Journal of Antimicrobial Chemotherapy (2000) **46**, 657–668

JAC

Reviews

Prevention of perinatal HIV transmission during pregnancy

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Transmission of the human immunodeficiency virus (HIV) from mother to child can occur *in utero*, during labour or after delivery from breastfeeding. The majority of infants are infected during delivery. Maternal HIV-1 plasma viral load at delivery is the most important predictor of vertical transmission. For this reason, efforts to interrupt transmission have focused on the use of antiretroviral therapy. Zidovudine has been shown to reduce significantly vertical HIV transmission when used antepartum and intrapartum by the mother and postpartum by the newborn for 6 weeks. However, zidovudine monotherapy increases the risk of developing zidovudine resistance and may jeopardize the goal of durable viral suppression and allow HIV disease progression in the mother and transmission to the infant. Potent antiretroviral therapy is now recommended for all HIV-infected pregnant women using the same criteria for non-pregnant individuals. If possible, combination antiretroviral regimens should include the use of zidovudine but not at the expense of long-term viral suppression. The use of elective Caesarean section should probably be reserved for women who fail to achieve viral suppression at the time of delivery or if indicated for obstetrical reasons. The practice of breastfeeding has been shown to diminish the long-term efficacy of perinatal antiretroviral therapy. All HIV-infected mothers should avoid breastfeeding the newborn if possible. This review summarizes major prospective and retrospective antiretroviral treatment studies in HIV-infected pregnant women. Pharmacokinetic information as it relates to pregnancy and adverse event profiles of antiretroviral agents are also discussed. The impact of recent advances in the management of HIV infection in pregnancy is discussed with regard to their feasibility in resource-poor countries.

Introduction

The World Health Organization (WHO) has estimated that worldwide 10 million babies have been born infected with the human immunodeficiency virus (HIV).[1] Approximately 600 000 babies were infected with HIV from perinatal transmission in 1999 alone.[2] The developing nations of the world, those with the least available resources, shoulder the lion's share of this burden. These sobering statistics emphasize that the issues of perinatal HIV transmission, in common with most in the current HIV epidemic, differ from country to country. Rates of perinatal HIV acquisition in the industrialized nations have dropped dramatically since 1994 with the widespread use of zidovudine, a nucleoside analogue HIV-1 reverse transcriptase inhibitor (NRTI), during and after pregnancy. The advent of potent antiretroviral combinations and the emphasis on early identification of HIV infection during pregnancy should continue to curtail this aspect of the epidemic. In developing nations, attention has focused on identifying effective, simple, optimally timed and tolerable interventions to benefit the largest number of individuals. The results of these efforts will be of potential broad benefit since they may help to define the time and modes of HIV transmission from mother to child.

The incidence of HIV infection among women in

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resource-rich nations has increased greatly in recent years.[3] The introduction of potent, highly effective antiretroviral therapy (ART) in the mid-1990s has had a profound effect on AIDS mortality, leading to an increase in the prevalence of people living with HIV.[4] The combination of these two trends is likely to result in greater numbers of HIV-infected women choosing to become pregnant.

The Pediatric AIDS Clinical Trials Group Protocol 076 (PACTG 076) demonstrated the effectiveness of ART for prevention of perinatal transmission of HIV.[5] This trial was the proof of principle upon which many subsequent controlled trials and treatment guidelines have been based. The study, conducted in the USA and published in 1994, used zidovudine monotherapy in three parts: (i) prenatally beginning at/after 14 weeks' gestation; (ii) as an iv infusion during labour; and (iii) as chemoprophylaxis for 6 weeks in exposed newborns. Zidovudine use was associated with a significant decrease in perinatal HIV transmission from 25.5% in the placebo group to 8.3%.

The results of PACTG 076 were exciting and, where possible, zidovudine prophylaxis in HIV-infected pregnant women has been widely adopted. However, a number of important issues have evolved with regard to the interpretation and extrapolation of these findings for broader use. First, what aspect of zidovudine activity is responsible for its benefit, and does its reduction of HIV viral load account fully for decreased transmission? If so, more potent combinations, with less potential for viral resistance to emerge, might be expected to do even better. Also, is zidovudine unique among antiretrovirals as a prophylactic agent at reducing perinatal transfer of HIV? If so, does it need to be included in the therapeutic regimen of all pregnant HIV-infected women even if the mother harbours a zidovudine-resistant strain? Secondly, which aspect of prophylaxis (i.e. ante-partum, intra-partum or post-partum) is most critical, and are all components necessary? The answer to this question is important since the estimated cost of the full PACTG 076 course of therapy (approximately US$800) and its complexity restrict the use of this regimen in nations with limited resources.[6] If prophylaxis could be given when its effect would be most profound, more limited intervention might be possible, and hence more individuals could be treated for a given cost. Knowledge of the optimal timing of ART would be helpful also in developed countries since many women present late in pregnancy or at the time of labour. Another issue not addressed by PACTG 076 was the role of breastfeeding on perinatal transmission of HIV and the safety and efficacy of alternatives, such as formula feeds or more extensive post-partum ART. None of the women enrolled in PACTG 076 practised breast-feeding. Lastly, non-ART interventions may affect HIV transmission. Elective Caesarean section, antiseptic washes and vitamin supplementation have been suggested as potentially useful adjuncts to ART.

