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Complications of Treatment in Youth with HIV

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Abstract

While combination antiretroviral therapy allows HIV-infected patients to have life expectancies similar to that of the general population, it may also contribute to the development of co-morbidities, such as cardiovascular disease and osteoporosis. Such complications could compromise long-term quality of life, especially in HIV-infected youth whose lifetime cumulative exposure to antiretrovirals is likely to be many decades. Recent studies continue to demonstrate abnormalities associated with antiretroviral therapy, although clinical manifestations are rare in this younger population, especially with modern antiretrovirals. The purpose of this paper is to review the most recent literature on complications of treatment in youth with HIV.

Keywords

HIV; pediatrics and adolescence; antiretroviral therapy; HIV-exposed infants; complications

Introduction

HIV-infected adults exhibit an increased risk of co-morbidities, such as metabolic syndrome and dyslipidemia, cardiovascular disease (CVD), osteoporosis and fractures, and renal disease. HIV-infected children and adolescents appear to be at an increased risk of these complications, too, although clinical manifestations are less common. While combination antiretroviral therapy (cART) has an overwhelming positive effect on HIV disease progression and mortality, its use still contributes to the development of HIV-related co-morbidities. This review summarizes the most recent data on complications of treatment in HIV-infected youth.

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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Metabolic Alterations

Antiretroviral therapy (ART) has long been known to cause a variety of metabolic abnormalities, including dyslipidemia, lipodystrophy and insulin resistance. In general, the incidence of these complications has declined over time as newer, less toxic antiretrovirals (ARVs) have replaced many of the older, more toxic medications. However, in some settings (*e.g.*, resource-limited countries, pregnancy, infants, salvage treatment), these ARVs are still used in clinical practice.

Lipodystrophy and Lipid Abnormalities

Three recently published studies have assessed the occurrence of lipodystrophy and dyslipidemia in HIV-infected children and adolescents. Bwakura-Dangarembizi, *et al.* [1] evaluated the contribution of zidovudine (ZDV) to lipodystrophy in a population of African children who had been randomized to receive first-line combination antiretroviral therapy that did not contain stavudine (d4T), an inexpensive and efficacious ARV that is also an established cause of lipoatrophy. The authors performed a cross-sectional, unblinded analysis of 590 children ages 3 months to 17 years who were available for follow-up 3 years after enrollment. They showed no increased risk of lipoatrophy or body shape changes between subjects on short-term or no ZDV use compared to those with long-term ZDV use and between those on ZDV vs. abacavir (ABC).

Changes in lipids were also evaluated in 325 subjects from the same study. Generally, lipids remained within normal ranges, except subjects on long-term ZDV had a lower high-density lipoprotein (HDL) cholesterol compared those on short-term or no ZDV, and subjects receiving efavirenz (EFV) had higher low-density lipoprotein (LDL) cholesterol compared to those on nevirapine (NVP). The results of this study support the switch from d4T- to ZDV-containing cART regimens and suggest that there is little evidence to support regular lipid monitoring in resource-limited settings.

Another large clinical trial conducted in Zambia and Uganda included 477 HIV-infected children aged 1 month to 13 years who were randomized to either ABC, ZDV, or d4T [2]. Two children in the d4T group developed facial lipoatrophy compared to zero in the other two groups ($P=0.08$). However, there were no differences in body circumferences or skin-fold thicknesses, nor were there any changes in total cholesterol, LDL, HDL, or triglycerides (TG) among the treatment groups after 96 weeks of follow up. Both of these studies reinforce the World Health Organization's guidelines that have eliminated the use of d4T for the treatment of HIV unless there are no other viable options [3].

In contrast, another cross-sectional analysis of 99 HIV-infected children and young adults aged 12–20 years conducted in Spain noted an overall high prevalence of dyslipidemia (40% with hypertriglyceridemia, 27% with elevated total cholesterol, 26% with elevated LDL cholesterol, and 14% with low HDL cholesterol) [4]. The authors did not find an association between HDL cholesterol and ART treatment, but they did find an association between higher levels of TG and protease inhibitor (PI) use. However, these children were followed prospectively on a variety of treatment regimens with varying degrees of disease severity.

Thus, the study design limited the ability to evaluate the contribution of specific ART regimens and other potential confounders to the measured outcomes.

Insulin Resistance

Two recent studies addressed glucose alterations and insulin resistance, including the aforementioned cohort study by Blasquez, *et al.* [4]. In this study, 4.6% had fasting glucose levels >100 mg/dL, and 30.6% had evidence of insulin resistance, based on a homeostatic model assessment of insulin resistance (HOMA-IR) level exceeding the 90th percentile for sex and Tanner stage. As noted for the lipid assessments, study limitations like sample size precluded any meaningful examination of covariates that might be associated with these abnormalities.

