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Current Treatment Strategies, Complications and Considerations for the Use of HIV Antiretroviral Therapy during Pregnancy

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Abstract

The global prevalence of HIV infection in the female population presents a significant healthcare burden in terms of mother-to-child transmission (MTCT) of the disease. This review aims to discuss current trends and treatment guidelines for the use of antiretroviral therapy during pregnancy and associated complications in this population. Historically, antiretroviral monotherapy with zidovudine was commonly used for preventing MTCT, and monotherapy with single-dose nevirapine is still used for prevention in resource-limited settings. Evidence suggests that combination therapy with HAART is a more effective treatment option than monotherapy when managing HIV in pregnant women. Current treatment guidelines recommend the use of HAART with a protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTI) as first-line therapy for the management of HIV infection in pregnant women and for preventing MTCT. Complications associated with the use of antiretroviral therapy during pregnancy should be taken into consideration when selecting a new antiretroviral regimen, or when continuing certain antiretroviral regimens in HIV-infected women who become pregnant while on therapy. NNRTI have been associated with severe and sometimes fatal hepatoxicity in some pregnant women and potentially teratogenic side effects in the fetus, and their use raises concerns regarding the development of drug- and class-resistant mutations. PI-based HAART has been associated with an increased risk of adverse effects such as premature delivery, low birth weight, dyslipidemia, glucose intolerance, and lipodystrophy. Despite this, initiating antiretroviral therapy with a PI plus two NRTI may become the preferred treatment option in pregnant women. Many of the side effects associated with PI were more prevalent when older PI and PI-based regimens that included those in combination with thymidine analog NRTI were used. An individual's history and baseline clinical and laboratory parameters should also be taken into consideration when choosing the most appropriate antiretroviral regimen during pregnancy. **(AIDS Rev. 2011;13:198-213)**

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Key words

HIV. Pregnancy. Antiretroviral therapy. Efficacy. Tolerability. MTCT.

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Introduction

In addition to the burden of disease for women themselves, the global prevalence of HIV infection in the female population has a significant impact in terms of mother-to-child transmission (MTCT) and presents an additional healthcare burden in terms of an ever-increasing population of HIV-infected individuals. Approximately half of the people living with HIV/AIDS worldwide are women, and women account for ~ 60% of HIV-infected individuals in sub-Saharan Africa[1]. Most HIV-infected women are of child-bearing age, and many are sexually active and express a desire to have children[2-4]. There are an estimated two million HIV-infected children (i.e. < 15 years of age) worldwide, almost 90% living in sub-Saharan Africa[1]. Approximately 90% of children acquire HIV either during pregnancy, at birth, or through breastfeeding[1], all of which represent preventable routes of transmission. Advances in antiretroviral (ARV) therapy (ART) have increased the life expectancy of perinatally infected HIV-positive children, presenting a new population of adults with a distinct natural history of the disease[5]. Additionally, 45% of new horizontally transmitted infections worldwide are in young people (aged 15-24 years) of child-bearing age[1]. Both of these populations are likely to be sexually active and to have a desire to have children.

When providing ART to pregnant women, the primary goals are to maintain viral suppression in the mother, keeping both her and the baby healthy, and preventing MTCT (PMTCT) of HIV without jeopardizing future treatment options for the mother and her infant. Without ART, as is often the case in resource-limited settings, the risk of MTCT ranges from 20 to 50%[6] and depends on the clinical status of the mother, i.e. whether or not she is virally suppressed or in advanced stages of the disease, and whether or not the child is breastfed. As a result of early diagnosis of HIV and the subsequent provision of adequate combination ART and effective multidisciplinary perinatal intervention, MTCT rates have been reduced to < 2%, particularly in developed countries[7,8], although the risk of MTCT increases in infants who are breastfed[9].

There are special factors to consider when treating HIV infection in pregnant women. Women undergo specific physiological changes during pregnancy that can significantly impact ARV pharmacokinetics. Pregnancy may lead to reduced plasma levels of protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI) in the mother and/or infant, often requiring higher doses to achieve the same pharmacokinetics that are observed in non-pregnant HIV-infected individuals[10-15]. Pregnant women are also likely to experience changes in their gastrointestinal function, such as nausea and vomiting, which can affect drug absorption and resulting efficacy. Higher rates of development and transmission of viral drug resistance have been associated with the use of nevirapine (NVP)[16-18] or nelfinavir (NFV)[18], and may be linked to the interruption of ARV after delivery, and to the passage of ARV agents from the mother to the child via breast milk[18]. Adverse effects of ART for both the mother and child must also be taken into consideration.

There are few adequate, well-controlled trials of ART in pregnant women. Thus, publications on this topic are generally confined to retrospective reviews, or are based on studies with small numbers of patients or subpopulations of larger cohort studies, and have often produced conflicting results. In recent years, a more concerted effort has been made to analyze the efficacy and safety of ART in pregnant women. This review focuses on current trends and treatment guidelines for the use of ART in pregnant women and complications associated with HIV during pregnancy and postpartum.

Antiretroviral therapy during pregnancy: monotherapy versus combination therapy

Historically, ARV monotherapy was commonly used in PMTCT. The use of a three-part regimen of zidovudine (ZDV) monotherapy rapidly became standard practice in the 1990s when it was shown to reduce the risk of MTCT by 67.5% in women with $CD4^+$ cell counts > 200 cells/mm^3 [19]. In Western cohorts, perinatal MTCT has declined significantly since the implementation of ZDV prophylaxis[20]. The protective effect of ART against MTCT increases with the complexity and duration of the regimen, with combination ART or highly-active ART (HAART) – defined as two NRTI plus a PI or a nonnucleoside reverse transcriptase inhibitor (NNRTI) – providing significantly better protection against MTCT than ZDV monotherapy[7]. Prenatal treatment with ZDV in combination with other ARV can reduce MTCT to ~ 3%, whereas ZDV monotherapy given prenatally, intrapartum and/or neonatally has been associated with higher MTCT rates ranging from 6-14%[19,21]. Zidovudine monotherapy does not sufficiently reduce HIV RNA viral load[22], which is the most important risk factor for MTCT[7]. The majority of vertical infections occur at or near delivery, and higher viral loads at > 28 weeks gestation and peripartum have been associated with significantly

increased rates of MTCT compared with viral loads of < 1,000 copies/ml[23]. In the current US recommendations for the use of ARV drugs in HIV-infected pregnant women, the use of ZDV prophylaxis alone is controversial, but may be considered in combination with Cesarean section for women with plasma HIV RNA levels < 1,000 copies/ml who are not on therapy[24]. The 2008 version of the British HIV Association Guidelines for the Management of Pregnant Women still considers ZDV monotherapy as an alternative approach in women who do not require treatment for themselves and who repeatedly have a viral load < 10,000 copies/ml[25]; it should be combined with Cesarean section at 38 weeks, with ZDV infusion commencing four hours prior to the section. There is, however, no recommendation for ZDV monotherapy in the 2009 revised version of the European AIDS Clinical Society (EACS) guidelines[26].

Current treatment guidelines for antiretroviral therapy in pregnant women

The key recommendations from current treatment guidelines for managing HIV infection in pregnant women are summarized in table 1[24,26-28]. Although there are differences between the guidelines for different regions and between developed and developing nations, in general the key recommendations are similar. Not surprisingly, HAART is the predominant recommendation for treating HIV-infected pregnant women in developed and developing countries. The US and European guidelines both recommend that pregnant women should be treated with HAART consisting of two NRTI plus a either a PI or a NNRTI[24,26]. Nevertheless, the US guidelines emphasize that NVP should not be initiated in women with $CD4^+$ cell counts > 250 cells/mm^3 [24], whereas the European guidelines recommend that NVP should only be used if it was initiated before pregnancy[26]. For developing nations, current WHO guidelines recommend first-line therapy with NVP plus two NRTI[27,28]. In ART-naive women who become pregnant, treatment initiation and choice of regimen should be based on recommendations for non-pregnant individuals, although women in their first trimester may wish to delay ART until 10-12 weeks' gestation. In women who are already on ART and who become pregnant, it is recommended that they continue with their current regimen unless efavirenz (EFV) is being used, which is contraindicated due to risks of teratogenicity[24,26-28]. In asymptomatic pregnant women or in those with $CD4^+$ cell counts ≥ 350 cells/mm^3, ART should be started between 14 and 28 weeks of gestation[26]. Exposure to viral loads > 1,000 copies/ml in the first 28 weeks of pregnancy has been shown not to be associated with an increased risk of MTCT[23]. Temporary discontinuation of HAART during the first trimester has also been shown to have no significant impact on the rate of HIV infection in newborns or on long-term maternal immunologic or virologic outcomes[29,30].

