Contemporary Issues in Pregnancy (and Offspring) in the Current HIV Era

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Abstract

Purpose of Review Although antiretroviral therapy (ART) has dramatically reduced mother to child transmission of HIV, data continue to mount that infants exposed to HIV in utero but are not infected (HEU) have serious negative health consequences compared to unexposed infants. This review evaluates recent literature on contemporary issues related to complications seen in pregnant women with HIV and their offspring.

Recent Findings Current studies show that HEU infants are at a high risk of adverse outcomes, including premature birth, poor growth, neurodevelopmental impairment, immune dysfunction, infectious morbidity, and death. Etiologies for the observed clinical events and subclinical alterations are complex and multifactorial, and the long-term consequences of many findings are yet unknown.

Summary HEU infants have an unacceptable rate of morbidity and mortality from perinatal HIV and ART exposure, even in the modern ART era. Continual monitoring and reporting is imperative to protect this vulnerable population in our everchanging landscape of HIV treatment and prevention.

Keywords Perinatal HIV · HIV-exposed · Uninfected infants · Antiretroviral therapy · Drug safety in pregnancy · Mitochondrial toxicity · Morbidity and mortality

Introduction

Few can argue the dramatic impact that antiretroviral therapy (ART) given to pregnant women and their infants has had on the prevention of maternal to child transmission (PMTCT) of HIV. It is arguably one of the best achievements to date toward the end to the HIV epidemic. Yet, data continue to mount that infants exposed to HIV in utero but are not infected (i.e., HIV-exposed/HIV-uninfected (HEU)) have serious negative health consequences compared to infants who have not been exposed (HIV-unexposed/HIV-uninfected (HUU)). During the early years of ART, concerns centered around mitochondrial toxicity related to antiretroviral drug exposure. Clearly, however, the

observed clinical events and subclinical alterations in HEU infants extend well beyond these complications and are complex and multifactorial. Moreover, as new antiretrovirals (ARVs) become available and with the upscale of Option B+ (universal, lifelong ART for all pregnant and breastfeeding women with HIV), we must stay vigilant to a rapidly changing landscape of risk in these vulnerable infants. This review evaluates recent literature on contemporary issues related to complications seen in pregnant women with HIV and their offspring.

Mitochondrial Dysfunction

Since early in the HIV epidemic, numerous studies have reported alterations in mitochondrial DNA (mtDNA) levels, abnormal histological morphology of mitochondria, and mtDNA mutations in HEU infants exposed to ART [1, 2]. Nucleoside reverse transcriptase inhibitors (NRTIs), in particular, have been implicated for this effect due to their affinity to bind to mitochondrial gamma DNA polymerase and disrupt mitochondrial replication [3]. Zidovudine, the most commonly used antiretroviral for PMTCT, has received the most

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attention. However, this effect is possible with all NRTIs, which continue to be the backbone of ART therapy for both pregnant women with HIV and their exposed infants. These mitochondrial alterations can lead to mitochondrial dysfunction, which most often manifests as mild and transient laboratory abnormalities, such as hyperlactatemia. Several concerning early reports of children with seizures, cognitive and motor delays, cardiac dysfunction, among other abnormalities [4, 5] have not been duplicated in subsequent studies, and severe clinical symptoms are generally thought to occur only rarely [6].

However, new studies continue to emerge describing adverse events and poorer clinical outcomes among HEU infants compared to HUU infants, which are described in detail in subsequent sections. Many of these have plausible links to mitochondrial dysfunction; relevant studies are highlighted in each section. Admittedly, these adverse outcomes are often multifactorial, and establishing causal relationships is difficult. Yet, we must stay open to the possibility that the well-recognized aberrations in mtDNA play a role in some of these effects. Moreover, despite some reassuring longitudinal data, it is too soon to know the long-term consequences of mtDNA alterations and mitochondrial dysfunction.

