Antiretroviral Therapy and Adverse Pregnancy Outcome: The Elephant in the Room?

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(See the major article by Li et al on pages 1057–64.)

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Combination antiretroviral therapy (ART) during pregnancy has resulted in a remarkable shift in the pediatric human immunodeficiency virus (HIV) epidemic, opening the opportunity for global elimination of new pediatric HIV infections. In 2013, the World Health Organization (WHO) recommended all pregnant and breastfeeding women with HIV infection should initiate ART, continued at least for the duration of mother-to-child transmission (MTCT) risk, with the option of continuing ART lifelong regardless of clinical or immune status in high HIV prevalence settings ("Option B+") [1]. Due to programmatic simplicity, many countries have adopted the Option B+ approach [2]. Additionally, ART started before conception and continued throughout pregnancy results in extremely low MTCT rates [3–6]. Given the Strategic Timing of Antiretroviral Therapy (START) trial results, demonstrating a 53% reduction in AIDS, other serious illness or death with immediate therapy at CD4 lymphocyte cell count above 500 cells/µL compared to deferring treatment until CD4 drops below 350 cells/µL, immediate lifelong treatment will likely be recommended by WHO for all HIV-infected individuals, including pregnant women [7, 8].

While the initiation of lifelong ART in all HIV-infected pregnant women has the potential to make perinatal HIV infection a rare event, as well as to improve maternal health and survival, it will also lead to a rapid rise in the number of fetal antiretroviral (ARV) drug exposures as pregnant and lactating women started on ART have subsequent pregnancies. Although there are overwhelming benefits of ART for both mother and infants, these do not come without potential risks. However, despite nearly 2 decades of ART use in pregnancy, evidence regarding safety remains limited and conflicting.

Most drugs, including ARVs, receive approval without specific testing in or labeling for use during pregnancy and, as a consequence, dosing and safety guidance are often based on only anecdotal data [9]. This poses particularly difficult problems for pregnant women with life-threatening diseases that require treatment with drugs of unknown safety or that have known safety concerns. For example, women with epilepsy need to continue antiepileptic drugs during pregnancy, yet many of these agents may increase risk of adverse pregnancy outcome, congenital defects, early cognitive delay, and infant mortality [10–12]. Managing epilepsy during pregnancy requires balancing the risks to the mother and fetus of uncontrolled seizures against risks of antiepileptic drugs. Assessment of drug safety in pregnancy, in turn, requires availability of scientifically valid studies regarding gestational effects on drug disposition and adequately powered studies to determine whether there are adverse effects and whether these differ among drugs/regimens. Current treatment strategies for epilepsy in pregnancy are to administer a single drug at the lowest dose required to achieve seizure control, avoiding valproic acid and multidrug therapy, and to monitor drug concentrations [13, 14].

Like epilepsy, HIV causes a serious disease that can affect the fetus and requires treatment during pregnancy. Administration of combination ART as opposed to a single drug is required, both for maternal health as well as optimal prevention of MTCT, which complicates evaluation of safety. The benefits of ART for mother and fetus/infant are clear, but we, unfortunately, have only incomplete data on safety [15, 16]. Several studies suggest antenatal ART may be associated with adverse pregnancy outcomes; the article by Li and colleagues [17] in this issue of The Journal of Infectious Diseases provides another piece of evidence suggesting that preterm delivery is associated with maternal ART in pregnancy, particularly when started preconception.

The association of antenatal ART and risk of preterm delivery and other adverse pregnancy outcomes remains controversial. Studies were initially restricted to resource-rich countries, and are primarily observational in nature, use different comparison groups, and provide conflicting data. In resource-rich countries, protease inhibitor (PI)–based ART has been...
preferred by many clinicians because of nevirapine-related toxicity and initial concerns regarding potential birth defects with efavirenz [18, 19]. Data on the association of antenatal PI-based ART and adverse pregnancy outcome have been suggestive, but inconsistent and primarily observational [20]. Two randomized trials comparing PI-based ART to non-ART regimens showed a significant association with preterm delivery <37 weeks' gestation. In the Botswana Mma Bana trial [21], women with CD4 cell count >200/µL were randomized to lopinavir-ritonavir-based ART versus a triple nucleoside reverse-transcriptase (NRTI) regimen; there was no difference in MTCT but a significant association of PI-ART with preterm delivery (16.2% vs 14.7%, P = .003). In the Promoting Maternal-Infant Survival Everywhere (PROMISE) trial [22], which randomized women with CD4 cell count >350/µL to lopinavir-ritonavir-based ART versus zidovudine/lopinavir during pregnancy. However, the Ugandan randomized trial [23] comparing 2 ART regimens—lopinavir-ritonavir-based versus efavirenz-based ART—found no significant difference in preterm delivery between regimens (16.2% vs 14.7%, respectively), although there was no non-ART comparator.

Other studies, particularly those from resource-limited countries where nonnucleoside reverse transcriptase inhibitor (NNRTI)-based ART is preferred in pregnancy, suggest preterm delivery is not confined to PI-based ART. In a prospective observational study in Botswana [24], including 22 609 HIV-uninfected and 9504 HIV-infected pregnant women delivering between 2009–2011, although most (96%) of HIV-infected women received ARVs (36% ART, 51% zidovudine), HIV-infected women compared to HIV-uninfected women had significantly higher rates of stillbirth (4.6% vs 2.5%, respectively), preterm delivery (23.7% vs 17.2%), small-for-gestational-age (SGA) infants (18.4% vs 11.5%), and neonatal death (2.3% vs 1.5%). In HIV-infected women, those receiving ART (87% nevirapine-based) compared to those receiving zidovudine alone had a significantly higher risk than of preterm delivery (19.8% vs 14.2%, SGA (21.5% vs 14.2%), and stillbirth (4.7% vs 1.7%), which persisted after adjustment for CD4 count, maternal age, parity, hypertension, and anemia. Additionally, women starting ART before pregnancy had higher odds of preterm delivery, SGA, and stillbirth compared to women first initiating ART or zidovudine during pregnancy.