The US guidelines recommend that women with nadir $CD4^+$ cell counts < 350 cells/mm^3, or with symptomatic HIV infection, should be encouraged to continue HAART with no interruption in treatment postpartum. For women with a nadir $CD4^+$ cell count ≥ 350 cells/mm^3 when they began ART for PMTCT, the decision on whether to continue HAART postpartum should be made in consultation with her clinician and should take into account current and nadir $CD4^+$ cell count, viral load, and patient preference[24]. However, treatment interruption in pregnant women after delivery is controversial as there are no large well-controlled studies on the risks/benefits of interrupting therapy after short-course ART. While data from the PACTG 076 and PACTG 185 studies did not suggest harm from short-term use of ZDV for PMTCT or from stopping ZDV monotherapy at delivery[31,32], recent data from studies comparing scheduled treatment interruptions versus continuous therapy in non-pregnant adults have suggested that stopping HAART may be detrimental. Several small studies have not suggested harm from scheduled treatment interruptions, although all of these studies showed lower $CD4^+$ cell counts in treatment interruption groups by the end of the study[33-35]. In contrast, others have shown significantly increased morbidity with treatment interruption (15.2/100 person-years) versus continuous therapy (6.7/100 person-years; RR: 2.27; 95% CI: 1.15-4.76)[36]. The SMART study, which enrolled subjects with $CD4^+$ cell counts ≥ 350 cells/mm^3, is the largest randomized trial to date (n = 5,472), where patients either continued therapy or had therapy interrupted; for those who interrupted therapy, treatment was reinstated when the CD4 count was < 250 cells/mm^3. The rate of opportunistic disease or death was significantly higher in the interruption group (3.3/100 person-years) versus the continuous therapy group (1.3/100 person-years; HR: 2.6; 95% CI: 1.9-3.7). In addition, the hazard ratio for major cardiovascular, renal and hepatic disease was 1.7 (95% CI: 1.1-2.5) for the interruption versus continuous therapy group despite less time on ART, and was associated with rapid changes in inflammatory and coagulation markers, factors that may influence the risk of various end organ damage[37]. Studies of drug interruption after a short course of ART in pregnant women are, however, limited.

Table 1. Current treatment guidelines for managing HIV infection in pregnant women

	2010 US Public Health Service Task Force Guidelines[24]	European AIDS Clinical Society (EACS) 2009 Guidelines[26]	WHO 2008/2009 Guidelines[27,28]
Objective(s)	– Effective viral suppression – Restoration/preservation of immune function – Behavioral modification – Reduction/elimination of at-risk behaviors	– Full viral suppression by third trimester and specifically at time of delivery	– All pregnant women with indications for ART should receive ART to address their own health and well-being and to reduce the risk of MTCT, particularly those who are at an advanced stage of disease
When to start	a) Women on HAART who become pregnant: continue current successful HAART; avoid use of EFV in first trimester b) ARV-naive women who require ART: initiate HAART (including in first trimester if needed) c) ARV-naive women who do not require ART: consider delaying HAART till second trimester d) ART-experienced women not currently on HAART: initiate HAART with regimen based on resistance testing results and prior ART	a) Woman already on ART while becoming pregnant should maintain ART but switch drugs that are potentially teratogenic b) For ARV-naive women with CD4$^+$ cell count < 350 cells/mm^3 or HIV RNA threshold > 100,000 copies/ml, starting ART in second trimester is considered optimal c) ARV-naive women who do not fulfill criteria for ART (i.e. CD4$^+$ cell count ≥ 350 cells/mm^3) should start at week 28 d) ARV-naive women presenting after week 28 of pregnancy should start ART immediately	Criteria are the same as for non-pregnant women and ART should be started in all women with: a) Clinical stage 3 or 4 disease irrespective of CD4$^+$ cell count b) Clinical stage 1 and 2 and a CD4$^+$ count < 200 cells/mm^3
What to start with	2 NRTI* + PI† or 2 NRTI* + NNRTI‡ – Three-part ZDV therapy should be prescribed for all HIV-infected pregnant women regardless of HIV RNA viral load as well as women requiring ART (ZDV alone may be considered in cases where viral load is < 1,000 c/ml on no therapy) – Scheduled cesarean in all cases if HIV RNA threshold > 1,000 c/ml	2 NRTI§ + PI¶ or 2 NRTI§ + NNRTI** – ZDV should be part of the regimen if possible	Preferred first-line: NVP + ZDV/3TC or TDF/3TC or FTC+ NVP – Triple NRTI or a PI-based ART are recommended alternatives where an NNRTI is contraindicated – EFV is an alternative to NVP for women in the second or third trimester only

ARV: antiretroviral; ART: antiretroviral therapy; 3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/ritonavir; EFV: efavirenz; FTC: emtricitabine; IDV/r: indinavir/ritonavir; LPV/r: lopinavir/ritonavir; NRTI: nucleotide reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; NVP: nevirapine; PI: protease inhibitor; SQV/r: saquinavir/ritonavir; TDF: tenofovir; ZDV: zidovudine; MTCT: mother-to-child transmission.
*Recommended agents: ZDV and 3TC; alternate agents: ABC, ddI, TDF, FTC.
†LPV/r is the only recommended PI for pregnant women, whereas ATV/r, IDV/r and SQV/r are alternative boosted PI.
‡NVP should generally not be initiated in women with CD4$^+$ cell count > 250 cells/mm^3 (only if benefits outweigh risks of hepatotoxicity); EFV is not recommended for use in first trimester or in sexually active women who are not using effective contraception.
§ABC and TDF not to be initiated, but continuation is possible if started before pregnancy.
¶LPV/r, ATV/r or SQV/r are preferred.
**NVP not to be initiated, but if started before pregnancy, continuation is possible; EFV to be avoided.

Although currently there are no controlled studies to support postpartum interruption of HAART, an observational study of short-term ART for PMTCT in pregnant women who presented with CD4+ cell counts ≥ 300 cells/mm^3 did not show faster progression to AIDS[38]. The PROMISE (Promoting Maternal and Infant Survival Everywhere) study is a large, multicenter, international trial that is currently recruiting patients and aims to determine whether pregnant women with a CD4+ cell count ≥ 350 cells/mm^3 who receive HAART for PMTCT will be healthier if they either continue or stop HAART after delivery[39]. If women who become pregnant but do not meet current guidelines for initiating HAART derive significant benefit from HAART for PMTCT, then it will be important to reassess standards of care in many parts of the world. Alternatively, if women who receive HAART for PMTCT incur some penalty in terms of their own health, this may offset any benefits of a maternal HAART strategy for PMTCT. If continuing HAART at the end of the PMTCT intervention is associated with reduced morbidity, these data will add to the growing body of evidence suggesting that earlier HAART has benefits. The PROMISE study design provides an opportunity to address several of these questions regarding optimal use of ART among childbearing HIV-infected women.

Antiretroviral safety

Preterm delivery, low birth weight, and pre-eclampsia

Studies have suggested that preterm delivery (PTD) is more common among HIV-infected women than non-infected women, irrespective of ART use[40-42]. In a report of hospitalization rates between 1993 and 2004, the 2003 rates for PTD were 16.7/100 deliveries for HIV-infected women compared with 10.1/100 deliveries for non-infected women, regardless of ART use[40].

The association between HAART use and an increased rate of PTD has also been evaluated in several large cohort studies, although the data have been inconsistent (Table 2). Some studies suggest higher rates of PTD are associated with combination ART versus monotherapy[43-47]. The European Collaborative Study/Swiss Mother and Child HIV Cohort Study, for example, showed that women on combination therapy before pregnancy were twice as likely to deliver prematurely as those starting therapy in the third trimester, whereas ZDV monotherapy was not associated with PTD[43].

There are also inconsistencies with regards to the data reported on the association of prematurity and PI-based HAART regimens. In one cohort study, the use of antenatal PI-based HAART initiated before or during pregnancy was associated with a significantly increased risk of premature delivery at < 36 weeks' gestation[44]. In another large cohort study from the USA, only PI-based combination ART was significantly associated with an increased risk of PTD versus any other combination ART after adjustment for confounders[46]. In contrast, other cohort studies and meta-analyses have shown that rates of adverse delivery outcomes or PTD are not increased or are only slightly increased in association with different ART regimens, including monotherapy and combination ART with or without PI, administered either in the early or late stages of pregnancy[48-52]. In an adjusted analysis from one large prospective cohort study, PI-based ART was not significantly associated with spontaneous PTD compared with ART without a PI[52]. In a retrospective analysis, HIV-infected women receiving lopinavir/ritonavir (LPV/r) during pregnancy had a PTD rate of 21% compared to a rate of 10% among uninfected women ($p < 0.01$) who were matched by age, parity, and geographical area of delivery[53]. In a multivariate analysis of these data, PTD was associated with a previous history of PTD and HIV viral load ≥ 50 copies/ml[53]. This rate of PTD of 21% is consistent with the PTD rates of 25.5 and 29.6% found in other reports of pregnant women treated with any combination of HAART[46,47]. In another small retrospective chart review of women who were already receiving LPV/r during pregnancy or who initiated LPV/r at some point during pregnancy, the rate of PTD was 25% of live births[54]. However, PTD in this study was not related to maternal age, baseline CD4+ cell count, duration or time (i.e. first versus second or third trimester) of LPV/r exposure, or delivery method[54].