Adverse Birth Outcomes

Many recent studies continue to show that women with HIV have an increased risk of preterm delivery (PTD) and delivering infants who are small for gestational age (SGA), have a low birth weight (LBW), or have a birth weight significantly lower than HUU controls [7–10]. Not surprisingly, increasing ART use appears to decrease risk in some settings, presumably due to improved maternal health; however, the risk remains increased [10•, 11•], and the etiology is clearly complex. Indeed, even in studies where the majority of women are virologically suppressed, the risk of adverse birth outcomes is higher compared to uninfected women [8]. This is likely due to the numerous immunological, metabolic, and cardiovascular alterations that occur in HIV despite virological suppression. There is little doubt that these same alterations continue during pregnancy as well, even with virological suppression [12].

Moreover, other studies have suggested that pre-conception ART actually increases the risk of adverse birth outcomes. In Snijdewind et al. [13•], the risk of delivering an SGA infant was higher in women who had started ART prior to conception vs. those who started after conception, and there was a similar nonsignificant trend toward pre-conception ART and PTD. Similarly, two other studies have shown a significant relationship between pre-conception ART and PTD [9, 14•]. A higher rate of spontaneous abortion or stillbirth was also seen in women who conceived on ART, but the findings did not remain significant in the as-treated analysis [15].

Importantly, protease inhibitors (PIs), in particular, appear to increase the risk of PTD [8, 13, 14•, 16]. The highest PTD rates were observed in women who conceived on lopinavir/ ritonavir (LPV/r), irrespective of baseline CD4 count. Women who conceived on other PI/r-based regimens also had a higher PTD risk when their CD4 counts were ≤350 cells/mm3 [14]. More data are needed, but the effect of PIs on progesterone levels provides a potential mechanism [17]. On the other hand, rates of adverse birth outcomes with regimens that include tenofovir disoproxil fumarate (TDF) appear comparable to other regimens [18, 19], but data are limited.

Notably, a recent study showed that higher levels of soluble endoglin (which inhibits the actions of transforming growth factor and acts as an antiangiogenic factor) were associated with PTD and stillbirths in women with HIV on ART, and lower levels of placental growth factor were associated with SGA births [20]. This study was limited, however, by a lack of an HIV-uninfected comparator group. Another small cross-sectional study investigated mitochondrial, oxidative, and apoptotic placental abnormalities in 24 pregnant women with HIV and the relationship with adverse birth outcomes. The authors found a significantly depleted mtDNA content, an increase in oxidative stress, and a trend toward increased apoptosis in the placenta; however, there was no correlation between these abnormalities and PTD or SGA infants, which may have been due to the limited sample size [21]. Clearly, additional studies are needed to further delineate the risk and etiology of these adverse birth outcomes in HEU infants.

Infant Growth

Equally important are subsequent growth patterns and weight gain after birth, especially given that many HEU infants are born SGA or premature. Early infant growth and weight gain appear to be impaired compared to controls in several studies [9, 22–25], although the implementation of Option B+ may have a positive impact on postnatal weight gain [26–28]. A recent study showed that HEU infants had small but consistent deficits in early growth trajectories which were associated with a doubled risk of stunting by 12 months of age. Interestingly, however, overweight status (weight-for-length z-score > 2) was common in both HEU and HUU infants (16% and 18%, respectively). These findings likely reflect the current environment of universal maternal ART and breastfeeding in this peri-urban area of South Africa, highlighting the changing landscape of HIV treatment and the need for on-going surveillance and continued research. Similarly, third trimester maternal vitamin D status was associated with infant growth parameters in a cohort of HEU infants in the USA [29]. Vitamin D supplementation trials in pregnant women with HIV and their infants are warranted.

