Antiretrovirals in Pregnancy: A Note of Caution

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(See the Major Article by Chen et al, on pages 1695–705.)

Maternal-to-child transmission (MTCT) of human immunodeficiency virus (HIV) has been reduced to <1% in resource-rich settings with universal HIV testing of pregnant women, antenatal highly active antiretroviral therapy (HAART) for all women regardless of maternal $CD4^+$ cell count, scheduled cesarean delivery for women without viral suppression near delivery, and avoidance of breast-feeding [1, 2]. The World Health Organization (WHO) recently issued guidance for resource-limited settings that emphasized the programmatic and operational advantages of using a single universal HAART regimen both to treat HIV-infected women and to prevent MTCT in women who do not require treatment for their own health; these guidelines discuss the potential benefits from initiating life-long HAART in all pregnant women (called Option B+) [3]. The 2010 WHO guidelines recommended HAART for treatment of all women with $CD4^+$ cell counts $\leq$350 cells/mm^3 or WHO stage 3 or 4 disease, and a choice of 2 effective regimens to reduce MTCT in women with $CD4^+$ cell counts >350 cells/mm^3 not yet requiring therapy: antenatal zidovudine (ZDV) with single-dose nevirapine (NVP) and 1-week ZDV–lamivudine (3TC) tail with daily infant NVP during breast-feeding (Option A) or a maternal triple-drug HAART regimen during pregnancy and breast-feeding (Option B) [4]. Available data in women with higher $CD4^+$ cell counts suggest similar in utero transmission rates for antepartum ZDV compared with HAART, as well as similar postpartum transmission rates for daily infant NVP compared with maternal HAART [5, 6]. Although the use of a single HAART regimen in all pregnant women is programmatically appealing, more data are needed regarding the potential benefits and risks of the 2 strategies for women not yet requiring therapy for their own health.

Although HAART has been the standard of care in high-resource settings, questions remain as to the potential for HAART to increase the risk of preterm birth. Several studies have suggested an increased risk of preterm birth among women receiving HAART, compared with those receiving ZDV alone or dual nucleoside regimens, for prevention of MTCT in resource-rich countries [7–9]. Initially, use of HAART in pregnancy was confined to treatment for women with lower $CD4^+$ lymphocyte counts, suggesting that the observed effect may have been confounded by maternal disease stage. However, some more recent studies [10, 11], but not all [12, 13], have also suggested increased risk even among women receiving HAART solely for the prevention of MTCT. Protease inhibitor (PI) regimens have been associated with increased preterm birth in many studies [7, 8, 11, 14, 15], although some studies have found increased risk of preterm birth with receipt of any HAART regimen [9, 16]. More recently, concern has been directed at a possible relationship specifically with ritonavir-boosted PI therapy and increased risk of preterm birth [17].

In resource-rich countries, the effects of preterm birth secondary to antenatal HAART on infant morbidity and mortality may be limited by the advanced healthcare that can be provided to such infants. However, an increased risk of preterm birth from HAART in resource-limited settings could have enormous impact, because options for care of preterm infants are limited, and millions of HIV-infected women become pregnant each year. Thus, data are critically needed on the effects of various regimens used in resource-limited countries to prevent MTCT.

In this issue of *The Journal*, Chen et al provide important data on rates of adverse pregnancy outcomes among HIV-infected women in Botswana, according to antiretroviral regimens received during pregnancy, and compared with HIV-uninfected women [18]. A remarkable 97% of 33 148 pregnant women delivering at 6 government hospitals underwent HIV testing, with 30%

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testing positive. The risk of stillbirth, preterm delivery, small size for gestational age, and neonatal death were all significantly increased with HIV infection, with adjusted odds ratios (AORs) of 1.3–1.8 among HIV-infected compared with HIV-uninfected women. It is not surprising that adverse pregnancy outcomes were increased among women with HIV infection, given their increased risk of coinfections such as tuberculosis and malaria, which are also associated with increased risk of adverse pregnancy outcomes [19, 20].

The HAART regimens used in Botswana were NVP based in 87% of women receiving HAART and lopinavir-ritonavir based in 9% of women. No increased risk of congenital anomalies was noted. Efavirenz-based HAART, which is now being recommended by WHO for treatment of nonpregnant and pregnant individuals [21], was not used, and hence no conclusions can be drawn regarding the safety of efavirenz in pregnancy.

HAART exposure continuing from before pregnancy was associated with preterm delivery (AOR, 1.2; 95% confidence interval [CI], 1.1–1.4). Of particular note, women initiating HAART during pregnancy had a significantly increased risk of preterm delivery compared with women initiating ZDV (AOR, 1.4, 1.2–1.8). Women initiating HAART compared with ZDV during pregnancy also had an increased risk of small-for-gestational-age infants (AOR, 1.5; 95% CI, 1.2–1.9), stillbirth (AOR, 2.5; 95% CI, 1.6–3.9), and neonatal death (1.9% vs 0.8%; $P = .002$). When analyses were limited to the 49% of women with available $CD4^+$ lymphocyte data, no differences were observed in the findings. The associations between HAART use and adverse birth outcome were independent of maternal $CD4^+$ cell count and seemed to be greatest among women with $CD4^+$ cell counts >200 cells/mm^3, suggesting that the associations were not all related to women with more advanced disease receiving HAART.