Li and colleagues [17] now report on a prospective observational study conducted at 10 HIV centers providing perinatal services in Dar es Salaam, Tanzania, from 2004 to 2011, a time when antenatal ART was provided only for women meeting WHO criteria, with zidovudine prophylaxis for others. Of 3314 HIV-infected women, 452 received no ARVs, 1768 zidovudine alone, and 1094 ART (512 started during pregnancy and 582 preconception), with most receiving NNRTI-based ART (91% nevirapine- and 3% efavirenz-based). After adjusting for maternal CD4 cell count and other potential covariates (eg, age, hypertension), preconception ART was significantly associated with preterm (<37 weeks gestation) (adjusted relative risk [aRR] 1.24, 95% confidence interval [CI], 1.05–1.47) and very preterm (<34 weeks) (aRR 1.42, 95% CI, 1.02–1.99) delivery compared to women receiving zidovudine alone. ART started during pregnancy was not associated with prematurity but with increased risk of severe SGA compared to women receiving zidovudine alone (aRR 1.47, 95% CI, 1.09–1.98). Women receiving efavirenz-based ART had higher preterm delivery rates than those receiving nevirapine-based ART (HR 1.45, 95% CI, 1.01–2.07), but very few women received efavirenz.

Although globally the number of women on ART prior to conception will dramatically increase in the near future, few studies (most with small sample sizes) have evaluated risks associated with preconception ART. In a meta-analysis of 14 studies, only 4 of which addressed preconception ART, preterm delivery was higher with ART started preconception or in the first trimester than ART started in the second or third trimester (odds ratio [OR] 1.71, 95% CI, 1.09–2.67) [25]. Two studies with larger sample sizes published subsequent to this meta-analysis also identified preconception ART as a risk factor for preterm delivery. In the Botswana observational study [24], preterm delivery was higher in 543 women receiving preconception ART compared to 1515 starting ART or zidovudine during pregnancy (26.5% vs 22.7%, adjusted OR [aOR] 1.2, 95% CI, 1.1–1.4), and in the French Perinatal Cohort [26], preterm delivery was higher in 3893 women receiving preconception ART compared to 7413 starting ARV during pregnancy (15.9% vs 11.2%, aOR 1.31, 95% CI, 1.11–1.55).

An important potential confounder in all studies, including the Li et al study [17], is maternal HIV disease stage; women starting ART prior to conception may be more likely to have started because of advanced HIV disease and have risk factors for adverse pregnancy outcome not present in women first starting ART during pregnancy. However, the Botswana cohort [24], French Perinatal Cohort [26], and the Li et al study [17] conducted multivariate analyses controlling for CD4 cell count as well as other potential confounders (such as age, parity, drug use, hypertension), although residual unmeasured confounding could still exist.

Although several mechanisms have been proposed to account for associations between ART and adverse birth outcomes, research in this area has been sparse. Successful pregnancy is characterized by a shift from Th1 to Th2 immune milieu and cytokines; a Th1 to Th2 shift is also seen in untreated HIV infection [27–29]. One hypothesis is that ART and immune reconstitution could modulate the Th1 to Th2 shift required by...
normal pregnancy [30, 31]. There are limited data on placental cytokines in HIV-infected pregnant women on ART: placental cytokines in HIV-infected women on ART differ from those in HIV-uninfected women; decreased placental interleukin-10 levels were observed in women on ART delivering prematurely; and placental leptin levels, elevated in women with preeclampsia, were higher in HIV-infected women on ART compared to those not on ART [31–33]. Other hypotheses include heightened fetal recognition by the maternal ART-reconstituted immune system, modulation of placental progesterone production by PIs, and ART-associated increased risk of hypertension/preeclampsia predisposing to placental insufficiency and preterm delivery [30, 34–37].

In resource-limited settings, preterm delivery can be associated with significant morbidity and increased postnatal mortality [38]. In Uganda, uninfected infants born to HIV-infected mothers receiving ART had elevated neonatal mortality within 28 days of birth compared to neonatal mortality data; severe prematurity was a strong predictor of mortality [39]. However, most studies other than the Li et al study [17] did not differentiate between severe prematurity (eg, <34 weeks gestation) compared to preterm delivery between 34–37 weeks. Additionally, data on neonatal/infant mortality were lacking in most studies. In the Botswana study [24], despite the association of preconception ART with prematurity, it was not associated with elevated neonatal mortality compared to starting ARV during pregnancy; however, mortality in HIV-exposed infants was low (2.3%), limiting the power of this comparison. Similarly, in the PROMISE study [22], while moderate prematurity was associated with ART, severe prematurity and infant mortality were not. Given the lack of delineation of the severity of prematurity in most studies, and lack of data on infant mortality, conclusions about the ultimate clinical impact of these findings on infant mortality and morbidity is limited.

While the benefits of ART for preventing MTCT and maternal health clearly outweigh the risks identified to date, with global treatment scale-up, 1.5 million HIV-infected pregnant women and their fetuses will annually be exposed to ART [40]. We need to recognize that we have limited data on what these risks are; further research is needed to identify how to optimize ART to allow safe, healthy pregnancies for HIV-infected women and enhance health outcomes for their uninfected infants. As lifelong ART is implemented for HIV-infected pregnant women in resource-limited settings, it will be critical to monitor for adverse pregnancy outcomes and determine if these exceed those of the general population.

Note
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References