Risk factors for perinatal HIV infection

The timing of HIV transmission from mother to child has great implication when planning prevention strategies. A number of studies suggest that most (50–80%) vertical transmission of HIV takes place at around the time of birth.[7–10] Interventions used to interrupt transmission at the time of delivery, such as ART given only in late gestation or peri-partum and elective Caesarean section, have been shown to be effective in reducing vertical HIV acquisition.[11,12]

In industrialized nations, perinatal HIV transmission rates without ART range between 14 and 26%, whereas in developing nations the rates range from 21 to 43%.[5,13] Breastfeeding probably accounts for this disparity. Since the risk is not uniform it is important to recognize the factors that affect perinatal acquisition of HIV (Table I).

Maternal plasma HIV viral load appears to be the best predictor of vertical HIV transmission.[7,14,15] Increased rates of transmission occur in pregnant women with primary HIV infection, when plasma viral loads are often at their peak.[16] Little or no HIV transmission occurs with HIV plasma viral loads of <1000 copies/mL, regardless of zidovudine use.[17–19] In the absence of ART, Garcia and colleagues[19] reported perinatal HIV transmission in 21% and 63% of mothers with a mean viral load during pregnancy of <100 000 and >100 000 copies/mL, respectively. Although the maternal viral load at delivery is very useful for determining the risk of transmission, there is no level above which transmission always occurs nor a level below which transmission is never seen.[17–19] Notably, analysis of PACTG 076 data demonstrated that the effect of zidovudine therapy on maternal HIV viral load accounted for only part of its protective effect.[17] Therefore, the role of

Table I. Factors associated with risk of perinatal HIV transmission

Ante-partum	maternal plasma HIV-1 viral load, use of antiretroviral therapy, maternal $CD4^+$ T-lymphocyte count, vitamin A deficiency, HIV co-receptor mutation, malnutrition, illicit drug use, cigarette smoking, chorionic villus sampling, amniocentesis, baseline maternal weight
Intra-partum	maternal cervicovaginal HIV-1 levels, mode of delivery, prolonged membrane rupture, premature delivery, fetal scalp electrode use, active genital ulcer disease, vaginal laceration, chorioamnionitis, episiotomy
Post-partum	breast feeding, mastitis

zidovudine peri-partum may be as post-exposure prophylaxis for the newborn, similar to its action in healthcare workers exposed occupationally to HIV.[8,17,20]

Levels of HIV in maternal genital tract secretions may affect vertical transmission.[21] Elective Caesarean section has been studied as a way of preventing the newborn coming into contact with these infected fluids. Obstetric factors such as rupture of membranes for >4 h, placental abruption, amniocentesis, chorionic villus sampling, use of fetal scalp electrodes, episiotomy, the presence of vaginal lacerations during labour or preterm delivery associated with prolonged membrane rupture, may increase exposure of the fetus to maternal blood and body fluids and have been identified as important risk factors for perinatal HIV transmission.[22–24] The presence of chorioamnionitis or genital ulcers can further increase peri-partum risk of transmission.[15,25–27] Increased cervicovaginal HIV DNA levels are related to low $CD4^+$ cell counts, severe vitamin A deficiency and vaginal discharge.[21] ART has been shown to decrease HIV RNA levels in cervicovaginal lavage and reduce vertical transmission.[28]

Breastfeeding is responsible for most post-partum HIV transmission.[29] It has been estimated that the risk of HIV transmission from breastfeeding is 14% from mothers with established HIV infection and 29% from mothers who acquire HIV after birth.[30] Breast milk HIV viral loads correlate with plasma viral loads and are at their peak during and just after seroconversion. Most HIV infection of the infant from breastfeeding occurs during the first 6 weeks of life, with a lower risk thereafter.[31] Transmission of HIV by breastfeeding is increased in the setting of low maternal $CD4^+$ cell counts, mastitis and prolonged exposure.[32–34] Antibodies to HIV in breast milk are not protective.[35]

T-helper cell responses to HIV-specific antigens in newborns may also play an important role in determining whether infants exposed to HIV in all stages of pregnancy and via breastfeeding will become infected. A recent study of a breastfeeding population in Africa found no HIV transmission to infants in whom there was early development of T-helper cell responses to HIV envelope peptides, whereas there was 17% transmission in those without such a response.[36] The time of development and protective role of these immune responses need further study.

