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Metabolic Complications of *in utero* Maternal HIV and Antiretroviral Exposure in HIV-Exposed Infants

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Abstract

Background—Despite a wide body of literature supporting the use of antenatal antiretrovirals (ARV) for the prevention of mother to child transmission, there remains a need for continued monitoring as the intrauterine interval is a critical period during which fetal programming influences the future health and development of the child.

Methods—We conducted a systematic review of the current literature addressing potential metabolic complications of *in utero* HIV and ARV exposure. We describe studies evaluating metabolic outcomes such as intrauterine and early postnatal growth, bone health, and mitochondrial toxicity.

Results—Overall, infants exposed to HIV/ARV do not appear to exhibit vastly compromised intrauterine or early postnatal growth. However, some studies on the effect of combination antiretroviral therapy (cART) on small for gestational age (SGA) and low birth weight (LBW) outcomes in low-middle income countries show a risk for SGA/LBW while those in the U.S. do not. Postnatal growth to 1 year does not appear to be affected by *intrauterine* tenofovir exposure in African studies, but a U.S. study found statistically significant differences in length for age *z* scores (LAZ) at 1 year. Little data exists on long term bone health. Mitochondrial toxicity including abnormal mitochondrial morphology and DNA content, as well as neurologic deficits and death have been demonstrated in HIV/ARV–exposed infants.

Conclusion—Though gross measures of metabolic well-being appear to be reassuring, careful vigilance of even small risks for potential serious adverse effects to infants exposed to intrauterine HIV/ARVs is warranted as intrauterine fetal metabolic programming may substantially impact the future health of the child.

Keywords

Metabolic; Complications; Exposure; HIV; ARV

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Since the introduction of zidovudine (AZT) for the prevention of mother-to-child transmission (PMTCT) in 1994(1), a wide body of literature has emerged evaluating the overall safety of *in utero* antiretroviral (ARV) exposure.(2–4) While some uncertainty still shrouds this issue, research largely suggests that the benefits of perinatal ARVs far outweigh the potential risks, supporting the use of antenatal antiretroviral therapy (ART) for PMTCT. Nonetheless, continued monitoring is necessary as the intrauterine interval is a critical period in which fetal programming influences the future health of a child. Fetal programming has been implicated as an important epigenetic mechanism whereby changes in the *in utero* environment can affect later disease development.(5, 6) In essence, the prenatal environment may have profound effects on intracellular signaling and metabolic pathways which, in turn, affect future development of chronic diseases.

Fetal metabolism, and consequently growth, depends on placental sufficiency and nutrients crossing the placenta. Maternal HIV may restrict placental size (7, 8) and cause morphologic changes,(8, 9) leading to deficient nutrient transfer and aberrant fetal metabolism. Metabolic complications from these changes may include compromised intrauterine and postnatal growth from placental insufficiency, poor bone health from decreased vitamin D and calcium transfer, as well as mitochondrial toxicities attributed to ARV exposure. In this review, we summarize the current literature addressing potential metabolic complications of *in utero* HIV/ARV exposure.

METHODS

We reviewed all English, French, and Spanish articles identified using a PubMed/Medline database search up to October 2013 using combinations of keywords including fetal, intrauterine, growth, birth weight (BW), low birth weight (LBW), small for gestational age (SGA), bone, mitochondrial toxicity, mitochondrial dysfunction, pregnancy, outcomes, infant, neonatal, perinatal, HIV exposure, maternal HIV, antiretrovirals, zidovudine, tenofovir, nucleoside analogues, combination antiretroviral therapy (cART), and highly active antiretroviral therapy (HAART) as well as a MeSH term search. Reference lists of all papers identified were reviewed for additional papers. We considered the article relevant if it contained information on HIV-infected pregnant women and any infant metabolic outcome including but not limited to fetal growth, postnatal growth, bone health, and mitochondrial toxicity (MT).

INTRAUTERINE GROWTH

Several studies have evaluated the association of maternal HIV and *in utero* ARVs with birth outcomes such as BW, LBW (<2500 g), SGA, and preterm birth. (Figure 1) We focus on BW, LBW, and SGA in our discussion, as the causes of preterm birth, while often overlapping with those of LBW/SGA, are generally more multifactorial in nature and may be less directly associated with metabolic complications related to placental insufficiency. Unless otherwise noted, outcomes of SGA for BW were defined in the highlighted studies as <10th percentile according to standards specific to each study.