Despite the multifactorial nature of infant growth in HEU infants, malnutrition, gastrointestinal infections, and systemic immune activation undoubtedly have negative impacts [24]. There may also be a differential effect of various ARVs on growth parameters. In a recent study, infants born to asymptomatic mothers who did not qualify for ART were randomized to receive 7 days of either LPV/r or lamivudine [30]. At 26 weeks, infants who received LPV/r had poorer weight gain than infants who received lamivudine. Tenofovir, in contrast, does not appear to have a significant effect on general infant growth [31–33]. However, due to TDF's detrimental bone effects in people with HIV [34], a number of studies have evaluated fetal and infant bone growth in HEU infants. Despite an earlier study showing significantly lower neonatal bone mineral content [35], subsequent studies have not found a similar association even up to 12 months of follow-up [31, 36, 37••]. While reassuring, more sensitive measures of bone health may be needed, as well as a longer duration of follow-up to adequately assess long-term bone effects from TDF and other ARVs in HEU children.

Metabolic Complications

One aspect of mitochondrial health includes the biochemical reactions which produce cellular metabolites or energy and localize to the mitochondria, such as fatty acid oxidation, glycolysis, and parts of amino acid catabolism. Intermediary metabolites involved in these metabolic pathways include acylcarnitines and amino acids, the latter of which includes branched-chain amino acids (BCAAs). Previous studies have shown that HEU infants exhibit higher rates of abnormal acylcarnitine profiles than HUU infants, which are associated with in utero PI exposure [38]. Moreover, Jao et al. [39] demonstrated that there was a strong relationship between long-chain acylcarnitines and lower levels of mtDNA content and between short-chain and BCAA-related acylcarnitines and higher mtDNA content among HEU infants exposed to zidovudine. Likewise, another study by Jao et al. [40] showed that the acylcarnitine profile and BCAA were associated with altered insulin metabolism in HEU infants at 6 weeks of age. Together, these studies raise concerns that mtDNA alterations and dysfunction alter fuel utilization. Whether these changes affect neonatal growth and weight gain need to be explored. Moreover, whether these changes affect the long-term risk of metabolic complications, such as obesity or diabetes, deserve investigation.

Infectious Morbidity and Mortality

Dozens of studies over the last several decades have reported an increased risk of mortality in HEU infants and children compared to HUU infants, even when adjusted for confounders. A recent meta-analysis by Brennan et al. confirmed this finding [41]. The authors evaluated 22 studies with a total of 29,212 participants, demonstrating a 60–70% increased risk of death in HEU vs. HUU infants at every age strata over the first 2 years of life. The increased mortality remained even after 2002, when the availability of PMTCT services was widespread. In these and other newer studies, mortality is predominately driven by infections, which occur at a greater rate, with increased severity, and with higher rates of treatment failure [42–47]. The differential effect is certainly multifactorial, with contributions from a variety of factors, such as HIV-related immunosuppression, poorer maternal health, poor transplacental maternal IgG antibody transfer, and differences in modes of feeding [48–51]. Importantly, infants born in high-income countries are not immune from this increased risk [52].

Not surprisingly, uncontrolled HIV infection appears to play a role. For example, Yeganeh et al. [53] evaluated infants in HPTN 040/PACTG 1043 trial, whose mothers received no antiretroviral agents during pregnancy. They observed high rates of undernutrition, stunting and serious infectious morbidity within this cohort of 1000 HEU infants. Notably, viral loads greater than 1 million copies/mL were associated with increased rates of infectious serious adverse events, suggesting a direct role of the HIV virus in immune dysregulation in HEU infants. This study had a number of confounders, such as a lack of breastfeeding, high rates of no prenatal care, and maternal immunosuppression. Nevertheless, pre-conception ART appears to reduce the risk of infection-related hospitalizations [54•], emphasizing the positive impact of virological control on these outcomes.