Decreased $CD4^+$ cell counts are a measure of worsening immune deficiency and have been associated with enhanced perinatal HIV transmission.[15] However, a low $CD4^+$ cell count may result from a high viral load and, therefore, may not be an independent risk factor for vertical acquisition of HIV.[15] Vitamin A deficiency and malnutrition can cause immune deficiency and disruption of mucosal integrity and are associated with increased vertical HIV transmission.[37] However, vitamin A supplementation during pregnancy has not provided significant benefit in prevention of perinatal HIV infection.[38,39]

Maternal use of illicit drugs such as cocaine and heroin has been associated with a risk up to three-fold higher of delivering an HIV-infected baby.[40] Cigarette smoking during pregnancy may also increase the risk of transmission.[41] The potential risk from drug use appears to be most pronounced when the proportion of $CD4^+$ cells is high (>29%).[40]

HIV must interact with both $CD4^+$ cells and a chemokine receptor to infect a T-lymphocyte.[42] Recent studies have demonstrated that mutations in these co-receptors or the genes that regulate their expression may render a $CD4^+$ cell more or less vulnerable to infection by HIV.[43–45] Philpott *et al.*[46] studied HIV transmission rates among 552 mother–infant pairs and found no infected babies among those homozygous for a 32 base pair deletion in a chemokine receptor gene (CCR5). Further understanding of the effect of HIV co-receptors on vertical transmission rates is needed.

Antiretroviral therapy to prevent perinatal HIV transmission

Prospective clinical trials

The major prospective clinical trials of ART to prevent perinatal HIV transmission are summarized in Table II. As mentioned above, PACTG 076[5] showed a 68% reduction of vertical HIV transmission with the use of zidovudine in three stages: prolonged antenatal, intra-partum and post-partum dosing. PACTG 185[47] was designed to determine whether HIV-specific immunoglobulin administered prenatally with a single post-partum dose was more effective than zidovudine alone. The protective effect of maternal or passively administered antibody to prevent vertical HIV transmission has been controversial.[48–50] The study demonstrated no benefit from the addition of HIV-specific immunoglobulin. However, the low transmission rate (5%) confirmed the efficacy of zidovudine given as in PACTG 076. This benefit was also observed in women with lower $CD4^+$ cell counts (median 306 cells/mm^3 in PACTG 185 and 550 cells/mm^3 in PACTG 076) and in the 24% of mothers in the study who had zidovudine exposure before pregnancy.

Three studies, one from Thailand and two from Africa (Côte d'Ivoire and Burkina Faso), were designed to determine whether an abbreviated course of zidovudine was effective.[51–53] This approach, if successful, would simplify the regimen and maximize the number of mothers that could be treated. ART was provided at the time of greatest risk of transmission by giving zidovudine only late in the third trimester and intra-partum. The majority of the ART effect was still seen even when short-course therapy was used. The Thai study,[51] in which mothers did not breastfeed, demonstrated *c.* 50% reduction in HIV transmission compared with placebo, while the two African studies,[52,53] in which virtually all mothers breastfed, demonstrated *c.* 38 %

Table II. Major prospective trials of antiretroviral therapy to prevent perinatal HIV transmission (studies listed chronologically)

Study	Site	Breast feeding	Arm (*n*)	Antiretroviral regimen			Transmission	
				ante-partum	intra-partum	post-partum	(%)	*P*
PACTG 076[5]	USA	no	A (205)	ZDV[a] at ⩾14 weeks	ZDV[b]	ZDV[c] for 6 weeks	8.3	0.00006
			B (204)	placebo	placebo	placebo	25.5	
PACTG 185[47]	USA	no	A (230)	as per primary care + HIVIG[d]	ZDV[b]	ZDV[c] + HIVIG[e]	4.1	NS
			B (224)	as per primary care + IVIG[d]	ZDV[b]	ZDV[c] + IVIG[e]	6.0	
Thai[51]	Thailand	no	A (198)	ZDV[f] at ⩾36 weeks	ZDV[g]	none	9.4	0.006
			B (199)	placebo	placebo	none	18.9	
Côte d'Ivoire[52]	Côte d'Ivoire	yes	A (140)	ZDV[f] at ⩾36 weeks	ZDV[g]	none	15.7	0.07
			B (140)	placebo	placebo	none	24.9	
DITRAME[53]	Côte d'Ivoire/ Burkina Faso	yes	A (203)	ZDV[f] at ⩾36 weeks	ZDV[h]	ZDV[f] to mother for 7 days	18.0	0.028
			B (211)	placebo	placebo	placebo	27.5	
PETRA[55]	Uganda/Tanzania/ South Africa	yes	A (359)	ZDV + 3TC[i] at ⩾36 weeks	ZDV + 3TC[j]	ZDV + 3TC[k] to mother and child for 7 days	8.6	0.001
			B (343)	placebo	ZDV + 3TC[l]	ZDV + 3TC[k] to mother and child for 7 days	10.8	0.02
			C (351)	placebo	ZDV + 3TC[l]	placebo	17.7	NS
			placebo	placebo	placebo	placebo	17.2	
HIVNET 012[56]	Uganda	yes	A (302)	none	ZDV[m]	ZDV[n] to childfor 7 days	25.1	0.0006
			B (307)	none	NVP[o]	NVP[p] to child single dose	13.1	