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Maternal HIV Exposure

Since most HIV-infected pregnant women now receive antenatal ARVs, it has been increasingly difficult to disentangle the effects of *in utero* HIV and ARV exposure. One study in Tanzania demonstrated that untreated HIV-infected women were more likely to have SGA infants than HIV-uninfected women [Odds Ratio (OR):1.64, Confidence Interval (CI):1.1–2.44]. (10) (see Table, SDC 1) Another South African study reported comparable associations [Relative Risk (RR): 1.28, CI: 1.06–1.53) (11), suggesting an association between maternal HIV infection and poor BW outcomes. The latter study also found evidence for an association between maternal CD4 cell count <200 cells/mm^3 and SGA in adjusted subgroup analyses (RR: 1.43, CI: 1.0–2.07, p=0.05) as well as a lack of difference in SGA by infant HIV infection status. Two African studies conducted prior to the availability of ARVs for PMTCT report similar associations with LBW,(12, 13) and another reported lower mean BWs and birth lengths (p=0.01 for both) in infants born to HIV-infected women.(14) Several of these studies did not report results stratified by maternal immunosuppression or disease severity, limiting interpretation of these findings.(10, 12, 13)

ARV Exposure

As PMTCT prophylaxis has advanced from AZT monotherapy to combination antiretroviral therapy (cART), we highlight studies assessing effects of specific ARVs as well as cART. Unless otherwise noted, cART refers to the use of three drugs, generally two NRTI with a PI or NNRTI.

Zidovudine—Several studies have confirmed the overall safety of AZT on fetal growth. (15–19) Secondary data analysis on the Pediatric AIDS Clinical Trials Groups (PACTG) 076 revealed no difference in mean weight, length or head circumference through 18 months amongst uninfected infants between AZT and placebo groups. Rates of SGA in this study were also no different, though this latter finding should be interpreted with caution as both infected and uninfected infants were included in the birth cohort. (15) In addition, randomized clinical trials (RCTs) from Africa and Thailand revealed no increased risk of SGA births in women receiving AZT vs. placebo.(16–18) The West African DITRAME study reported no differences in LBW between infants exposed to *in utero* AZT vs. placebo, but this analysis included infected infants.(16) One RCT in Thailand also did not demonstrate any differences in mean BW (17) between AZT-exposed and unexposed infants. Another reported decreased birth weight-for-age (WAZ) and weight-for-length (WLZ) z scores in those with ≥7.5 vs. <7.5 weeks of *in utero* AZT exposure, though the actual difference, 50g, was small. (18) Lastly, the European Collaborative Study (ECS) reported a protective effect of antenatal AZT against LBW (OR: 0.55, CI: 0.39–0.79). (19) The varied nature of these cohorts, particularly around the inclusion of HIV-infected infants, has made it challenging to properly compare studies and reach consistent conclusions.

Tenofovir disoproxil fumarate—The introduction of the TDF/emcitritabine once-daily combination pill has shifted the landscape of cART administered in pregnancy. Its benefits in ease of dosing, decreased risk of MT,(20, 21) and 2010 designation by the World Health Organization (22) as first-line ART in HIV-infected adults have played a role in the doubling of its use in developing countries.(23, 24)

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The Pediatric HIV/AIDS Cohort Study (PHACS) evaluated 2029 HIV/ARV-exposed infants and found no increased risk of LBW (OR:0.87, CI:0.63–1.2), SGA (OR:1.01, CI:0.65–1.64), or birth LAZ < −1.5 (OR:1.28, CI:0.73–2.25) or differences in birth WAZ between TDF-exposed (21%) and TDF-unexposed infants.(25) In an analysis of 2025 infants exposed to maternal HIVARV, the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) protocol P1025 found no differences in rates of SGA (as defined by BW z score <10th percentile) (OR: 1.09, CI: 0.77–1.52) or mean BW z scores between TDF-exposed and -unexposed neonates (p=0.9).(26) The DART study in Uganda and Zimbabwe assessed infants born to women enrolled in this RCT from 2004–2009 and also found no difference in rates of LBW by TDF exposure [19% (19/130) in TDF-exposed vs. 15% (13/69) in TDF-unexposed, p=0.44]. (27)