Importantly, exclusive breastfeeding also decreases mortality in HEU infants, regardless of maternal ART status [55], and current World Health Organization (WHO) Consolidated Guidelines recommend that mothers with HIV should either breastfeed exclusively and receive ART or avoid breastfeeding entirely. A new study shows that exclusive breastfeeding also mitigates the infectious morbidity risk in these infants [56•]. However, in some settings, such as in high-income countries with access to clean water, high-quality formula, and specialized medical treatment, the benefits of breastfeeding must be weighed against the risk of HIV transmission. There is still a risk of HIV transmission via breastmilk, even with maternal virological suppression (undetectable HIV-1 RNA levels), albeit the risk is small (in Flynn et al. [57], 0.3% and 0.6% at 6 and 12 months, respectively).

Immune Dysfunction, Immune Activation, and Inflammation

Infectious morbidity and mortality among HEU infants led to investigations of possible immune abnormalities, which have

revealed the wide range of immune dysfunction in this vulnerable population [58, 59]. Some of these abnormalities clearly affect immune function [60] and may account for some of the observed infectious morbidity and mortality. However, other abnormalities, namely increased inflammation and immune activation [24, 61–63] could have additional implications, as this is a driver of non-AIDS comorbidities in people with HIV [64].

Dirajlal-Fargo et al. [62•] compared 86 HEU infants (80% born to mothers with undetectable HIV-1 RNA) to 88 HUU infants from a cohort in Brazil. The study reported statistically higher levels in HEU infants at birth for a number of inflammatory markers, including soluble tumor necrosis factor receptor I (sTNFR-I), interleukin-6, interferon gamma-induced protein 10, oxidized low-density lipoprotein, high-sensitivity C-reactive protein, soluble CD14 (sCD14), and soluble CD163. Mean differences between the two groups, however, were small (e.g., mean (standard deviation) sTNFR-I in HEU infants was 3.32 (0.16) vs. 3.25 (0.14) pg/mL in HUU infants). Differences between the two groups diminished further by 6 months of age, with some markers significantly higher in the unexposed group by this second time point, raising some doubt to the clinical significance of these findings.

Arguably, the more interesting finding in the aforementioned study was that levels of inflammatory markers in HEU infants were not significantly correlated with maternal levels and remained unchanged after adjustment for maternal levels, demonstrating that increased levels are not solely due to exposure to a pro-inflammatory in utero milieu. In fact, another study reported data that support this finding. In Baroncelli et al. [24], plasma levels of lipopolysaccharide-binding protein, a marker of microbial translocation, was strongly correlated with the immune activation marker, sCD14, in HEU infants, but neither was correlated with maternal parameters (viral load, CD4 cell count, or WHO stage). This study demonstrates that HEU infants have an intestinal barrier disruption that contributes to systemic immune activation and emphasizes the multiple pathways and complexities that affect the immune system in this population.

Similarly, another recent study has made a crucial link between metabolic stress, mitochondrial dysfunction, and altered fetal immune responses among HEU infants [65••]. Pregnancy, even in the best of circumstances, places extreme metabolic and nutritional requirements on both the mother and infant. In the face of maternal infection, pharmacological exposure, and often malnutrition, metabolic demands activate stress responses in the endoplasmic reticulum and mitochondria, which induce potent pro-inflammatory pathways. As described above, certain ARVs, such as zidovudine, can also reduce mitochondrial DNA polymerase, contributing to further mitochondrial stress. By using novel, highly sensitive metabolomic techniques, Schoeman et al. [65••] detected extensive lipid and mitochondrial dysregulation in cord blood

from 15 ART-exposed HEU infants compared to 12 HUU infants. For example, 13 reactive oxygen species (ROS)-catalyzed lipid peroxidation metabolites (generated by mitochondria upon cell stress) were identified in HEU infants compared to none in HUU infants, indicating altered mitochondrial functioning. Likewise, lipid profiles in HEU infants were characterized by increased triglyceride species and decreases in phospholipid species, indicative of endoplasmic reticulum stress. Moreover, not only were pro-inflammatory cytokines higher in the HEU infants, but the accumulated pro-inflammatory metabolic mediators were significantly and extensively associated with pro-inflammatory cytokines and chemokines. These results reveal potential mechanisms by which mitochondrial dysfunction and altered metabolic processes can lead to pro-inflammatory immune responses and altered immune function in HEU infants.