PACTG, Pediatric AIDS Clinical Trials Group; ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine; HIVIG, HIV-specific immunoglobulin; IVIG, HIV-negative immunoglobulin.

[a]ZDV 100 mg po five times per day.

[b]ZDV 2 mg/kg iv × 1, then 1 mg/kg iv every hour in labour.

[c]ZDV 2 mg/kg po every 6 h to child for 6 weeks beginning 8–12 h after birth.

[d]Immunoglobulin dose 200 mg/kg iv every 4 weeks from 20–30 weeks' gestation until delivery.

[e]Immunoglobulin dose 200 mg/kg iv to child within 12 h of birth.

[f]ZDV 300 mg po bd.

[g]ZDV 300 mg po every 3 h during labour.

[h]ZDV 600 mg po once at onset of labour.

[i]ZDV 300 mg po bd; 3TC 150 mg po bd.

[j]ZDV 300 mg po every 3 h; 3TC 150 mg po every 12 h until delivery.

[k]Maternal ZDV and 3TC as in footnote *i*; for child, ZDV 4 mg/kg po every 12 h and 3TC 2 mg/kg po every 12 h.

[l]As in footnote *j* except 600 mg po ZDV dose once at onset of labour to mother.

[m]ZDV 600 mg po at onset of labour followed by 300 mg po every 3 h during labour.

[n]ZDV 4 mg/kg po every 12 h.

[o]NVP 200 mg po × 1 at onset of labour.

[p]NVP 2 mg/kg oral suspension 72 h after birth, with additional dose immediately after birth to any child whose mother did not receive the intra-partum dose or received it <1 h before delivery.

reduced transmission with zidovudine. Although cross-study comparisons are not reliable because of differences in study populations, post-partum transmission via breastfeeding may account for most of the difference in outcome. Indeed, while all HIV-infected children were identified in the Thai study[51] by 2 months of age, in the DITRAME study[53] there was an increase in probability of infection of 2.9% in newborns in the zidovudine arm and 5.7% in the placebo arm between days 45 and 180 of age, which suggests late peripartum or post-partum HIV transmission. Neither the Thai study nor the African one achieved efficacy rates equivalent to those seen in PACTG 076. This difference may be explained by the abbreviated ante-partum exposure to zidovudine and recent data showing that intra-partum zidovudine dosing as used in two of these studies[51,52] (300 mg po every 3 h) provided lower plasma concentrations than the iv zidovudine dosing used in PACTG 076.[54]

The PETRA trial[55] compared HIV vertical transmission rates in pregnant women who received either a combination of two NRTIs, zidovudine and lamivudine (3TC), or placebo. The study had three active arms, A, B and C, in order to identify which components of peri-partum ART were most important. Transmission was lowest in arm A, when all three components of therapy (late prenatal, intrapartum and abbreviated post-partum) were used. Intrapartum therapy alone (arm C) was no more effective than placebo, while intra-partum plus post-partum therapy (arm B) was intermediate in efficacy. Data from PETRA support the use of combination ART in pregnancy. The rate of perinatal HIV transmission with combined zidovudine and lamivudine in PETRA arm B was less than half that of zidovudine monotherapy in a similar population with equivalent drug exposure in the HIVNET 012 trial described below.[53,56] Most infants were breastfed in both studies.