Combination Antiretrovirals—Combination ART has been shown to have inconsistent associations with LBW and SGA. Studies in the U.S./Europe have largely reported no associations between cART and LBW/SGA, whilst some in low-middle income countries have reported otherwise. This may be explained by differences in sample size, population characteristics, and access to obstetrical care. A combined analysis of 3266 participants including three single site studies, PACTG 076 & 185, the Perinatal AIDS Collaborative Transmission Study (PACTS), and the Women and Infants Transmission Study (WITS) reported no increased risk for LBW when cART exposure was compared to both AZT monotherapy and no cART in multivariate analysis.(28) The ECS reported no evidence of increased LBW rates in children exposed to any vs. no *in utero* ART.(29) An analysis of 9504 infants born to Botswanan women, however, identified cART in pregnancy as an independent predictor of SGA. Other factors associated with SGA included a prior adverse pregnancy outcome, alcohol use, gestational hypertension, and a maternal CD4 cell count ≤200 cells/mm^3. (30) Another study in Côte d'Ivoire evaluated LBW outcomes and reported similar results.(31) Both reported an additional risk with cART initiated pre-pregnancy compared to that initiated during pregnancy, a finding which was not seen in the U.S. PHACS.(32) When evaluating the effect of maternal CD4, it is interesting that both the Botswanan and U.S. PHACS studies found maternal CD4 cell count ≤200 cell/mm^3 to be associated with SGA while the study in Côte d'Ivoire did not find a similar association with LBW. Unlike these studies, a combined analysis of ACTG 5190/IMPAACT 1054 including participants in Africa, Thailand, India, and Brazil found no risk of SGA in infants exposed to *in utero* cART vs. AZT in univariate analysis, though this study may not have been adequately powered to detect true differences in SGA as only 10% (n=24/236) were born to women on cART. Maternal ARV exposure groups were also reasonably varied in levels of viremic control: 92% of women on cART reached HIV RNA levels <1000 copies/mL but only 36% of those on AZT plus intrapartum ARV reached this level of viremic control. The study did not report multivariate analyses adjusting for these or other factors such as maternal regimen or immunosuppression. (33)

Because of a wider range of ART choices available in North America, studies in the U.S. have attempted to distinguish effects between ART classes on intrauterine growth. Though the earlier PACTG 076 & 185/ PACTS/WITS combined analysis demonstrated a lack of association between cART and LBW, it did find a slightly increased risk of very (V)LBW

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with PI-based cART (OR=3.03, 95% CI: 1.04–12.19).(28) Neither the PHACS study (32) nor a U.S. study of 183 HIV-infected pregnant women (34) revealed an association of PI-based cART with SGA. However the latter did report a small protective effect of non-nucleoside reverse transcriptase inhibitors (NNRTIs) on SGA (OR=0.28, 95% CI: 0.1–0.75).(34)

POSTNATAL GROWTH

While some infants may be born SGA, whether *in utero* maternal HIV/ARV exposure has lasting impact on infant growth remains unknown. The worldwide heterogeneity of HIV-infected maternal/child dyad cohorts, chiefly around risk behaviors and nutritional/socioeconomic status, has complicated our ability to properly assess postnatal growth in HIV-exposed uninfected (HEU) children.

Maternal HIV Exposure

Unlike studies assessing intrauterine growth, studies assessing postnatal growth have not reported a direct association with maternal HIV.(35, 36) This may be because a number of studies assessing intrauterine growth have included both HIV-infected and uninfected infants, while those assessing postnatal growth have excluded HIV-infected infants. A British study conducted prior to the widespread use of ARVs in pregnancy (1984–1992) showed no differences in growth to 3 years between HEU and HIV-unexposed children.(35) In a study of 1403 HEU children, the ECS reported no differences in growth to 10 years when comparing HEU children to British 1990 standards.(36)

ARV Exposure

Zidovudine—Consistent with results evaluating intrauterine growth, long term follow-up of infants exposed to *in utero* AZT has not revealed detrimental effects on postnatal growth. PACTG 076 & 219 reported no differences in growth to 4 years between those exposed to *in utero* AZT and placebo.(37) RCTs in Thailand have reported the same after an 18 month follow up.(17, 18)