A recent Italian study reported data on 981 HIV-infected mothers who delivered between 2002 and 2008 (Table 3)[55]. Data showed that the use of LPV/r had increased from 4.8% in 2002 to 32.5% in 2007/2008 ($p < 0.001$). Despite an increase in LPV/r use, there were no significant changes in PTD, Apgar score, low birth weight, or birth defects observed during the study period, and the rate of HIV transmission remained < 2%. These data would suggest that the rates of PTD and other labor complications in HIV-infected pregnant women have remained stable over time, despite the increased prescription of combination ART regimens, including PI-based HAART. Most recently, data from the Mma Bana Study[56] demonstrated that although

Table 2. Incidence of preterm delivery in HIV-infected women

First author, year, reference	(n)	Study overview	Rates of preterm delivery
Lopez, 2007[41]	1,191	Matched retrospective cohort study; 397 HIV-infected and 794 non-infected pregnant women; assessed the association between HIV-infection and PTD	PTD rate 18.6% (HIV-infected) vs. 8.2% (uninfected); overall PTD, OR: 2.6 (95% CI: 1.8-3.7; p < 0.00001)
Muñoz, 2007[42]	141	Patient cohort at Hospital 12 de Octubre (Madrid), May 2000 to Dec 2005; incidence and risk factors for PTD and MTCT in HIV-infected women (with or without ART)	PTD rates 50% higher in women without ART during pregnancy (OR: 2.27; 95% CI: 1.28-4.02); dual therapy 7.1%; HAART with PI, 26.1%; HAART without PI, 9.5% (p = 0.10); rate in general population during study period 9.8%
2000[43]	3,920	European Collaborative Study (n = 3,015) Swiss Mother-Child HIV Cohort Study (n = 905); association between type/timing of initiation of ART in pregnancy and duration of pregnancy	Overall PTD rate 17%; monotherapy was not associated with PTD; multivariate analysis for PTD (vs. no ART): cART with PI, OR: 2.60 (95% CI: 1.43-4.75); cART without PI, OR: 1.82 (95% CI: 1.13-2.92); PTD twice as likely with cART pre-pregnancy vs. starting in third trimester (OR: 2.17; 95% CI: 1.03-4.58)
Grosch-Woerner, 2008[44]	183	Prospective cohort study; 13 centers in Germany and Austria (1995-2001); assessed risk of adverse pregnancy outcomes after antenatal ART	Multivariable analysis of 176 pregnancies; increased risk of PTD with PI-based HAART vs. monotherapy (OR: 3.40; 95% CI: 1.13-10.2; p = 0.029)
Martin, 2007[45]	211	Prospectively documented management/outcome of HIV-infected pregnant women at St. Mary's Hospital, London	PTD rate: 14.2% of 211 deliveries; 6% with ZDV monotherapy; 10% with pre-conception HAART; 24% with new and continued HAART; 22% with short-term HAART
Cotter, 2006[46]	1,337	Prospective data for HIV-infected women treated at University of Miami/Jackson Memorial Medical Center (1990-2002)	After adjustment for confounders, only cART with a PI was associated with increased PTD risk vs. any other combination (OR: 1.8; 95% CI: 1.1-3.0)
Thorne, 2004[47]	4,372	European Collaborative Study of PTD among HIV-infected women identified before or during pregnancy	PTD rate: 16.8% for monotherapy (mostly ZDV); 13.4% for dual therapy; 25.5% for HAART (p < 0.002); HAART strongly predictive of PTD (AOR: 2.50; 95% CI: 1.19-5.24; p = 0.016 when started during pregnancy; AOR: 4.41; 95% CI; 2.06-9.41; p < 0.002 when started pre-pregnancy)
Kourtis, 2007[48]	20,426	Meta-analysis; 13 prospective cohorts and 1 retrospective study on PTD with ART in pregnant HIV-infected women	Overall PTD risk, OR: 1.01 (95% CI: 0.76-1.34); no therapy vs. monotherapy (mostly ZDV) OR: 0.86 (95% CI: 0.73-1.01); no therapy vs. cART, OR: 1.13 (95% CI: 0.79-1.63); PI-based vs. non-PI-based ART, OR: 1.24 (95% CI: 0.76-2.02); initiation before pregnancy/in first trimester vs. second/third trimesters OR: 1.71 (95% CI: 1.09-2.67)
Tuomala, 2002[49]	2543	Women and Infants Transmission Study (WITS); multicenter, prospective, cohort study of HIV-infected pregnant women and their infants	Logistic regression showed: increased PTD risk for 10 women with late use of ART not containing ZDV (OR: 7.9; 95% CI: 1.4-44.6); late use of ART containing ZDV associated with decreased risk of PTD (OR: 0.5; 95% CI: 0.3-0.8) and stillbirth (OR: 0.06; 95% CI: 0.02-0.18); NNRTI-based ART during early and late pregnancy associated with decreased PTD risk (OR: 0.3; 95% CI: 0.2-0.7)

(continue)

Table 2. Incidence of preterm delivery in HIV-infected women *(continued)*

First author, year, reference	(n)	Study overview	Rates of preterm delivery
Hojman, 2005[50]	35	Prospective follow-up of all HIV-infected pregnant women in Argentina (June 2002 to Dec 2004); case-control study performed in women on HAART or those not taking HAART during pregnancy	In women on HAART (ZDV/3TC/NVP), 54.5% of deliveries were > 37 wGA, 27.3% at 34-37 wGA, and 18.2% at < 34 wGA; in women not on HAART, 81% of deliveries were > 37 wGA
Patel, 2010[52]	777	PACTG 1025: Prospective cohort study in HIV-positive pregnant women who were not receiving ART at conception	Adjusted analyses: cART with PI not significantly associated with spontaneous PTD vs. ART without PI (OR: 1.22; 95% CI: 0.70-2.12); sensitivity analyses including women who received ART pre-pregnancy also did not show significant association (OR: 1.34; 95% CI: 0.84-2.16)
Azria, 2009[53]	100	Single-centre cohort of HIV-infected women receiving LPV/r during pregnancy and who delivered after 15 wGA (Jan 2003 to June 2007); for each HIV-infected woman, two uninfected matched control women were selected	PTD higher in HIV-infected women (21%) vs. controls (10%; $p < 0.01$); in HIV-infected women, PTD associated with previous history of PTD (AOR: 16.9; 95% CI: 2.6-110; $p = 0.003$) and HIV RNA ≥ 50 copies/ml at delivery (AOR: 6.15; 95% CI: 1.83-20.63; $p = 0.003$); no association between PTD and LPV/r use at < 14 wGA
Senise, 2008[54]	64	Retrospective review of medical records from pregnant women who were already receiving LPV/r during pregnancy or who initiated LPV/r at some point during pregnancy (47% had previously failed another PI)	PTD observed in 25% and LBW in 20.3%; time on LPV/r during pregnancy and GA at initiation of LPV/r not associated with PTD
Machado, 2009[58]	696	Prospective cohort of Brazilian pregnant women followed up in one single centre (1996 and 2006); patients who had ART pregnancy were compared with those treated after the first trimester	Higher rates of PTD (26.3 vs. 17.7%; $p = 0.09$) and LBW (33.3 vs. 16.5%; $p < 0.001$) with ART started pre-conception vs. after first trimester; HAART used pre-conception associated with increased risk for PTD (AOR: 5.0; 95% CI: 1.5-17.0; $p = 0.009$) and LBW (OR: 3.6; 95% CI: 1.7-7.7; $p = 0.001$)
Toure, 2005[59]	205	Pregnancy outcomes for women on HAART in MTCT-Plus Initiative in Abidjan, Cote d'Ivoire (Aug 2003 to Dec 2004); 91 patients began HAART at 30 wGA and 114 were included in a PMTCT group	HAART vs. PMTCT group: PTD rate 3.4 vs. 2.0% ($p = 0.67$); median birth weight 2,800 vs. 3,000 g ($p = 0.01$); rate of LBW 23.5 vs. 12.0% ($p = 0.04$); stillbirth rate 4.6 vs. 4.0% ($p = 0.85$); neonatal mortality rate 3.4 vs. 2.0% ($p = 0.67$)
Shapiro, 2009[56]	730	Mma Bana Study (Botswana); compared HAART vs. PMTCT in HIV-positive women: 560 randomized (CD4 ≥ 200 cells/mm^3) to ABC/ZDV/3TC (Arm A) or LPV/r/CBV (Arm B) from 26-34 wGA through to planned weaning by 6 months postpartum; 170 women with CD4 < 200 cells/mm^3 received NVP 18-34 wGA (observational group)	PTD more common in Arm B than Arm A (23 vs. 15%; $p = 0.04$); stillbirths occurred in 3% (Arm A, ABC/ZDV/3TC), 2% (Arm B) and 7% (observational); LBW did not differ by HAART regimen (17 vs. 13%)

3TC: lamivudine; AOR: adjusted odds ratio; ABC: abacavir; ART: antiretroviral therapy; cART: combination antiretroviral therapy; CBV: Combivir; LBW: low birth weight; LPV/r: lopinavir/ritonavir; MTCT: mother-to-child transmission; NVP: nevirapine; PACTG: Pediatric AIDS Clinical Trials Group; PI: protease inhibitor; PMTCT: prevention of MTCT; PTD: preterm delivery; wGA: weeks gestational age; ZDV: zidovudine.