The HIVNET 012 study[56] showed the superiority of nevirapine, a non-nucleoside analogue HIV-1 reverse transcriptase inhibitor (NNRTI), used intra-partum with a single post-partum dose to the newborn, over zidovudine given intra-partum and for 1 week post-partum. In this Ugandan study, nevirapine was 47% more effective than zidovudine at reducing perinatal HIV transmission. Nevirapine has a long elimination half-life, providing appreciable blood concentrations for up to 1 week after administration. The pharmacokinetics of nevirapine allow very simplified dosing to obtain sustained serum concentrations at a low cost (approximately US$4). An earlier study demonstrated a 1.3 log decrease in plasma HIV viral load 1 week after a single 200 mg nevirapine dose, and substantial (60.5% of plasma) concentrations of nevirapine in breast milk at 1 week.[57] In HIVNET 012, the prolonged potent activity of nevirapine enabled a single dose to be given to the newborn under direct observation, whereas the post-partum zidovudine regimen had to be measured out and administered by mothers to the newborn twice a day for 7 days. Therefore, lack of strict adherence to this component of the regimen may have contributed to the superiority of nevirapine over zidovudine. Nevirapine, unlike zidovudine, does not require intracellular phosphorylation to become active against HIV-1 reverse transcriptase. Rapid onset of potent antiretroviral activity may explain the relative advantage of nevirapine over zidovudine initiated once labour has started.[56] In that regard, nevirapine may be useful for HIV-infected women who present in labour without previous ART during pregnancy.

Although the results from HIVNET 012 are promising for resource-poor countries, there are some caveats to the widespread adoption of perinatal nevirapine monotherapy. Nevirapine is metabolized via the hepatic cytochrome P450 enzyme pathway. During the initial 2 weeks of therapy, nevirapine induces the activity of these enzymes and thereby alters its plasma concentration until a steady state is achieved. Therefore, if nevirapine is initiated during pregnancy rather than intra-partum as in HIVNET 012, plasma concentrations of the drug in newborns may not be sustained since autoinduction of fetal hepatic metabolism has already taken place.[58] In addition, HIV easily develops resistance to nevirapine: a single mutation at one of two primary sites in the reverse transcriptase gene (Y181C or K103N) can reduce the antiretroviral activity of nevirapine.[59] Prolonged exposure to low doses of nevirapine during the washout period after a single intra-partum dose has selected for strains of HIV with nevirapine resistance.[60] The development of HIV strains resistant to nevirapine may also compromise drug regimens which contain other NNRTIs, such as efavirenz and delavirdine, as these reverse transcriptase mutations often confer cross-resistance. Therefore, if antiretroviral agents that can be combined with nevirapine are readily available, use of nevirapine alone should be discouraged until further resistance data are reported.

In summary, recent prospective clinical trials indicate that: (i) for ART to be effective in prevention of perinatal HIV transmission, it should be started at or before the onset of labour; (ii) breastfeeding can lead to a decrease in response by allowing post-partum transmission to occur; and (iii) combination therapy is superior to monotherapy.

Retrospective clinical trials

A retrospective review of zidovudine use by HIV-seropositive pregnant women in New York State, USA, after the publication of PACTG 076 revealed that, in clinical practice, adherence to the full protocol was often incomplete.[11,61] The rate of HIV transmission was 6.1% if therapy was started prenatally, 10.0% if initiated intra-partum, and 5.9% when begun in the newborn within 12 h. However, if zidovudine treatment was begun >48 h after birth, the rate of HIV transmission was 18.4%, which did not differ significantly from the rate in untreated newborns (26.6%). Therefore, as shown in studies conducted in the developing world, an abbreviated peri-partum course of zidovudine retains some of the protective effect of the full PACTG 076

regimen. The efficacy of ART initiated as soon as possible (within a few hours) after birth stresses that a significant proportion of its effect is as 'post-exposure prophylaxis'; it essentially aborts an infection when a less diverse virus population is present in small numbers and before it can become established in the newborn.[16,62]

Highly active antiretroviral therapy (HAART), composed of three or more agents including either an HIV-1-specific protease inhibitor or NNRTI, is the current standard of care for treatment of HIV infection.[63,64] The most recent guidelines of the USA Public Health Service Task Force recommend a similar approach for the treatment of HIV infection in pregnancy.[65] This strategy will lead to maximal viral suppression, more durable efficacy of therapy, delayed development of drug resistance and preserved maternal options for future therapy. Perinatal transmission of ART-resistant HIV has been documented.[66] The prevalence of these resistant strains is expected to rise with widespread use of combination therapy and its requirement for strict dosing adherence. As the HIV epidemic advances in women, the potential for increased transmission of drug-resistant virus from mother to child will increase, especially if zidovudine monotherapy is the preferred perinatal regimen. Genotypic or phenotypic viral resistance testing may help guide choice of therapy in newborns as well as in pregnant women who are failing ART or naïve to therapy with recent infection in areas with a high prevalence of resistant HIV.[67]

The use of HAART in pregnancy has been reported in a number of small series.[68–70] Low rates (<2%) of perinatal HIV transmission have been observed in >200 pregnant women so treated. We have published outcomes of 30 pregnant HIV-infected women with advanced disease treated with combination ART (including 13 with protease inhibitors) in New York.[68] The women had a median $CD4^+$ cell count of 285 (56–1100) cells/mm^3, 53% had AIDS, 37% had evidence of active illicit substance use and 67% had previous ART exposure. None of the 28 infants was infected with HIV (one was lost to follow-up, and one was stillborn). Prospective clinical trials of regimens containing protease inhibitors are in progress. While results of these studies are pending, careful monitoring and reporting of adverse events while on combination therapy and maintenance of antiretroviral pregnancy registries will assist practitioners in making decisions with their patients regarding optimal HIV treatment during pregnancy.