The increased risk of preterm birth among women initiating HAART compared with ZDV is concerning. The benefits of HAART for women with $CD4^+$ lymphocyte counts <350 cells/mm^3 are clear, because 92% of maternal mortality and 88% of perinatal and breast-feeding transmission occur in this group, and these rates can be reduced with prompt initiation of treatment with HAART [22]. Any increased risk of preterm birth would need to be very high to outweigh benefits for this group of women. However, the benefits and risks of using HAART to prevent MTCT may differ in women with high $CD4^+$ cell counts not yet requiring treatment for their own health.

The efficacy of Option A and Option B for prevention of MTCT seem equivalent when implemented appropriately in women with $CD4^+$ lymphocyte counts >350 cells/mm^3. The rate of infant infection at birth among women with $CD4^+$ lymphocyte counts between 350 and 500 cells/mm^3 in the Kesho Bora trial was 1.7% in both the ZDV/single-dose NVP arm and the triple-therapy arm [5]. In the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study, rates of transmission during breast-feeding were 2.9% (95% CI, 1.9%–4.4%) among women receiving triple therapy, compared with 1.7% (95% CI, 1.0%–2.9%) among infants receiving NVP [6]. The advantage of universal HAART use lies in the simplicity of having one regimen for all pregnant women, and assuring that therapy will be initiated quickly in women with more advanced disease, without the need to await $CD4^+$ cell counts. However, it will be critical to monitor the rate of HIV-free survival as well as infant HIV infection with implementation of this strategy, because an increase in preterm birth could lead to increased infant mortality in low-resource settings, which could offset the benefits of preventing MTCT. The rate of neonatal death among women initiating HAART during pregnancy was 1.9% vs 0.8% ($P = .002$) among those initiating ZDV and did not differ between those with $CD4^+$ cell counts >200 or <200 cells/mm^3. However, it is difficult to determine how this difference translates to overall infant mortality, compared with neonatal mortality, for the larger population of HIV-infected pregnant women receiving various regimens to prevent MTCT. A previous randomized trial in Botswana found a doubled risk of preterm delivery among women with $CD4^+$ lymphocyte counts >200 cells/mm^3 randomized to ZDV-3TC-lopinavir-ritonavir compared with ZDV-3TC-abacavir but no difference between groups in rates of infant hospitalizations or mortality by 6 months of age.

The assessment of risks and benefits is further complicated by potential differences in risk of preterm birth depending on class of drugs used. In the current study, women with low $CD4^+$ cell counts received NVP-based HAART regimens, whereas those with $CD4^+$ cell counts >250 cells/mm^3 received lopinavir-ritonavir–based HAART regimens. Although data have been inconsistent regarding an association between HAART and preterm birth, PI-based regimens, particularly ritonavir-boosted PI regimens, have been most often implicated in increased risk [17]. However, a recent study from South Africa of pregnant women with $CD4^+$ lymphocyte counts <250 cells/mm^3 found an increased risk of preterm birth with NVP- and efavirenz-based HAART regimens compared with PI-based HAART regimens [23]. Because HAART regimens are used more broadly in pregnant women in resource-limited countries, it will be important to conduct surveillance of rates of adverse events to determine the optimal HAART regimen for use in pregnancy for both maternal and infant health.

The pathogenesis of preterm delivery among all women and the potential increased risk among HIV-infected women are not well understood. Differentiating the cause of preterm birth—

either spontaneous after preterm labor or membrane rupture or indicated because of complications, such as hypertension—may help focus research into the pathogenesis of preterm birth among HIV-infected women [12, 24]. Although the inflammatory changes of immune reconstitution syndromes could contribute to preterm birth among women initiating HAART at lower $CD4^+$ lymphocyte counts, other mechanisms may be operative among women with higher counts. Antiretroviral drugs might be associated with preterm birth by inducing changes in systemic or local genital tract immunology, thereby precipitating preterm labor or membrane rupture, or drug-induced changes in systemic cytokines could increase hypertensive disorders and lead to preterm birth [24–26]. As HAART is rolled out more widely for pregnant women in resource limited settings, it will be critical to carefully monitor pregnancy outcomes, including congenital anomalies, preterm birth, stillbirth, and infant mortality, to assess risks and benefits of the different regimens used to treat and prevent MTCT and to determine optimal regimens for improving maternal health and maximizing HIV-free survival in infants.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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