Table 3. A six-year analysis of data from the National Program on Surveillance on Antiretroviral Treatment in Pregnancy in Italy reporting changes in antiretroviral treatment in pregnancy and outcomes among HIV-infected women (n = 981) evaluated from 2002 to 2008[55]

	2002 (n = 188)	2003 (n = 221)	2004 (n = 183)	2005 (n = 180)	2006 (n = 124)	2007-2008 (n = 85)	P-value
Antiretroviral treatment							
ARV-naive before pregnancy, %	47.6	37.7	34.5	35.2	33.1	40.0	**0.048**
On ARV at conception, %	41.7	46.2	45.9	45.3	52.0	47.6	0.161
On ddI + d4T at conception, %	13.4	5.1	7.8	8.0	6.1	0.0	0.077
ARV for MTCT prophylaxis only, %	35.6	35.5	28.8	26.0	26.1	24.0	**0.007**
Week at start of ARV in pregnancy, median (range)	14.0 (1-41)	11.5 (0-41)	10.0 (1-40)	12.0 (0-38)	12.0 (0-36)	12.0 (0-36)	**0.041**
ARV interruption at first trimester, %*	48.3	46.8	46.9	50.8	46.7	41.4	0.676
RTV-boosted PI at delivery, %	4.5	5.2	9.8	10.2	24.1	35.2	**0.001**
Use of ≥ 3 drugs at delivery, %	63.0	75.1	79.3	82.8	91.4	95.5	**0.001**
Outcomes							
CD4 count at third trimester (cells/mm^3), median (range)	443 (10-1867)	475 (21-1,839)	460 (30-1,332)	439 (50-1,350)	512 (30-1,658)	470 (121-1,090)	0.557
HIV-RNA < 50 copies/ml at third trimester, %	37.3	42.4	59.7	59.1	65.2	80.9	**0.001**
Preterm delivery (< 37 weeks), %	21.2	23.8	26.3	22.2	23.9	19.2	0.863
Birth weight (g), median (range)	2,870 (1,260-4,350)	2,810 (550-4,090)	2,890 (1,000-3,945)	2,817 (850-4,180)	2,860 (810-4,130)	2,950 (1,310-4,470)	0.099
Birth defects, %	3.5	5.3	5.4	1.8	4.5	2.7	0.487

ARV: antiretroviral; EFV: efavirenz; ddI: didanosine; d4T: stavudine; MTCT: mother-to-child transmission; RTV: ritonavir; PI: protease inhibitor.
*Among women already on ARV treatment at conception.

PTD was significantly more prevalent in HIV-infected women who received LPV/r/Combivir (CBV) versus those who received Trizivir (abacavir [ABC], lamivudine [3TC] and ZDV), the proportion of infants with low birth weight, infant six-month mortality, and stillbirths was not different between LPV/r vs. ABC/3TC/AZT[56]. Several other studies have shown an association between low birth weight and the use of HAART, particularly PI-based HAART, versus ART monotherapy or dual therapy[54,57-59]. In contrast, a retrospective analysis demonstrated no differences in rates of low or very low birth weight among PI-based HAART-treated women[53], and in another cohort of HIV-infected women who received ART during pregnancy, no differences in the rates of low birth weight or still birth were seen regardless of the type of therapy received[46].

Studies on the risk of pre-eclampsia and antepartum hemorrhage associated with HIV-infection and ART use during pregnancy have also reported contradictory outcomes[40,60-63]. For example, some studies have reported a significantly higher risk of pre-eclampsia and fetal death in HIV-infected pregnant women treated with HAART[60,61]. However, in a separate study, no significant difference in the rates of pre-eclampsia between HIV-infected and uninfected pregnant women were reported[40]. In another study, the rate of pre-eclampsia was higher in HAART-treated versus untreated HIV-infected women; however, the same study failed to show any significant difference between HAART-treated pregnant women when compared to uninfected pregnant controls[63]. Such variance in outcomes might reflect differences in the populations studied and, as many factors unrelated to HIV infection are involved in the development of pre-eclampsia, it is difficult to draw definitive conclusions regarding the role of HAART in the development of pre-eclampsia.

Discrepancies observed in the rates of PTD, low birth weight, and pre-eclampsia highlight the importance of antenatal care and close monitoring of HIV-infected pregnant women. Additional factors that are likely play a role in negative pregnancy outcomes that should also be considered include smoking, drug or alcohol use, anemia, low $CD4^+$ cell count, chronic inflammation, and other active infectious processes.

Birth defects and congenital abnormalities

Data from several studies have shown that there is no increase in the prevalence of birth defects among ART-treated HIV-infected women, with rates of reported birth defects consistent with the general population, ranging from 3-4%[64-67]. Data from the Antiretroviral Pregnancy Registry (APR) has showed no increase in the prevalence of overall birth defects among live births from women exposed to NFV, atazanavir (ATV), LPV/r, indinavir (IDV), EFV, NVP, stavudine (d4T), ZDV, 3TC, tenofovir (TDF), emtricitabine (FTC), or ABC when compared with observed rates for "early diagnosis" in population-based birth defects surveillance systems[68,69]. Furthermore, the prevalence of birth defects observed with these drugs is similar regardless of the trimester of ARV exposure, type of ART (i.e. HAART vs. monotherapy or dual therapy), or class of ARV agent[65,66]. Data on EFV safety in the first trimester are conflicting and it is currently not recommended for the treatment of pregnant women as it is known to be associated with malformations in animal reproductive studies and neural tube defects and other birth defects in humans[62]. Prevalence of overall birth defects with first trimester EFV exposure has been observed to be similar to the ranges reported in the general population[70]; however, the limited sample size in this cohort prevents a definitive conclusion on the risk of rare birth defects such as neural tube defects.

Anemia

The use of ZDV is known to cause anemia. Significant anemia and neutropenia in newborns of HIV-infected mothers has been associated with the use of ZDV alone and in combination with another NRTI, or as a component of HAART with PI-, NNRTI-, or triple-NRTI-based regimens[71-74].

Hepatotoxicity

Treatment with NVP-based ART during pregnancy has been associated with serious and sometimes fatal hepatotoxicity in some women[75-79]. Studies have shown rates of severe (grade 3-4) hepatic adverse events varying from 0.8-6.5%[76,78,80,81]. The occurrence of severe hepatic adverse events (including one case of hepatic failure where the woman died and one case of Stevens-Johnson syndrome) in response to treatment with NVP led to the early termination of the PACTG 1022 study[75]. An increased risk of severe NVP-related hepatoxicity in pregnant women is associated with higher $CD4^+$ cell counts (> 250 cells/mm^3)[75-78,82], and significantly more women starting NVP therapy in their third trimester versus earlier in pregnancy have been shown to develop severe hepatic adverse events[77]. As a result, US guidelines

emphasize that NVP should not be initiated in women with $CD4^+$ cell counts > 250 cells/mm^3.

Ritonavir-boosted saquinavir (SQV/r) has also been associated with increased hepatotoxicity[83]. In 45 women treated with SQV/r/ZDV/3TC in their third trimester, 36% developed hepatotoxicity[83], although only 16% had a ≥ grade 2 reaction and there was no association between hepatotoxicity and higher SQV trough levels, morbidity, or excess mortality in this population. Additionally, several cases of severe hepatotoxicity in HIV-infected pregnant women treated with EFV-, NFV- and LPV/r-based regimens have been reported. These cases are, however, isolated, spontaneously reported events and are not derived from robust clinical trials or even cohort trial data[84,85]. Thus, quantifying the precise risk associated with these individual agents is challenging.

Mitochondrial toxicity

It is known that NRTI induce mitochondrial dysfunction and depletion of mitochondrial DNA (mtDNA)[86,87], and such toxicity is a concern in pregnant women and infants with *in utero* exposure to NRTI. The use of perinatal ZDV has been linked to postpartum mitochondrial dysfunction in infants born to HIV-infected mothers[88-90]. Therapy with ZDV for PMTCT causes significant depletion of mtDNA at birth in both cord and peripheral blood mononuclear cells of infants born to HIV-positive mothers[89,90]. In one study, this depletion remained significant up to two years after birth[90]. Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Hyperlactemia and lactic acidosis are commonly reported side effects in infants exposed *in utero* to NRTI[91-93]. However, several studies, including large population-based surveillance studies, have shown no deaths attributable to mitochondrial dysfunction in the infants of HIV-infected woman[94-96]. Furthermore, both US and European guidelines recommend that ZDV should be included as part of combination therapy for pregnant women because of its efficacy and extensive experience in this population[24,26], and, worldwide, ZDV plus 3TC is one of the most commonly used combinations in pregnant women. Alternatives to ZDV include d4T or ddI plus 3TC; however, the combination of ddI plus d4T is not recommended for pregnant women due to an increased risk of lactic acidosis caused by mitochondrial toxicity[24]. The impact of long-term developmental implications and related costs associated with prenatal NRTI exposure remains an open question.

Hyperbilirubinemia

The impact of ART on the development of hyperbilirubinemia also presents a potential concern in the infants of HIV-infected women. Indirect hyperbilirubinemia in neonates is usually physiological in nature, and occurs as a result of increased lysis of red blood cells, leading to an increase in the release of hemoglobin, decreased hepatic uptake and conjugation of bilirubin, and increased enterohepatic reabsorption. Elevated indirect bilirubin can be associated with encephalopathy in neonates. Milder forms of encephalopathy can result in sensorineural hearing loss due to damage of the cochlear nuclei, with the most severe form of encephalopathy causing kernicterus. In infants at term, total bilirubin is usually elevated to a mean peak value of 6 mg/dl (levels are higher in Asian infants). In contrast, preterm infants may be at a higher risk of increased levels of indirect bilirubinemia, due to lower serum albumin concentrations, and increased risk for acidosis and sepsis. Decreased hepatic uptake and conjugation of bilirubin is associated with immature glucuronyl transferase activity in all newborns: term infants have 1% of adult activity, whereas preterm infants have 0.1%. In infants exposed to ARV agents, either *in utero* or via breastfeeding, it is important to assess the interaction of these drugs with the normal physiology. Elevation of indirect (unconjugated) bilirubin attributable to ATV/r-related inhibition of hepatic uridine diphosphate glucuronosyltransferase occurs frequently during treatment with ATV. Similarly, IDV may also exacerbate physiologic hyperbilirubinemia in the neonate. Both drugs have reported minimal placental transfer, and several pharmacokinetic studies have demonstrated that infants born to mothers who received ATV/r during pregnancy do not have pathological or dangerous bilirubin elevations in the newborn period[10,97-99]. Despite not showing pathological elevations, the mean peak bilirubin value in one small study appeared to be higher in term infants exposed to ATV/r than in those not exposed to ARV[10]. Another challenge faced by physicians is how to differentiate physiological elevations versus those that might be attributable to ATV/r exposure intrapartum. These findings merit further monitoring and investigation to assess the effects of ARV in premature infants exposed *in utero*.