Tenofovir disoproxil fumarate—The only studies which have evaluated the effect of *in utero* TDF exposure on postnatal growth in HEU infants are those mentioned above. (25–27) DART reported no differences in mean WAZ between groups when growth was followed to 3 years.(27) Increased LAZ in TDF-exposed infants were noted during year 1 to year 2, but this difference did not persist thereafter. PHACS evaluated WAZ, LAZ, and HCAZ at 1 year of age and found that TDF-containing regimens were associated with lower mean LAZ and HCAZ (p=0.04 & 0.02).(25) IMPAACT 1025 reported no differences in WAZ at 6 months between groups (p=0.61).(26) Further studies will be required to assess in *utero* TDF exposure and long term growth.

Combination Antiretrovirals—Two large European cohorts have evaluated the impact of cART on growth through 18 months in HEU but reported somewhat contradictory findings. The ECS reported decreased WAZ (−0.1, p=0.019), LAZ (−0.12, p=0.008), and HCAZ (−0.14, p=0.001) associated with cART vs. no ART or AZT monotherapy.(38) A

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study in Spain found no evidence for abnormal WAZ, LAZ, or HCAZ when comparing infants exposed to any vs. no *in utero* ARVs and those exposed to PI vs. non-PI based cART. (39) A small U.S. study comparing growth to 2 years in HEU and HIV-unexposed children found no differences in growth.(40) A combined analysis of ACTG 5190/ IMPAACT 1054 participants did not find evidence of decreased WAZ, LAZ, or HCAZ in infants exposed to cART vs. AZT.(33) Lastly, a secondary analysis of two RCTs in Botswana reported no differences in WAZ or WLZ by 6 months of age in infants exposed to *in utero* cART vs. AZT prophylaxis.(41)

BONE HEALTH

Bone mineral content has been shown to be decreased in HIV-infected adults(42) and children(43–45) on ART. TDF-containing regimens have been associated with decreased bone density in adults (46, 47), though reports in children have been conflicting.(48–50) Studies in rhesus macaques have demonstrated compromised intrauterine growth, diminished insulin-like growth factor-1 (IGF-1), and slightly decreased fetal bone porosity in infants born to high dose TDF-treated SIV-infected and –uninfected monkeys,(51, 52) raising concern regarding possible detrimental effects of *in utero* TDF exposure on infant bone health.

Few studies have directly evaluated early markers of bone health in ART-exposed infants. One study assessed neonatal bone status by quantitative ultrasonography as well as bone formation and resorption via bone alkaline phosphatase and C-terminal telopeptide of type I collagen in cord blood.(53) No differences were found between HIV/ARV-exposed and unexposed infants. Another study specifically evaluated the effect of *in utero* TDF exposure on bone health using these measurements in addition to serum calcium, phosphate, albumin, parathyroid hormone, 25-hydroxyvitamin D, 1,25-hydroxyvitamin D, IGF-1, and urinary calcium and creatinine.(54) Neither growth, measured via quantitative ultrasound, nor parameters of bone metabolism were statistically different between groups. As these studies were small and conducted in the same cohort their generalizability should be interpreted with caution. A current TDF safety substudy of the IMPAACT 1077 Promoting Maternal and Infant Survival Everywhere (PROMISE) study evaluating bone health via serum markers and dual energy x-ray absorptiometry (DEXA) in mothers/infants exposed to TDF-containing antepartum regimens is underway and will bridge gaps in knowledge in this critical area.(55)

MITOCHONDRIAL TOXICITY

Since the first report of mitochondrial dysfunction in HIV/NRTI-exposed infants exhibiting neurologic impairment, concern has evolved regarding the effects of *in utero* ART on the fetus.(56) Proposed mechanisms of MT include: 1) inhibition of mitochondrial DNA (mtDNA) polymerase-γ, 2) production of defective mtDNA, and 3) inefficient repair of errors in mtDNA replication. NRTIs inhibit mtDNA polymerase-γ, required for mtDNA replication.(57) This results in decreased levels of mtDNA/RNA and disruption of proper oxidative phosphorylation (OXPHOS), thereby leading to mitochondrial dysfunction.(58, 59) Additionally, because NRTIs can be incorporated into mtDNA by mtDNA polymerase,

