines Working Group and the WHO do not recommend breastfeeding for HIV-infected women where safe, affordable, and feasible alternatives are available and culturally acceptable.<sup>5,162</sup>

Where avoidance of breastfeeding is not feasible, however, multiple studies have evaluated the role of ARV prophylaxis in preventing HIV transmission. In the MASHI Study, breastfeeding with a concurrent six months of AZT infant prophylaxis was not as effective as formula feeding with a concurrent one month of AZT infant prophylaxis in preventing HIV transmission to the infants at seven months (9.0% vs 5.6%, respectively); however the formula-feeding regimen had a higher cumulative mortality rate than the breastfeeding regimen (9.3% vs. 4.9%), resulting in comparable HIV-free survival rates at 18 months.<sup>163</sup> In the Mitra Study, in which breastfed infants received daily 3TC for up to six months, the cumulative infection rate, 3.8% at six weeks, increased only to 4.9% at six months.<sup>164</sup> Other studies have examined the efficacy of giving HAART to mothers during breastfeeding. In the single-arm Kisumu Breastfeeding Study in which maternal HAART was continued until weaning at six months and infants received a single dose of NVP at birth, the infant HIV infection rate at 12 months was 5.9%.<sup>165</sup> In the Drug Resource Enhancement against AIDS and Malnutrition (DREAM) program, MTCT rates at six months were 0.8% among breastfed infants of women receiving HAART and 1.8% among formula-fed infants ( $P = 0.38$ ).<sup>166</sup> The AMATA Study compared formula feeding to breastfeeding in women who all received NNRTI-based triple therapy; 1.4% of children were already infected at birth there but there were no additional children infected through breastfeeding.<sup>167</sup> While further work is required, to better define these MTCT rates, these data support the continued administration of HAART to women in contexts where suspension of breastfeeding is impractical.

## Mother and child perinatal/postnatal HIV care: the future

As women comprise a growing proportion of the HIV-infected population, it is important to consider gender-specific,

perinatal, and postnatal issues when assessing treatment options. Different ARV pharmacokinetic profiles in women (relative to men) and in pregnant versus nonpregnant women merit more research to define therapeutic ranges in drug metabolism before and during pregnancy. The maternal and fetal efficacy and toxicity of ARVs remain important concerns for women of childbearing potential and warrant future studies to ensure the safety and long-term well-being of both mother and fetus.

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