Lipid abnormalities and lipodystrophy

During pregnancy, changes in body fat and lipid profiles occur that are necessary to provide essential

nutrients to support fetal development[100]. Maternal hypertriglyceridemia is a characteristic feature during pregnancy, with changes in phospholipids and cholesterol seen less often during gestation[100]. Accumulation of triglycerides, very low-density lipoprotein (VLDL), LDL and high-density-lipoprotein (HDL) act as sources of essential fatty acids for the developing fetus[100]. There is now a wealth of data demonstrating the increased risk of cardiovascular disease, lipodystrophy, and dyslipidemia in non-pregnant, HIV-infected individuals, which reflects, in part, the interaction of multiple risk factors. In terms of host-related risk factors, obesity, hypertension, a positive family history, and smoking all contribute to the development of cardiovascular disease risk. The consequences of HIV viral replication and the use of ART are emerging as other important factors that contributed to the overall risk of cardiovascular disease. Together, HIV infection and HAART increases the risk of cardiovascular disease through a range of mechanisms, including HIV-specific immune dysfunction, upregulation of inflammatory and thrombotic factors, vessel damage, and adverse changes in blood lipids[101-105]. Also, HIV infection can cause a decrease in total cholesterol, HDL cholesterol, and LDL cholesterol. Along with a decrease in total LDL, HIV has been associated with an increase in proatherogenic small LDL particles and elevations in triglyceride levels[101].

The use of ART has been associated with increased cardiovascular disease risk and dyslipidemia[105]. Combination ART that includes PI and thymidine NRTI have in particular been associated with elevations in serum cholesterol and triglycerides and lipodystrophy[101,102,105,106], although it is estimated that approximately half of the cardiovascular risk associated with ART is due to unexplained factors other than lipid abnormalities[102]. Although there is accumulating data concerning hyperlipidemia and other aspects relating to cardiovascular disease risk in HIV-infected individuals, there is a paucity of data regarding lipid changes and its impact in HIV-infected pregnant women. Data collected from HIV-infected pregnant women during routine care demonstrates that serum lipids increase progressively during pregnancy, with significant mean increases in LDL cholesterol, triglycerides, and total cholesterol between the first and third trimesters[107]. However, similar increases in lipid profiles between the first and third trimesters have also been observed in uninfected pregnant women[108]. It is important to note, however, that there have been no studies directly comparing changes in lipid profiles during pregnancy in uninfected versus HIV-infected women. In terms of the impact of ART drug class in HIV-infected pregnant women, one study showed that in all trimesters, women on PI-based HAART had elevated triglycerides compared with women on non-PI-based HAART, although the mean difference in total cholesterol levels was not statistically significant[107]. These data were confirmed in a study by the ACTG that demonstrated significant elevations in triglycerides and cholesterol in PI-based versus non-PI-based HAART in 150 pregnant HIV-infected women[109]. In this study, 58% of patients were receiving NFV, 33% were receiving LPV/r, and the remaining 9% were on other PI (SQV, SQV/r, IDV, amprenavir/r)[110,111].

Lipodystrophy is characterized by abnormal or degenerative conditions of the body's adipose tissue. Manifestations of HIV-associated lipodystrophy can range from lipohypertrophy (abnormal central fat accumulation) to lipoatrophy (localized loss of fat tissue) and has been associated with HIV-infected individuals receiving ART. Data collected from the Italian National Program on Surveillance on ART in pregnancy, however, have suggested that in pregnant HIV-infected women, lipodystrophy is probably not a consequence of short-term ART use[112]. Among 261 pregnant HIV-infected women on HAART, 14% of whom had a previous history of lipodystrophy at any time prior to pregnancy, a previous history of lipodystrophy was strongly associated with the development of hypertriglyceridemia, and women with a history of lipodystrophy had significantly higher triglyceride levels during all trimesters compared with women with no history and this association was independent of ART regimen[112].

HIV infection, the use of ART, and pregnancy itself are all associated with an increase in plasma lipid levels. Therefore, HIV-infected pregnant women may be particularly susceptible to developing clinical and metabolic abnormalities, with specific groups, such as women with a previous history of lipodystrophy, having a greater risk of developing complications. Data on the association between metabolic disorders and ARV drugs during pregnancy are conflicting as pregnant women are at a higher risk for metabolic disorders independent of ART usage. Furthermore, other variables such as smoking, BMI pre- pregnancy, and nutritional habits also have an important role in the development of lipid disorders during pregnancy. Moreover, maternal hypertriglyceridemia is a characteristic feature during pregnancy. Although triglycerides do not cross the placental barrier, the presence of lipoprotein receptors in the placenta, together with lipoprotein lipase, phospholipase A2, and intracellular lipase activities,

allows for the release of polyunsaturated fatty acids, initially transported as triglycerides in maternal plasma lipoproteins to the fetus. In addition, normal fetal development requires the availability of both essential fatty acids and long-chain polyunsaturated fatty acids with adequate nutritional status of the mother during gestation essential for normal fetal growth. The ability to accurately evaluate the impact that additional HIV factors have on the hypertriglyceridemia associated with pregnancy and whether these factors contribute deleteriously to the developing fetus or to the mother is challenging. There are limited number of well controlled clinical studies assessing associations between specific ARV drugs and lipid disorders in the context of pregnancy and its relationship between elevated lipid levels and fetal outcomes. Similar to the management of HIV-negative pregnant women in general, careful monitoring of metabolic disorders during pregnancy should be considered, especially for women who are identified during their first prenatal visit to be at a higher risk for metabolic disorders. Well controlled clinical studies are needed in HIV-positive pregnant women receiving ART to better assess the short- and long-term maternal and infant effects resulting from various metabolic disorders that can occur during pregnancy.

Glucose intolerance

Gestational diabetes mellitus, i.e. the development of glucose intolerance with onset or first recognition during pregnancy, presents a significant health risk to both mother and child and a potentially huge economic burden to society. Among pregnant women in general living in industrialized countries, the rates of gestational diabetes vary from 4-10% depending on the cohort and some, although not all, studies suggest that gestational diabetes in the general population may be increasing over time[113-116]. Despite concerns regarding the use of ART, and PI-based regimens in particular, and the potential for adverse metabolic glycemic events, rates of gestational diabetes of 7-9% have been reported among HIV-infected pregnant women receiving combination ART, which is within a similar range to those observed in the general non-HIV-infected population[117,118]. Hospitalization rates for gestational diabetes among pregnant HIV-infected women have increased since 1994[40], which may reflect increasing rates among the general population.

Available data on the impact of PI-based ART on the development of gestational diabetes are inconsistent. Several studies have shown an association between the use of PI and the development of gestational diabetes or glucose intolerance[117-119]. In a Spanish cohort of 669 HIV-infected pregnant women with a prevalence of gestational diabetes of 7%, risk factors for developing gestational diabetes among pregnant women on HAART included older maternal age, hepatitis C coinfection, and d4T and PI exposure[117]. In contrast, a multicenter, prospective, observational study of 149 HIV-infected pregnant women showed no increased risk of glucose intolerance or insulin resistance with PI use[110], and another study showed that, while high rates of glucose intolerance (up to 38%) were observed in pregnant HIV-infected women, they were not associated with the use of PI or HIV infection[110]. In a study of 100 consecutive HIV-infected women receiving LPV/r during pregnancy and who delivered after gestational age of 15 weeks, rates of glucose intolerance were not higher among LPV/r-treated HIV-infected women versus matched uninfected controls[53]. These conflicting data, in terms of the impact of PI-based ART on gestational diabetes, could reflect differences in patient populations studied and make it difficult to draw conclusions. Additionally, although rates of gestational diabetes among HIV-infected pregnant women have increased over time, this may be due in part to the increasing prevalence of diabetes mellitus and gestational diabetes worldwide. It has also been suggested that, as with the general population, traditional risk factors, such as age, high mean body mass index (BMI), and high percentage of body fat, as well as a family history of diabetes, are major contributing factors to the development of diabetes in HIV-infected patients on HAART[110,120]. Further study on the impact of HIV infection and ART use on gestational diabetes is warranted.

Conclusions and caveats

Despite significant advances in the field of HIV therapy, MTCT continues to be an important route of HIV transmission for women living in resource-limited settings, where the availability of ARV remains limited, and for women living in developed countries who have had limited perinatal care before presenting late to the healthcare system. In both situations, PMTCT could be successfully achieved if access to HAART were more widely available.