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early mtDNA chain termination and inefficient NRTI excision may occur resulting in defective mtDNA.(60–62)

Animal Studies of MT from in utero ART

Studies in HIV-uninfected pregnant *Erythrocebus patas* mother/infant monkey dyads exposed to AZT have shown dose-dependent decreases in mtDNA levels, decreases in OXPHOS Complex I activity and abnormal mitochondrial morphology in cardiac and skeletal muscle cells at birth.(63) Similar findings were reported in studies evaluating brain cells of *patas* monkeys at birth, though no abnormal mitochondrial morphology was noted.(64) (see Table, SDC 2) Another study found evidence of abnormal mitochondrial morphology, and specific NRTIs (3TC, d4T) were associated with abnormal respiratory chain activity.(65) Lastly, a recent study evaluating the effects of NRTI incorporation into nuclear DNA (nDNA) and mtDNA in *patas* monkeys from birth to 3 years reported an 8-fold increase in cells with centrosomal amplification and an increase in cells with genetic material separated from nuclei in AZT/3TC-exposed *patas* at birth.(66)

Abnormal mtDNA

Both mtDNA mutations as well as overall levels of mtDNA have been studied in humans. When compared to HIV-unexposed infants, infants exposed to HIV/AZT-containing cART have demonstrated increased mtDNA(67) and nDNA abnormalities(68) in umbilical cord cells. A recent study on the latter even found evidence of increased aneuploidy and consistent alterations in gene expression affecting pathways of cell signaling, transcription, DNA recombination, replication, and repair in cord cells of infants exposed to AZT-containing cART.(68) Reports of mtDNA levels in infants exposed to *in utero* HIV/ART are conflicting. Earlier studies in smaller U.S. cohorts reported decreased mtDNA levels in cord blood mononuclear cells (CBMCs), peripheral blood mononuclear cells (PBMCs), and placental cells(69–71) in those exposed to HIV/AZT *in utero* compared to those unexposed to HIV as well as in those exposed to AZT vs. no AZT. A subsequent larger U.S. study confirmed this former finding when evaluating PBMCs but did not report the latter association with AZT. In fact, infants exposed to *in utero* AZT-3TC or AZT were found to have higher mtDNA levels than those unexposed to either.(72) Other studies in North America(73, 74) and Africa(75) have shown similar findings of increased mtDNA levels or no differences in mtDNA levels(76) in those exposed to cART. Several explanations may account for these conflicting results. Maternal HIV infection itself causes mitochondrial injury which may be mitigated by initial ART use, causing a rise in mtDNA levels. As women in the smaller studies were significantly more immune-compromised than those in subsequent studies, the effect of HIV on MT may have outweighed a possible beneficial effect of ART. In addition, the heterogeneity of results may reflect the wide range of cell line/tissue types used to detect mtDNA toxicity in these studies. Lymphocytes may produce more mtDNA, and mtDNA changes in PMBCs have not been shown to correlate well with mtDNA in tissue.(77) Another possibility is that fetal tissues may respond to maternal HIV/AZT-induced MT through a compensatory rise in mtDNA genesis.

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Aberrant Mitochondrial Morphology

In the first case report of mitochondrial dysfunction from *in utero* ART, two of eight infants were found to have ultra-structural mitochondrial abnormalities by electron microscopy, one of whom died and both of whom exhibited seizures and neuromuscular abnormalities.(56) Aberrant mitochondrial morphology has also been demonstrated in endothelial cells of umbilical cord arteries (70) but not placental tissue (78) of infants exposed to *in utero* HIV/cART vs. those unexposed. Abnormal histology included excessive and swollen mitochondria with multiple membrane disruptions, extensive loss of cristae and matrix material, and in some, complete effacement of the central architecture.

Respiratory Chain Compromise

Mitochondrial DNA specifically encodes the subunit II of cytochrome c-oxidase (Complex II), while nDNA encodes subunit IV (Complex IV). Several studies have evaluated Complex II:IV ratios to further assess mitochondrial function in infants exposed to ART. Decreased Complex II:IV ratios have been reported in placental tissue (78) and CBMCs(76) of HIV/ART-exposed infants vs. -unexposed infants.