Pharmacokinetic considerations of antiretroviral therapy in pregnancy

Maternal weight may alter the effectiveness of antiretroviral drugs during pregnancy.[71] In a substudy of PACTG 076, in which maternal weight was divided into quartiles, it was found that zidovudine use reduced transmission less well in the heaviest women (26% for women >82 kg) than in those in the other three quartiles (79% effective).[71] This discrepancy in efficacy may have been a result of weight-related differences in the volume of distribution of zidovudine with altered plasma (and potentially intracellular) concentrations. Fetal concentrations of zidovudine may also depend on on maternal weight since placental transfer of zidovudine is dependent on passive diffusion from the mother.[71] Pharmacokinetic studies of ART concentrations during pregnancy are needed to elucidate the potential need for dosing modification based on maternal weight as well as pregnancy-related changes in hepatic drug metabolism, serum protein concentrations, drug absorption and clearance of drug by the placenta and fetus. Before changing dosing, one must consider the potential of increased drug-related toxicity.

Safety of antiretroviral therapy in pregnancy

Exposure of the fetus to antiretroviral agents may have long-term complications. Fetal contact with these agents during the first trimester may occur inadvertently with increased frequency as more HIV-infected women are maintained on combination regimens. More data are needed to establish the safety of these agents to meet the dual goals of protecting the fetus from HIV and avoiding potential late morbidity in those children born uninfected. The most recent interim report from the Antiretroviral Pregnancy Registry in the USA found no increase in birth defects or any specific pattern of birth defect associated with antiretroviral use either with or without first trimester exposure during 860 pregnancies.[72] This report included data from 140 pregnancies in which protease inhibitors were used and 19 that included NNRTIs. However, reports from registries such as this are limited because of potential inconsistencies in practitioner reporting, incomplete data and lack of long-term follow-up. Any fetus being exposed to antiretroviral agents should be closely monitored for adverse effects by fetal sonography.

Animal studies have not provided conclusive evidence of specific teratogenicity or carcinogenicity of antiretroviral drugs. All NRTIs cross the placenta in human or animal studies.[65] Zidovudine has been associated with non-invasive vaginal tumours in rats and mice after prolonged exposure to high doses.[73] Zalcitabine has inhibited normal lymphocyte function and caused thymic lymphomas and hydrocephalus in rodents.[65,73] Animal teratogenicity studies with stavudine have been negative, except that decreases in bone calcification have been found in rodents.[65] High doses of abacavir have led to anasarca and skeletal malformations in rats.[65]

Efavirenz, an NNRTI, is not recommended for use during pregnancy because of its association with fetal malformations, including anencephaly, anophthalmia and cleft palate, in cynomolgus monkeys exposed *in utero*.[74] Delavirdine, another NNRTI, has caused ventricular septal defects in rodents.[65] Use of indinavir, a protease inhibitor, can lead to indirect hyperbilirubinaemia, which may have adverse

effects in newborns.[73] Cryptorchidism in rodents has been noted with ritonavir.[65] Amprenavir, a protease inhibitor licensed recently for use in the USA, has been associated with low body weight, bone ossification defects and thymic abnormalities in rabbits and rats.[65]

Animal teratogenicity studies on other available drugs [NRTIs (didanosine, lamivudine), an NNRTI (nevirapine) and protease inhibitors (saquinavir, nelfinavir)] are negative. Teratogenicity studies in humans are not available for any of the currently available antiretrovirals. Long-term animal carcinogenicity studies are chiefly incomplete.

Pregnant women are prone to hyperglycaemia and some develop frank gestational diabetes. Protease inhibitors have been linked with degrees of glucose intolerance, ranging from mild hyperglycaemia to ketoacidosis,[75] so, pregnant women receiving combination therapy with a protease inhibitor should be monitored closely for signs and symptoms of elevated glucose.