Congenital Abnormalities and Cardiac Dysfunction

The data estimating the risk of major congenital abnormalities associated with perinatal HIV and ART exposure continue to be generally reassuring [66–71], including a recent meta-analysis evaluating pre-conception ART use [67] and a study including elvitegravir [71]. The authors acknowledge, however, that data for the extent and severity of these risks are scarce and of lower quality. Thus, we must stay vigilant to possible risks, as new concerns arise. One study recently linked first trimester zidovudine exposure to congenital heart defects (ventricular septal defects) and postnatal myocardial remodeling in girls [72], again raising the concern over mitochondrial toxicity with zidovudine use. While another study did not find a similar risk of congenital heart defects [73], a third study did find subclinical differences in left ventricular structure and function [74]. Longitudinal studies are therefore needed to assess long-term risk of cardiac dysfunction in ART-exposed HEU infants.

Similarly, Berard et al. [75] described an increased risk of small intestine defects and other defects of the digestive system ($N = 2$) which evaluated 198 infants with first trimester ART exposure among 214,240 pregnancies from 1998 to 2015 using the Quebec Pregnancy Cohort. There was also a trend toward an increased risk of defects of the great arteries and other cardiac malformations ($N = 2$) and defects of the feet ($N = 3$). While the study had limitations and the absolute number of cases was small, continued surveillance is needed, especially within large cohorts. Of note, ART exposure occurred in the setting of pre-exposure prophylaxis (PrEP) for 10 pregnancies, highlighting the evolving nature of ART exposure and the growing number of susceptible infants.

Likewise, integrase inhibitors are now the preferred first-line treatment in many countries. While raltegravir is currently

the only approved integrase inhibitor in pregnancy, the others are often used off-label for a number of reasons, such as once daily dosing and/or well-controlled virus with one of these ARVs prior to conception. Preliminary results from the on-going Tsepamo surveillance study in Botswana triggered an early signal for a potential increased risk in neural tube defects (NTDs), despite earlier data reporting no concerns [76, 77]. Four cases of NTDs were identified out of 426 infants born to women with HIV taking dolutegravir (DTG)-based regimens at conception (0.94% prevalence vs. 0.12% in women not on DTG) [78••]. Continued surveillance showed no additional NTD cases, decreasing the prevalence to 0.67%, which is reassuring yet still higher than other non-DTG regimens [79]. Thus, avoidance of DTG in women desiring to conceive or during the first trimester is advisable until further data become available. The other integrase inhibitors have not yet been implicated, although few data currently exist for bictegravir. Integrase inhibitors do not appear to inhibit folate transport [80], but other mechanisms which could affect folic acid metabolism have not been adequately evaluated.

While much attention is paid to the potential consequences of ART drug exposure, adverse outcomes in HEU infants are complex and likely multifactorial. Importantly, Berard et al. did show a significantly higher prevalence of major congenital malformations in infants who were exposed to HIV without ART exposure ($N = 169$) compared to the control population (14.8% vs. 8.6%, $P = 0.004$). Thus, the role of HIV exposure independent of ART exposure should not be ignored.

Neuropsychological Development

A number of studies have evaluated the risk of neuropsychological development in HEU infants, given that HIV is neurotropic and some of the commonly used ARVs in the PMTCT, such as efavirenz, have neuropsychiatric side effects. While some studies are reassuring [81–86], other studies have demonstrated that HEU children have significantly lower neurodevelopmental outcomes than HUU controls [87–91]. The heterogeneous results likely reflect the numerous confounders, including differences in poverty levels, nutritional status, maternal education, PTD, and perinatal ART exposure. A recent meta-analysis did show lower cognitive and motor scores among HEU infants, while trying to control for a number of these confounders [92•], but more data are needed. Differences among various ARVs also need to be further evaluated, as some studies, but not all, show differential effects [90, 93, 94].