Pathways of intermediary metabolism such as fatty acid oxidation, organic acid and amino acid metabolism also require normal respiratory chain function. One study examined acylcarnitine and amino acid profiles, products of intermediary metabolism, from newborn metabolic screens in the U.S. and found a higher rate of abnormal screens in infants who also screened positive for HIV infection (2.2% vs. 1.2%, p=0.00025).(79) In addition, the rate of abnormal acylcarnitine levels was increased in ARV-exposed infants (43% vs. 0%, p=0.02).

Clinical Mitochondrial Dysfunction

Clinical manifestations of mitochondrial dysfunction may be varied as they depend on the tissue type affected. Lactate build-up is a result of mitochondrial dysfunction and known adverse effect of NRTIs. (80) Several studies have evaluated hyperlactatemia in infants exposed to *in utero* ART/HIV.(81–84) A Spanish study reported a 49.6% rate of hyperlactatemia (defined as >2.5 mmol/L) and reported an association with *in utero* didanosine exposure (OR: 1.06 per 1 week of fetal exposure, CI: 1.01–1.11).(82) An Ivorian study required ≥ 2 increased values and reported 13.4% with hyperlactatemia. No association was found between AZT or AZT-3TC *in utero* and hyperlactatemia, but *in utero* AZT-3TC was associated with increased mean lactate levels when compared with AZT monotherapy (p=0.009).(83) In a large U.S. cohort of HEU infants, only 3.4% were found to have hyperlactatemia when using a lactate threshold of >3 mmol/L.(84) Use of emcitritabine (OR: 2.23, CI: 1.12–4.42) and efavirenz (OR: 4.05, CI: 1.62–10.1) were found to be associated with hyperlactatemia. Variations in methods of lactate measurements as well as definitions of hyperlactatemia may account for the discrepancies in study findings.

Studies in France have shown an association of *in utero* HIV/ART with significant mitochondriopathy presenting as seizures, cognitive delays, motor and cardiac dysfunction, and even death.(56, 85) The French Pediatric Cohort (EPF) reported a significantly increased incidence of established/possible mitochondrial dysfunction in ARV-exposed

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infants (21/2644 vs. 0/1748, p=0.002). The relative risk (RR) of mitochondrial dysfunction was increased in those with *in utero* combination NRTI vs. AZT monotherapy exposure (RR: 2.5, CI: 1–6.5, p=0.046). Defects in respiratory chain complex enzyme units and abnormal mitochondrial morphology were also identified in available specimens.

In constrast, the Perinatal Safety Review Working Group reviewed 223 deaths amongst five cohorts of HIV-exposed children <60 months of age (n=23,265) and found no deaths associated with signs/ symptoms either suggestive of or proven to result from MT. (86) In addition, based on a population-based surveillance study of 9,067 HEU/ indeterminate infants, no deaths thus far have been directly linked to *in utero* HIV/AZT-induced MT in the U.S.(87) A secondary analysis of 984 HEU infants in the U.S. found only three cases of possible/established cases of MT. (88) No association between perinatal AZT and cardiac toxicity has been demonstrated in the U.S.(89) The PACTG 219 study did find an association between first exposure of 3TC or AZT-3TC in 3rd trimester with increased risk of mitochondrial dysfunction (RR: 10.57, CI: 1.93–75.61 and RR: 9.84, CI: 1.77–71.68). (90) However, the authors were unable to control for important factors such as maternal viremia or antenatal drug use.