The Swiss Neonatal HIV Study reported the outcome of 37 women treated with combination ART: 21 with dual NRTI therapy and 16 with regimens including a protease inhibitor.[76] Twenty-nine of the 37 women had some adverse event reported, chiefly anaemia (in 42%) associated with the combination of zidovudine and lamivudine. The most common adverse neonatal outcome was prematurity below 37 weeks' gestation in 33%, which differed significantly from the rates seen in the same population with zidovudine monotherapy (17%) and those who received no ART (14%). One case of extrahepatic biliary atresia in an infant exposed to indinavir was considered to be possibly drug related. Our experience with 30 HIV-infected pregnant women in New York on combination ART, including 13 taking protease inhibitors, demonstrated fewer adverse outcomes than the Swiss cohort.[68] Maternal complications included four cases of hypertension, one of gestational diabetes and one exacerbation of chronic hepatitis C. Newborn adverse events included one stillbirth, one case of microcephaly and five infants weighing <2500 g, including the only two babies (7%) born prematurely. Median birthweight was not affected by maternal protease inhibitor use. Preliminary data from a large review of perinatal ART use by 462 women in the USA in which 25% received zidovudine monotherapy, 36% protease inhibitor-containing regimens and 70% combination therapy revealed no association of protease inhibitor use with prematurity, low birth weight, stillbirth or malformation.[70]

Of concern is a recent French report of possible mitochondrial toxicity related to zidovudine and lamivudine combination therapy.[77] Significantly higher concentrations of zidovudine are required to inhibit human DNA polymerases than HIV RNA-dependent DNA polymerase; however, mitochondrial DNA polymerase γ may be inhibited at concentrations near those achieved with standard zidovudine dosing.[78] Cardiac and hepatic tissue may be affected disproportionately, because of their high mitochondrial content.[73] The French report[77] noted that of 1754 children exposed to perinatal ART (mostly zidovudine), five developed late (4–14 months of age) neurological symptoms (two of these five died) and three were asymptomatic but had elevated lactate and/or liver/pancreatic enzyme abnormalities; none was HIV infected. The atypical and varied presentations of these cases raise doubts about the causative role of mitochondrial toxicity.[79] A recent American review of NIH and CDC databases of the children of >20 000 HIV-infected mothers revealed no deaths attributable to mitochondrial toxicity among those exposed perinatally to NRTI and HIV uninfected.[80] Further information is required before recommendations can be made about mitochondrial toxicity and perinatal ART use.

General principles of antiretroviral therapy use during pregnancy

Screening for HIV infection should be done as early as possible in pregnancy to enable women to make informed decisions about ART use to reduce the risk of HIV transmission. In making the decision to initiate ART in any individual, one must balance the benefits (e.g. undetectable HIV viral load, immunological improvement, reduced AIDS-related events) with the risks (e.g. adverse events, effect on daily activities, incomplete viral suppression and development of drug resistance). In the HIV-infected pregnant woman, this decision takes on added significance as both the medical provider and the mother have to consider the effect of therapy on the baby. The short-term effect on the newborn of *in utero* antiretroviral drug exposure has been studied, but long-term consequences remain unclear. HIV-seropositive pregnant women should be provided with information on the use of antiretroviral drugs in pregnancy and counselled on its significance.

HIV-infected pregnant women who are not currently on ART should start therapy after the first trimester (14 weeks' gestation) based on the same criteria and guidelines used for non-pregnant patients.[65] For example, consideration is given to the woman's willingness to start therapy, her HIV viral load, $CD4^+$ cell count, and history and future risk of opportunistic infections. A major goal of HIV therapy in pregnancy is to improve maternal health by providing durable suppression of HIV while maintaining future therapeutic options. Combination ART is usually required to achieve this outcome. Zidovudine, if appropriate (based on previous antiretroviral exposure, drug resistance testing or tolerability) should be part of maternal therapy. Regardless of zidovudine use before birth, zidovudine should be given during labour and included in the regimen of the newborn. Combination therapy with zidovudine, lamivudine and/or nevirapine may also be considered for intrapartum use, especially in HIV-infected women who present in labour. If therapy is interrupted at any time during pregnancy, all antiretrovirals should be started and stopped together. Women already on ART who present during the

first trimester may choose either to continue or to stop therapy and restart at 14 weeks' gestation after a discussion of risks and benefits.

Potential drug interactions between non-HIV drugs and antiretrovirals, such as the reduction in methadone concentrations with nevirapine, should be taken into consideration because of their possible effect on efficacy and adherence. Appropriate prophylaxis of HIV-related opportunistic infections[81] should be provided to HIV-infected pregnant women.