Neurodevelopmental effects in HEU infants may also not be evident initially, requiring a longer duration of follow-up. For example, one recent cross-sectional, nested case-control study looked at the risk of autism spectrum disorder (ASD) among HEU children, as both have been associated with mtDNA alterations [95]. HIV-exposed, uninfected children with ASD were matched approximately 1:3 on age, sex, and ethnicity to HEU children without ASD, HUU children without ASD, and HUU children with ASD. Among 299 HEU children, 4.7% were diagnosed with ASD, which is higher than the general population prevalence estimates. HEU children with ASD had significantly higher leukocyte mtDNA content than all other study groups, suggesting that mitochondrial dysfunction may contribute to ASD risk in this population.

Cancer Risk

While we now recognize many of the short-term ramifications of HIV and ART exposure in infants, the long-term consequences of mtDNA, immune dysfunction, and other alterations are largely unknown. An increased cancer risk has been proposed, given that NRTIs all cross the placenta (with some actively concentrated in amniotic fluid), enter cells, and can integrate into human DNA after phosphorylation. Initial concerns were focused on mtDNA, as NRTIs bind to mtDNA and inhibit DNA polymerase-γ, which is responsible for mitochondrial DNA replication. Additional concerns, however, have been raised regarding genotoxicity due to interactions with nuclear DNA.

Ivy et al. [96] evaluated a cohort of children in New Jersey who had been exposed to ART from 1995 to 2008 with a median follow-up of 9.8 years and identified 4 cancer diagnoses. They did not observe a statistically different incidence of cancer compared to the expected number of cases. Although reassuring, this study lacked data on timing and duration of ART exposure and did not provide specific medication history. In contrast, HEU children exposed to NRTIs from a French cohort were evaluated for cancer risk compared to the general population. A total of 21 cancers were identified among 15,163 children with a median age of 9.9 years exposed to at least one NRTI in utero between 1990 and 2014. Five children were exposed to zidovudine monotherapy, and 16 were exposed to various combinations, 7 of which included didanosine. Didanosine accounted for only 10% of prescriptions but was associated with one-third of cancers. In a multivariate analysis, didanosine exposure was significantly associated with a higher risk [hazard ratio (95% confidence interval) = 3.0 (0.9–9.8)] which increased further with first-trimester exposure [hazard ratio (95% confidence interval) = 5.5 (2.1–14.4)]. While the total number of cancer cases did not differ significantly from that expected for the general population, the incidence was double that expected after didanosine exposure [97, 98••].

Fortunately, the harm of didanosine has now been recognized and has been replaced by newer, arguably safer, ARVs. However, children in these two aforementioned studies had median ages of only 10 years, necessitating continued

surveillance for cancer risk related to not just didanosine but other ARVs, as they age into adulthood.

Conclusions

Although ART has dramatically reduced maternal to child transmission of HIV, HEU infants continue to experience an unacceptable amount of negative health effects, even in the modern ART era. Similarly, despite some reassuring longitudinal data, it is too soon to know the long-term metabolic, immunologic, and oncogenic consequences of perinatal HIV and ART exposure. Adding to the complexity, newer agents are being used with greater frequency and for longer durations during pregnancy, and now ARVs are used not only in pregnant women with HIV but also as PrEP to women without HIV. Thus, the total number of potentially affected children will continue to dramatically increase worldwide. Continual monitoring and reporting is imperative to protect this vulnerable population in our everchanging landscape of HIV treatment and prevention.

Compliance with Ethical Standards

Conflict of Interest Dr. Kirk reports personal fees, non-financial support and other from Thera Technologies, outside the submitted work. Dr. Eckard reports personal fees and non-financial support from Theratechnologies, Inc. and Gilead Sciences, outside the submitted work. Dr. Hagood has nothing to disclose.

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•• Of major importance

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