CONCLUSION

The use of ARVs for HIV treatment and PMTCT has expanded tremendously since 1994. Possible adverse metabolic effects must be tempered with the overwhelming benefits of ARVs administered to HIV-infected pregnant women. Though gross measures of metabolic well-being such as intrauterine and early postnatal growth appear to be reassuring, more complex appraisals of metabolic health will require more sophisticated measures of bone health, mitochondrial function, and even pathways of intermediary metabolism. Careful vigilance of even small risks for potential serious adverse effects to infants exposed to *in utero* HIV/ARVs is warranted as intrauterine fetal metabolic programming poses a substantial impact on the future health of the child. Close monitoring of HEU children is essential in order to firmly establish the perinatal ART regimen with the most optimal long term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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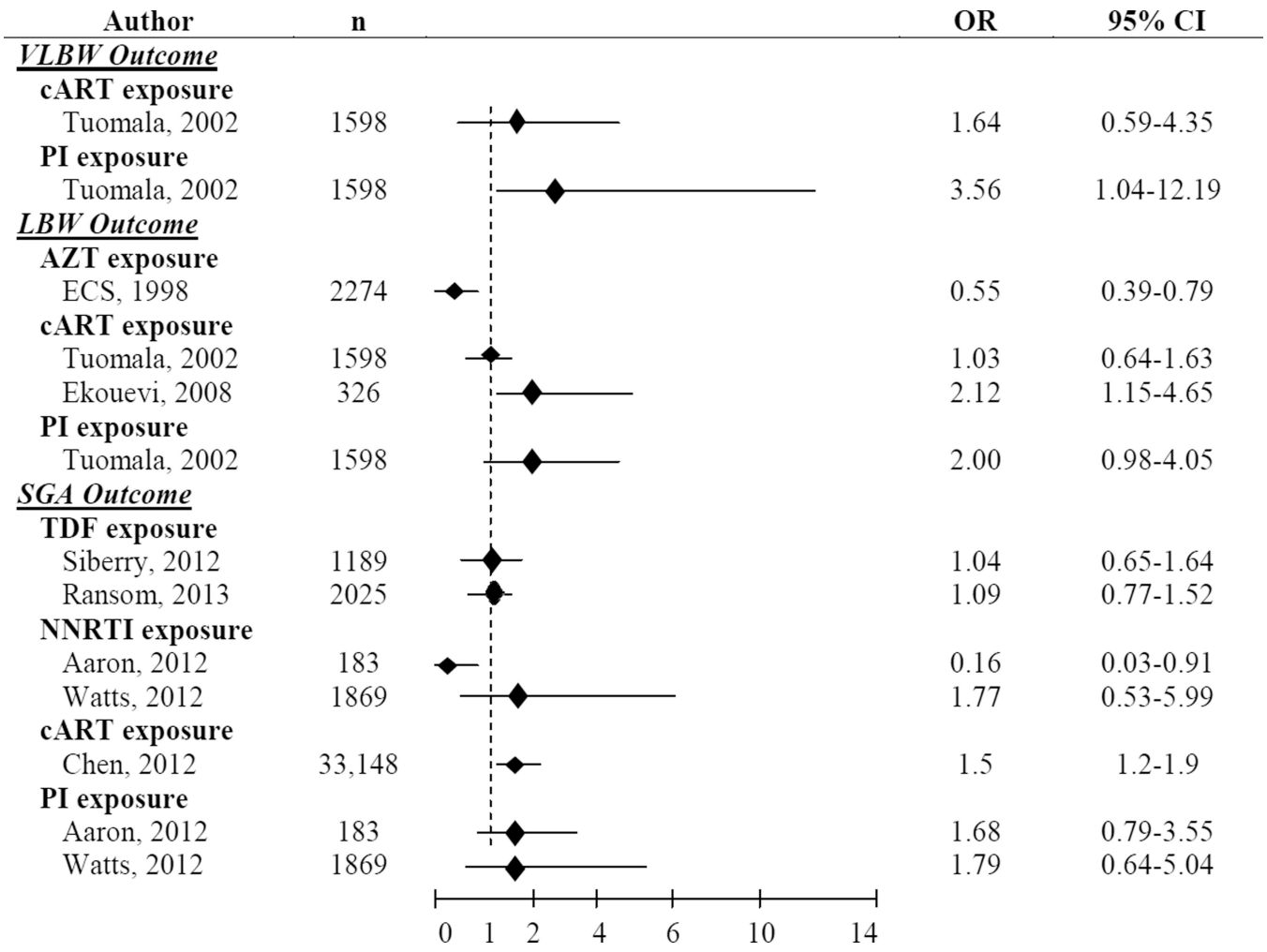

Figure 1.

Studies Evaluating Multivariate Associations with VLBW, LBW and SGA in HIV/ARV-exposed Infants

OR=Odds Ratio, CI=Confidence Interval, VLBW=Very Low Birth Weight (<1500 g), cART=Combination Antiretroviral Therapy, PI=Protease Inhibitor, LBW=Low Birth Weight (<2500 g), AZT=Zidovudine, ECS=European Collaborative Study, TDF=Tenofovir, SGA=Small for Gestational Age, NNRTI=Non-Nucleoside Reverse Transcriptase Inhibitor