Strategies to prevent perinatal HIV transmission without the use of antiretroviral therapy

Since the majority of HIV transmission appears to occur near or at the time of delivery when fetal exposure to maternal body fluids is most likely, elective Caesarean section may be a way of reducing risk.[82] A meta-analysis of 15 prospective studies of Caesarean section to prevent vertical HIV transmission was published recently.[82] The results, corrected for use of ART, stage of maternal HIV disease and newborn birthweight, indicate that elective Caesarean section before the onset of labour and membrane rupture reduced the risk of mother–infant transmission of HIV by almost 50% when compared with non-elective Caesarean section or vaginal delivery. Studies in France and Switzerland suggested that elective Caesarean section provided additional benefit to zidovudine in reducing HIV transmission.[83,84] The European Mode of Delivery Collaborative Study[12] supported the finding of lower risk of transmission with the use of elective Caesarean section, although the effect was most pronounced when zidovudine was not used (6.8% for elective Caesarean section compared with 18.9% for other modes) than with zidovudine use (2.1% compared with 3.3%). Maternal plasma viral load at the time of delivery was not reported in these studies. Towers *et al*.[85] described reduced perinatal transmission of HIV without zidovudine use if a technique called 'bloodless Caesarean section' was performed instead of routine Caesarean section or vaginal delivery. However, use of zidovudine alone achieved a reduction in HIV transmission comparable to that achieved with bloodless Caesarean section without zidovudine.[85] The use of more potent combination ART may further diminish the potential advantage of elective Caesarean section.[82] HIV-infected women are more likely to have surgical complications than seronegative women.[86] In addition, in developing countries, post-operative infections are more likely to occur, so the routine use of Caesarean section to prevent vertical HIV infection may not be of overall benefit.[82]

The use of antiseptic vaginal and cervical washes has been suggested as an inexpensive way to reduce potential viral exposure to newborns during delivery. Chlorhexidine has had widespread use as a disinfectant and can inhibit HIV viral replication *in vitro* at concentrations of 0.2%.[87] A clinical trial in Africa of 0.25% chlorhexidine for vaginal and newborn washing did not reduce HIV transmission, however.[88] Studies are under way to assess the benefit of chlorhexidine at higher concentrations.[8]

Screening and treatment for genital ulcer diseases, such as syphilis, in HIV-infected pregnant women can be of dual benefit to the newborn by reducing the risk of acquiring the sexually transmitted disease as well as transmission of HIV.[27]

In industrialized countries, HIV-infected women are strongly discouraged to breastfeed to prevent post-partum transmission of HIV. The widespread applicability of such an approach in developing countries is more problematical. Nduati and colleagues[89] conducted a randomized clinical trial in Kenya comparing the incidence of infant HIV infection and mortality in the first 2 years of life in breastfed and formula-fed infants. There was significantly more infant HIV-1 infection in the breastfeeding arm (cumulative probability of HIV infection of 36.7%) than in the formula-fed arm (20.5%). Most mother–child HIV transmission from breastfeeding was noted in the first 2 months of infant life. Since significant numbers of women (30%) in the formula group breastfed at least once, the rate of breast milk transmission of HIV was likely to be even higher. There are tremendous societal pressures for women to breastfeed in developing countries. Women who choose to feed with formula face the risk of being ostracized, because it may be seen as a sign that they are HIV infected. Although HIV transmission rates were strikingly different in the two groups, the 2 year mortality rate was 20% with formula and 24.4% with breastfeeding ($P = 0.3$).[89] If formula feeding is to be substituted for breastfeeding in HIV-infected women in the developing world, then it is essential that: (i) clean water is readily available; (ii) formula feeds are affordable; (iii) social support networks exist for women who use formula; and (iv) treatment for diarrhoeal diseases can be freely administered.

Conclusions

Therapeutic strategies for HIV infection in pregnancy must be planned with three goals in mind: (i) to maximize prevention of HIV transmission to the greatest proportion of newborns; (ii) to utilize ART that will be potent and durable to prevent HIV disease progression and development of drug resistance in the mother; and (iii) to time ART optimally for the minimum exposure necessary to provide both safety and efficacy. Early identification of HIV infection in the mother is important to maximize maternal options and allow optimal timing of therapy. The role of adjunctive therapies, such as elective Caesarean section, vitamin supplementation and antiseptic washes, requires further study. Understanding the risk factors which underlie mother–infant HIV transmission may lead to development of novel approaches that may be applicable

for large-scale, inexpensive deployment. Long-term follow-up of perinatally ART-exposed children and heightened vigilance for morbidity are essential.

Whilst tremendous progress has been made in this aspect of the HIV epidemic, much more work is needed not only to protect infants from infection with HIV but to ensure that they remain healthy after interventions, and to provide access to treatment for their parents so they will not be orphaned. This will require planning and the expenditure of resources with the same dedication that is deployed to wage military wars.

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Received 20 March 2000; returned 22 June 2000; revised 7 July 2000; accepted 20 July 2000