The use of HAART for PMTCT has led to a significant reduction in the rates of HIV transmission from mother to infants in regions of the world were ART is readily available. In an earlier study from 1994, which utilized

ZDV monotherapy for PMTCT, a transmission rate of 8.3% was reported[19]. More recently, a study that compared PI-based HAART (LPV/r + CBV) versus triple NRTI therapy (ZDV/3TC/ABC) for PMTCT demonstrated *in utero* transmission rates of 0.4 and 1.8%, respectively (range: 1.4%; 95% CI: –2.3-6.7%)[56], highlighting the potential role for PI in PMTCT. This study demonstrated significant reductions in MTCT with HAART, in particular with regimens that include a PI, which supports guideline recommendations that all HIV-infected pregnant women should receive ART for the PMTCT regardless of their immunologic or virologic status. Most treatment guidelines now recommend the use of a PI or NNRTI plus two NRTI as first-line therapy for the management of HIV in pregnant women and for PMTCT[24,26-28].

Many questions remain regarding optimal treatment in HIV-infected pregnant women. Most experts agree that ART should be initiated as early as possible, since early intervention has been associated with lower MTCT rates. In the Mma Bana study, a lack of HIV suppression to < 400 copies/ml at delivery was associated with higher baseline HIV RNA levels and later gestational age at enrolment ($p < 0.001$), reinforcing the importance of timely initiation of ART for PMTCT. When ART is not indicated for the health of the pregnant women (based on $CD4^+$ cell count or viral load), intervention to prevent transmission to the fetus is usually initiated in the second trimester of pregnancy. This timing avoids exposure to ARV during the first trimester of pregnancy, when the potential for teratogenicity of certain drugs is expected to be the greatest.

Despite NNRTI being used commonly in non-pregnant HIV-infected individuals, there is a concern regarding the use of EFV in women of child-bearing age due to potential teratogenicity that can occur during the first trimester. Data continues to be collected in women exposed to EFV during the first trimester, with conflicting reports regarding the exact risk EFV presents during this critical period of organogenesis. Another concern regarding the use of NNRTI during pregnancy, either as a component in short-course therapy or as a single dose, is the risk of developing NNRTI-associated resistance mutations. In resource-limited settings, intrapartum single-dose NVP has been widely used to reduce MTCT, although this strategy has led to NVP resistance for many women exposed to single-dose NVP. The OCTANE 1 trial assessed the impact of prior maternal single-dose NVP exposure for PMTCT on the subsequent virologic response in women given NVP for their own health[121]. This study suggested that women exposed to single-dose NVP in a previous pregnancy had a better virologic response (and less mortality) when receiving LPV/r/FTC/TDF versus those who received NVP/FTC/TDF. The difference in virologic response seen between the PI- versus NNRTI-based regimens decreased with increasing time between the initiation of current treatment and past single-dose NVP. Despite widespread use of NVP for PMTCT, NVP has also been associated with severe and sometimes fatal cases of hepatoxicity in pregnant women. As a result, it is recommended that the use of NVP in women with $CD4^+$ cell counts > 250 cells/mm^3 be avoided, regardless of pregnancy status. The concerns regarding the use of NVP in women with high $CD4^+$ cell counts, along with an increased, albeit not clearly quantified, risk associated with the use of EFV in the first trimester, coupled with the increase in virologic failure in women with a history of single-dose NVP use who subsequently receive NVP-based therapy for their own health, all reinforce the important role of other ART regimens, including PI, in the PMTCT.

Currently, PI are more widely prescribed to HIV-infected pregnant women for PMTCT for several reasons. There is limited potential for teratogenicity with the entire PI class. These agents are fairly well tolerated and are associated with lower toxicities; some studies, including the Mma Bana study, reporting grade 3 or 4 adverse events in 6% of women treated with a LPV/r-based regimen, with an additional 2% of women requiring HAART modification due to adverse events. The good virologic and immunologic responses seen with PI-based HAART and the higher genetic barrier to resistance are additional benefits associated with the use of such regimens in PMTCT. These benefits are seen for women who do not meet criteria for HAART for their own health (based on $CD4^+$ cell count or viral load) and for those who require ART and will continue to receive such therapy postpartum. The 2010 version of the US Department of Health and Human Services Guidelines for the use of ARV agents in pregnancy recommends LPV/r plus ZDV/3TC as the preferred regimen for HIV-infected pregnant women[24]. Although PI-based ART regimens have been associated with an increase in several adverse events, including PTD, dyslipidemia, glucose intolerance, and lipodystrophy, many of these adverse events were associated with the use of older PI such as NFV, and importantly, when PI were used in combination with thymidine analog NRTI. With more widespread availability of newer PI, including LPV/r, and the decrease in the use of thymidine analogues including d4T and ZDV in combination therapy, several of the

adverse events previously associated with PI use will likely decease. Moreover, there are several, non-pharmacological factors that have been associated with an increase in obstetrical adverse events, including traditional risk factors such as BMI, family history, and coinfection with hepatitis C virus. Clinicians need to be mindful of these additional risk factors and, whenever possible, provide aggressive intervention of modifiable risk factors to their patients to ensure limited obstetrical complications. Ideally, an individual's history and baseline clinical and laboratory parameters should also be taken into consideration when choosing the most appropriate ART regimen to use during pregnancy. In resource-limited settings, however, the choice of ART for pregnant women, as for HIV-infected individuals in general, is dictated by cost and drug availability, rather than the optimal regimen for an individual patient.

From the early days when ZDV monotherapy was found to have a protective role in PMTCT to more recent advances seen with combination therapy, the rate of MTCT has significantly decreased for women who have received such prevention. The most effective and safest choice of ARV for PMTCT is still not clearly delineated, although more recent studies have suggested a beneficial and safer role for PI-based regimens compared with previously used NNRTI-based therapy. Currently, most data are derived from cohort studies, retrospective studies with small patient numbers, and from clinical experience of experts in the field. The lack of randomized clinical trials data makes comparison between presently available studies difficult in terms of efficacy and safety regarding the various ARV regimens. More randomized, controlled clinical trials are needed to better define the role that PI- versus NNRTI-based regimens will have in the future for PMTCT.

Conflicts of interest

Jorge F. Senise discloses no conflict of interest; Adauto Castelo discloses that he has received research support and served as a consultant for Bristol-Myers Squibb, GSK, and Boehringer Ingelheim. Marisol Martinez is an Abbott employee and may hold Abbott stock.

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References

1. UNAIDS 2008 Report on the global AIDS epidemic. Geneva, Switzerland: UNAIDS. 2008. Available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp.
2. Fiore S, Heard I, Thorne C, et al. Reproductive experience of HIV-infected women living in Europe. Hum Reprod. 2008;23:2140-4.
3. Ndiaye C, Ag Aboubacrine S, Kalle A, et al. Implications of high fertility desire on reproductive health needs in men and women receiving ART in Mali. 5th IAS Conference on HIV Pathogenesis and Treatment, Cape Town, South Africa. July 2009. [Abstract CDC035].
4. Oladapo O, Daniel O, Odusoga O, Ayoola-Sotubo O. Fertility desires and intentions of HIV-positive patients at a suburban specialist center. J Natl Med Assoc. 2005;97:1672-81.
5. Phillips U, Rosenberg M, Dobroszycki J, Katz M, Wiznia A, Abadi J. Poor virologic control in pregnant adolescents with perinatally acquired HIV infection as compared to horizontally infected pregnant women. 15th CROI, Boston, USA. February 2008. [Abstract 605].
6. Roustit M, Jlaiel M, Leclercq P, Stanke-Labesque F. Pharmacokinetics and therapeutic drug monitoring of antiretrovirals in pregnant women. Br J Clin Pharmacol. 2008;66:179-95.
7. Cooper E, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr. 2002;29:484-94.
8. Dorenbaum A, Cunningham C, Gelber R, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. JAMA. 2002;288:189-98.
9. Dunn D, Newell M, Ades A, Peckham C. Risk of human immunodeficiency virus type 1 transmission through breastfeeding. Lancet. 1992;340:585-8.
10. Eley T, Vandeloise E, Child M, et al. Steady state pharmacokinetics and safety of atazanavir after treatment with ATV 300 mg once daily/ritonavir 100 mg once daily + ZDV/3TC during the third trimester in HIV+ women. 15th CROI, Boston, USA. February 2008. [Abstract 624].
11. Kiser J, Mawhinney S, Kinzie K, et al. Total and unbound lopinavir/ritonavir pharmacokinetics in a concentration-guided study of HIV-infected women throughout pregnancy and post-partum. 16th CROI, Montreal, Canada. February 2009. [Abstract 946].
12. Aweeka F, Tierney C, Stek A, et al. ACTG 5153s: Pharmacokinetic exposure and virological response in HIV-1-infected pregnant women treated with PI. 14th CROI, Los Angeles, USA. February 2007. [Abstract 739].
13. Dorenbaum A, Rodman J, Mirochnick M, Hernandez J, Fridland A. Systemic pharmacokinetics (PK) of oral zidovudine (ZDV) given during labor and delivery to HIV-1-infected pregnant women. 7th CROI, San Francisco, USA. February 2000. [Abstract 660].
14. Scott G, Rodman J, Shapiro D, et al. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-1 infected pregnant women and their infants. 9th CROI, Seattle, USA. February 2007. [Abstract 794-W].
15. Rodman J, Flynn P, Shapiro D, et al. Pharmacokinetics and safety of tenofovir disoproxil fumarate in HIV-1-infected pregnant women and their infants. 13th CROI, Denver, USA. 2006. [Abstract 708].
16. Arrive E, Newell M, Ekouevi D, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. Int J Epidemiol. 2007; 36:1009-21.
17. Martinson N, Morris L, Johnson J, et al. Women exposed to single-dose nevirapine in successive pregnancies: effectiveness and nonnucleoside reverse transcriptase inhibitor resistance. AIDS. 2009;27:809-16.
18. Zeh C, Weidle P, Nafisa L, et al. Emergence of HIV-1 drug resistance among breastfeeding infants born to HIV-infected mothers taking antiretrovirals for prevention of mother-to-child Transmission of HIV: The Kisumu Breastfeeding Study, Kenya. 15th CROI, Boston, USA. February 2008. [Abstract 84LB].
19. Connor E, Sperling R, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331:1173-80.
20. Volmink J, Siegfried N, van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev. 2007;1:CD003510.
21. Peters V, Liu K, Dominguez K, et al. Missed opportunities for perinatal HIV prevention among HIV-exposed infants born 1996-2000, pediatric spectrum of HIV disease cohort. Pediatrics. 2003;111:1186-91.
22. Harrigan R. Measuring viral load in the clinical setting. J Acquir Immune Defic Syndr Hum Retrovirol. 1995;10(Suppl 1):S34-40.

23. Senise J, Palacios R, Tanno Z, Lunardi L, Waghabi G, Vaz M. HIV-1 viremia during the first 28 weeks of pregnancy is not associated with mother-to-child transmission. Brazilian J Infect Dis. 2006;10:259-63.
24. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2010. Available at: http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.
25. de Ruiter A, Mercey D, Anderson J, et al. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. HIV Med. 2008;9:452-502.
26. European Aids Clinical Society (EACS). Guidelines: Clinical Management and Treatment of HIV-infected Adults in Europe, version 5. 2009. Available at: http://www.europeanaidsclinicalsociety.org/guidelinespdf/EACS-EuroGuidelines2009FullVersion.pdf.
27. Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. World Health Organization (WHO). 2008. Available at: http://www.who.int/hiv/pub/plhiv/plhiv_treatment_care.pdf.
28. Rapid advice: Antiretroviral therapy for HIV infection in adults and adolescents. 2009. Available at: http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf.
29. Bucceri A, Somigliana E, Matrone R, et al. Combination antiretroviral therapy in 100 HIV-1-infected pregnant women. Hum Reprod. 2002;17:436-41.
30. Palombi L, Marazzi M, Germano P, et al. Treatment interruption after HAART prophylaxis in HIV-infected pregnant women in Mozambique: the drug resource enhancement and malnutrition program. 15th CROI, Boston, USA. February 2008. [Abstract 668].
31. Bardeguez A, Shapiro D, Mofenson L, et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. J Acquir Immune Defic Syndr. 2003;32:170-81.
32. Watts D, Lambert J, Stiehm E, et al. Progression of HIV disease among women following delivery. J Acquir Immune Defic Syndr. 2003;33:585-93.
33. Ananworanich J, Gayet-Ageron A, Le Braz M, et al. CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. Lancet. 2006;368:459-65.
34. Krolewiecki A, Zala C, Vanzulli C, et al. Safe treatment interruptions in patients with nadir CD4 counts of more than 350 cells/microL: a randomized trial. J Acquir Immune Defic Syndr. 2006;41:425-9.
35. Marchou B, Tangre P, Charreau I, et al. Intermittent antiretroviral therapy in patients with controlled HIV infection. AIDS. 2007;21:457-66.
36. Danel C, Moh R, Chaix M, et al. Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: a randomized trial involving West African adults. J Infect Dis. 2009;199:66-76.
37. Kuller L, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008;5:e203.
38. Palacios R, Senise J, Vaz M, Diaz R, Castelo A. Short-term antiretroviral therapy to prevent mother-to-child transmission is safe and results in a sustained increase in CD4 T-cell counts in HIV-1-infected mothers. HIV Med. 2009;10:157-62.
39. Evaluating strategies to reduce mother-to-child transmission of HIV infection in resource-limited countries (PROMISE). Clintrials.gov. 2010. Available at: http://clinicaltrials.gov/ct2/show/NCT01061151?term=PROMISE+AND+HIV&rank=1.
40. Kourtis A, Bansil P, McPheeters M, Meikle S, Posner S, Jamieson D. Hospitalizations of pregnant HIV-infected women in the USA prior to and during the era of HAART, 1994-2003. AIDS. 2006;20:1823-31.
41. Lopez M, Figueras F, Hernandez S, et al. HIV infection is an independent risk factor for preterm delivery. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia. July 2007. [Abstract TUPEB114].
42. Muñoz E, Rojo C, Gonzalez-Tome M, et al. Risk factors for preterm birth and mother to child transmission in an HIV-infected pregnant women cohort. 11th European AIDS Conference, Madrid, Spain. October 2007. [Abstract P14.6/01].
43. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. AIDS. 2000;14:2913-20.
44. Grosch-Woerner I, Puch K, Maier R, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. HIV Med. 2008;9:6-13.
45. Martin F, Taylor G. Increased rates of preterm delivery are associated with the initiation of highly active antiretroviral therapy during pregnancy: a single-center cohort study. J Infect Dis. 2007;196:558-61.
46. Cotter A, Garcia A, Duthely M, Luke B, O'Sullivan M. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis. 2006;193:1195-201.
47. Thorne C, Patel D, Newell M. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS. 2004;18:2337-9.
48. Kourtis A, Schmid C, Jamieson D, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. AIDS. 2007;21:607-15.
49. Tuomala R, Shapiro D, Mofenson L, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med. 2002;346:1863-70.
50. Hojman M, Manonelles G. No differences in birth weight or time of delivery in newborns from HIV positive women with or without HAART. 10th European AIDS Conference, Madrid, Spain. November 2005. [Abstract PE14.7/1]
51. Watts D, Balasubramanian R, Maupin R, et al. Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. Am J Obstet Gynecol. 2004;190:506-16.
52. Patel K, Shapiro D, Brogly S, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. J Infect Dis. 2010;201:1035-44.
53. Azria E, Moutafoff C, Schmitz T, et al. Pregnancy outcomes in women with HIV type-1 receiving a lopinavir/ritonavir-containing regimen. Antivir Ther. 2009;14:423-32.
54. Senise J, Cruz R, Palacios R, et al. Low-birth weight and pre-term delivery in relation to lopinavir/ritonavir use in pregnancy. American J Infect Dis. 2008;4:209-14.
55. Baroncelli S, Tamburrini E, Ravizza M, et al. Antiretroviral treatment in pregnancy: a six-year perspective on recent trends in prescription patterns, viral load suppression, and pregnancy outcomes. AIDS Patient Care STDS. 2009;23:513-20.
56. Shapiro R, Hughes M, Ogwu A, et al. A randomized trial comparing highly active antiretroviral therapy regimens for virologic efficacy and the prevention of mother-to-child HIV transmission among breastfeeding women in Botswana (The Mma Bana Study). 5th IAS Conference on HIV Pathogenesis and Treatment, Cape Town, South Africa. July 2009. [Abstract WELBB101].
57. Ekouevi D, Coffie P, Becquet R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. AIDS. 2008;22:1815-20.
58. Machado E, Hofer C, Costa T, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. Sex Transm Infect. 2009;85:82-7.
59. Toure H, Tonwe-Gold B, Becquet R, et al. Adverse pregnancy outcomes in HIV infected women treated with HAART in Abidjan Côte d'Ivoire. 3rd IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil. July 2005. [Abstract TUFO0202].
60. Coll O, Suy A, Martinez E, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. 11th CROI, San Francisco, USA. February 2004. [Abstract 921].
61. Suy A, Martinez E, Coll O, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. AIDS. 2006;20:59-66.
62. Watts D. Treating HIV during pregnancy: an update on safety issues. Drug Saf. 2006;29:467-90.
63. Wimalasundera R, Larbalestier N, Smith J, et al. Pre-eclampsia, antiretroviral therapy, and immune reconstitution. Lancet. 2002;360:1152-4.
64. Covington D, Conner S, Doi P, Swinson J, Daniels E. Risk of birth defects associated with nelfinavir exposure during pregnancy. Obstet Gynecol. 2004;103:1181-9.
65. Townsend C, Tookey P, Cortina-Borja M, Peckham C. Antiretroviral therapy and congenital abnormalities in infants born to HIV-1-infected women in the United Kingdom and Ireland, 1990 to 2003. J Acquir Immune Defic Syndr. 2006;42:91-4.
66. Townsend C, Willey B, Cortina-Borja M, Peckham C, Tookey P. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007. AIDS. 2009;23:519-24.
67. Watts D, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. J Acquir Immune Defic Syndr. 2007;44:299-305.
68. The Antiretroviral Pregnancy Registry: Interim Report, 2009.
69. Watts D, Covington D, Beckerman K, et al. Assessing the risk of birth defects associated with antiretroviral exposure during pregnancy. Am J Obstet Gynecol. 2004;191:985-92.
70. Conway D, Scott G, Muenz D, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals: IMPAACT P1025. 17th CROI, San Francisco, USA. February 2010. [Abstract 923].
71. El Beitune P, Duarte G. Antiretroviral agents during pregnancy: consequences on hematologic parameters in HIV-exposed, uninfected newborn infant. Eur J Obstet Gynecol Reprod Biol. 2006;128:59-63.
72. Feiterna-Sperling C, Weizsaecker K, Buhrer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. J Acquir Immune Defic Syndr. 2007;45:43-51.
73. Pacheco S, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An

analysis of the women and infants transmission study. J Infect Dis. 2006;194:1089-97.
74. Thomas T, Masaba R, Ndivo R, et al. Prevalence of anemia among women in a trial of HAART including zidovudine for PMTCT in Kisumu, Kenya. 14th CROI, Los Angeles, USA. February 2007. [Abstract 748].
75. Hitti J, Frenkel L, Stek A, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. J Acquir Immune Defic Syndr. 2004;36:772-6.
76. Jamisse L, Balkus J, Gloyd S, Djedje M, Osman N, Farquhar C. Nevirapine-associated hepatic toxicity among HIV-1-seropositive pregnant women in Mozambique. XVI International AIDS Conference, Toronto, Canada. August 2006. [Abstract WEPE0173].
77. Joy S, Poi M, Hughes L, et al. Third-trimester maternal toxicity with nevirapine use in pregnancy. Obstet Gynecol. 2005;106:1032-8.
78. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. HIV Med. 2006;7:255-60.
79. van Schalkwyk J, Alimenti A, Khoo D, et al. Serious toxicity associated with continuous nevirapine-based HAART in pregnancy. BJOG. 2008;115:1297-302.
80. Black V, Rees H. Incidence of nevirapine-associated hepatitis in an antenatal clinic. S Afr Med J. 2008;98:116-8.
81. Marazzi M, Germano P, Liotta G, et al. Safety of nevirapine-containing antiretroviral triple therapy regimens to prevent vertical transmission in an African cohort of HIV-1-infected pregnant women. HIV Med. 2006;7:338-44.
82. Aaron A, Kempf M, Criniti S, et al. Risks associated with nevirapine use in pregnant and non-pregnant women. 15th CROI, Boston, USA. February 2008. [Abstract 983].
83. Hanlon M, O'Dea S, Clarke S, Mulcahy F. Maternal hepatotoxicity with boosted saquinavir as part of combination ART in pregnancy. 14th CROI, Los Angeles, USA. February 2007. [Abstract 753].
84. Hill J, Sheffield J, Zeeman G, Wendel G. Hepatotoxicity with antiretroviral treatment of pregnant women. Obstet Gynecol. 2001;98:909-11.
85. Roedling S, Jungmann E. Lopinavir-associated hepatotoxicity in a pregnant woman: a case report. HIV Med. 2006;7(Suppl 1):37 [abstract P104].
86. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. Antimicrob Agents Chemother. 2002;46:716-23.
87. Saitoh A, Haas R, Naviaux R, Salva N, Wong J, Spector S. Impact of nucleoside reverse transcriptase inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells. Antimicrob Agents Chemother. 2008;52:2825-30.
88. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet. 1999;354:1084-9.
89. Cote H, Raboud J, Bitnun A, et al. Perinatal exposure to antiretroviral therapy is associated with increased blood mitochondrial DNA levels and decreased mitochondrial gene expression in infants. J Infect Dis. 2008;198:851-9.
90. Poirier M, Divi R, Al-Harthi L, et al. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. J Acquir Immune Defic Syndr. 2003;33:175-83.
91. Alimenti A, Burdge D, Ogilvie G, Money D, Forbes J. Lactic acidemia in human immunodeficiency virus-uninfected infants exposed to perinatal antiretroviral therapy. Pediatr Infect Dis J. 2003;22:782-9.
92. Ekouevi D, Toure R, Becquet R, et al. Serum lactate levels in infants exposed peripartum to antiretroviral agents to prevent mother-to-child transmission of HIV: Agence Nationale de Recherches Sur le SIDA et les Hepatites Virales 1209 study, Abidjan, Ivory Coast. Pediatrics. 2006;118:e1071-7.
93. Noguera A, Fortuny C, Munoz-Almagro C, et al. Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals. Pediatrics. 2004;114:e598-603.
94. Bulterys M, Nesheim S, Abrams E, et al. Lack of evidence of mitochondrial dysfunction in the offspring of HIV-infected women. Retrospective review of perinatal exposure to antiretroviral drugs in the Perinatal AIDS Collaborative Transmission Study. Ann N Y Acad Sci. 2000;918:212-21.
95. Dominguez K, Bertolli J, Fowler M, et al. Lack of definitive severe mitochondrial signs and symptoms among deceased HIV-uninfected and HIV-indeterminate children < or = 5 years of age, Pediatric Spectrum of HIV Disease project (PSD), USA. Ann N Y Acad Sci. 2000;918:236-46.
96. Lindegren M, Rhodes P, Gordon L, Fleming P. Drug safety during pregnancy and in infants. Lack of mortality related to mitochondrial dysfunction among perinatally HIV-exposed children in pediatric HIV surveillance. Ann N Y Acad Sci. 2000;918:222-35.
97. Natha M, Hay P, Taylor G, et al. Atazanavir use in pregnancy: a report of 33 cases. 14th CROI, Los Angeles, USA. February 2007. [Abstract 750].
98. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. AIDS. 2007;21:2409-15.
99. Mirochnick M, Stek A, Capparelli E, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. 16th CROI, Montreal, Canada. February 2009. [Abstract 941].
100. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine. 2002;19:43-55.
101. Baker J, Henry W, Neaton J. The consequences of HIV infection and antiretroviral therapy use for cardiovascular disease risk: shifting paradigms. Curr Opin HIV AIDS. 2009;4:176-82.
102. Carr A. Pathogenesis of cardiovascular disease in HIV infection. Curr Opin HIV AIDS. 2008;3:234-9.
103. Currier J. Update on cardiovascular complications in HIV infection. Top HIV Med. 2009;17:98-103.
104. Friis-Moller N, Smieja M, Klein D. Antiretroviral therapy as a cardiovascular disease risk factor: fact or fiction? A review of clinical and surrogate outcome studies. Curr Opin HIV AIDS. 2008;3:220-5.
105. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. AIDS. 2003;17:1179-93.
106. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS. 1998;12:F51-8.
107. Floridia M, Tamburrini E, Ravizza M, et al. Lipid profile during pregnancy in HIV-infected women. HIV Clin Trials. 2006;7:184-93.
108. Alvarez J, Montelongo A, Iglesias A, Lasuncion MA, Herrera E. Longitudinal study on lipoprotein profile, high density lipoprotein subclass, and postheparin lipases during gestation in women. J Lipid Res. 1996;37:299-308.
109. Livingston E, Cohn S, Yang Y, et al. Lipids and lactate in human immunodeficiency virus-1 infected pregnancies with or without protease inhibitor-based therapy. Obstet Gynecol. 2007;110:391-7.
110. Hitti J, Andersen J, McComsey G, et al. Protease inhibitor-based antiretroviral therapy and glucose tolerance in pregnancy: AIDS Clinical Trials Group A5084. Am J Obstet Gynecol. 2007;196:331 e1-7.
111. Hitti J, Andersen J, McComsey G, et al. Effect of protease inhibitor-based antiretroviral therapy on glucose tolerance in pregnancy (ACTG A5084). 13th CROI, Denver, USA. 2006. [Abstract 711].
112. Floridia M, Guaraldi G, Tamburrini E, et al. Lipodystrophy is an independent predictor of hypertriglyceridemia during pregnancy in HIV-infected women. AIDS. 2006;20:944-7.
113. Dabelea D, Snell-Bergeon J, Hartsfield C, Bischoff K, Hamman R, McDuffie R. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. Diabetes Care. 2005;28:579-84.
114. Kaaja R, Ronnemaa T. Gestational diabetes: pathogenesis and consequences to mother and offspring. Rev Diabet Stud. 2008;5:194-202.
115. Lawrence J, Contreras R, Chen W, Sacks D. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005. Diabetes Care. 2008;31:899-904.
116. Shand A, Bell J, McElduff A, Morris J, Roberts C. Outcomes of pregnancies in women with pre-gestational diabetes mellitus and gestational diabetes mellitus; a population-based study in New South Wales, Australia, 1998-2002. Diabet Med. 2008;25:708-15.
117. Gonzalez-Tome M, Ramos Amador J, Guillen S, et al. Gestational diabetes mellitus in a cohort of HIV-1 infected women. HIV Med. 2008;9:868-74.
118. Marti C, Pena J, Bates I, et al. Obstetric and perinatal complications in HIV-infected women. Analysis of a cohort of 167 pregnancies between 1997 and 2003. Acta Obstet Gynecol Scand. 2007;86:409-15.
119. El Beitune P, Duarte G, Foss M, et al. Effect of antiretroviral agents on carbohydrate metabolism in HIV-1 infected pregnant women. Diabetes Metab Res Rev. 2006;22:59-63.
120. Sax P, Kumar P. Tolerability and safety of HIV protease inhibitors in adults. J Acquir Immune Defic Syndr. 2004;37:1111-24.
121. Lockman S; A5208/OCTANE Study Team. Lopinavir/ritonavir + tenofovir/emtricitabine is superior to nevirapine + tenofovir/emtricitabine for women with prior exposure to single-dose nevirapine: A5208 ("OCTANE"). 16th CROI, Montreal, Canada. February 2009. [Abstract 94LB].