In another study, Jao, *et al.* [5] performed a cross-sectional analysis of a prospective cohort from Cameroon comparing ART/HIV-exposed, uninfected (HEU) infants who received either postnatal ZDV (N=38) or NVP (N=118) to ART/HIV-unexposed, uninfected (HUU) infants (N=210). The objective of the study was to explore whether early exposures to ART might predispose these infants to long-term perturbations of energy metabolism and increase their risk of metabolic and cardiovascular disease. HIV-exposed, uninfected infants exposed to ZDV postnatally had the lowest pre-prandial insulin levels, highest glucose to insulin ratios, and lowest insulin resistance as measured by HOMA-IR, but had higher insulin levels at higher fuel inputs (a “thrifty” phenotype), suggesting that these infants process fuel differently and in a way that may provoke insulin resistance later in life. They also observed a positive association between certain patterns of branched-chain amino acids and short-chain acylcarnitines involved in fatty acid oxidation and both infant pre-prandial insulin and HOMA-IR levels. The authors suggest that “this reflects a diminished flux of protein and fat substrates through their catabolic pathways, a scenario with potential implications for metabolic gene regulation and the development of chronic metabolic disorders.” Taken together, these observations suggest that there may be a relationship between intermediary metabolism and insulin sensitivity in ART- and HIV-exposed infants that could affect energy utilization later in life.

Mitochondrial Dysfunction

There were two recently reported studies on mitochondrial function in prenatally ART-exposed, HEU infants. The first was a small cross-sectional study of HIV-infected (N=35) and HIV-negative (N=17) mother-infant pairs [6]. All of the HIV-infected mothers had HIV-1 RNA levels below the level of detection and were on a variety of cART regimens. The HEU infants were all treated postnatally with ZDV and evaluated at 6 weeks of age. The infants of the HIV-infected mothers had significantly lower birth weights and decreases in mtRNA and global mitochondrial enzymatic function, and showed a trend towards decreased mtDNA compared to HUU infants, suggesting a diminution of mitochondrial function in ZDV-exposed, HEU infants.

In a second study, mitochondrial function was measured over the first year of life in 133 HEU infants (88% exposed to ART prenatally) and 73 healthy control infants [7]. Most infants received ZDV as postnatal prophylaxis. Mitochondrial function as assessed by

complex IV enzymatic activity was lower at all time points in HEU infants, but showed a trend towards normalization over time. Enzymatic activity did not correlate with serum lactate levels. Maternal ZDV use was associated with lower mtDNA levels at each time point. Both of these studies support a number of previous studies showing similar findings of mitochondrial toxicity in ART-exposed, HEU infants, although clinically-apparent disease is rare [8–15].

Renal Toxicity

Most of the renal toxicity seen in the HIV-infected pediatric patient has centered on tenofovir disoproxil fumarate (TDF), a widely used, highly efficacious component of cART in both HIV-infected children and adults. Tenofovir disoproxil fumarate is a prodrug of tenofovir (TFV) that requires diester hydrolysis for conversion to TFV. Intracellularly, TFV is then phosphorylated to its active metabolite, tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competitive inhibition of the enzyme and subsequent termination of the DNA chain. Tenofovir disoproxil fumarate has been approved by the FDA for use in children as young as two years of age [16].

Because TFV is primarily eliminated unchanged in the kidneys (by a combination of glomerular filtration and active tubular secretion), a variety of renal side effects have been reported [16]. In HIV-infected adults, TDF usage is associated with a small but clinically significant decrease in renal function [17]. Similarly, in HIV-infected children, TDF has rarely been associated with renal dysfunction including proteinuria, hyperphosphaturia (with hypophosphatemia), and Fanconi's syndrome [18]. Although some studies show a measured change in estimated glomerular filtration rates (eGFR), most of the renal dysfunction associated with TDF is thought to be caused by subclinical proximal tubule toxicity [19]. In general, however, there is a paucity of data on the incidence, timing, management, and recovery of TDF-induced renal toxicity in HIV-infected children and adolescents, especially in children <12 years of age.

Recently, Aupibul *et al.* [20] conducted a prospective, non-randomized, open-label study comparing TDF-containing to TDF-sparing regimens in 80 HIV-infected children 3–18 years of age. They observed no difference in the eGFR between groups after 96 weeks of therapy, although there was an increase in the mean fractional excretion of calcium in the TDF group. Interestingly, there was no change in the fractional excretion of phosphate. One possible explanation for the lack of change in phosphate excretion or other renal dysfunction was the absence of PIs in the TDF-containing regimens. Protease inhibitors, especially ritonavir (r)-boosted lopinavir (LPV), atazanavir and darunavir have been shown to increase renal toxicity associated with TDF use by increasing TFV concentrations [16].

Likewise, Saez-Llorens *et al.* [21] performed an open-label, randomized study where children 2 to <16 years of age on ZDV- or d4T-containing regimens were either switched from ZDV or d4T to TDF or continued on their current regimen. Not only was TDF non-inferior to d4T and ZDV, but the authors did not observe any adverse renal effects during the randomized portion of the study. They then performed an extension phase where all participants were switched to or maintained on a TDF-containing regimen. In this phase,

four subjects discontinued TDF because of proximal renal tubulopathy, with increased creatinine over baseline and a concomitant decrease in serum phosphate. Incidentally, all four of these subjects were taking cART regimens containing LPV/r which may have contributed to the observed renal toxicity. In a continuation of this study out to 336 weeks [22], the authors showed a median change in eGFR of $-29.68 \text{ mL/L/min/1.73 m}^2$ that was consistent with a normal change with age. In total, six out of eighty-nine subjects discontinued TDF because of renal tubulopathies.

Similarly, a longitudinal, observational study of subjects on either ABC or TDF showed no significant differences in the rates of tubular dysfunction between the groups except where PIs were used in conjunction with TDF •[23]. Lastly, the final results of GS-US-104-0321 were recently published, which was the open-label TDF extension phase that followed the randomized, placebo-controlled, double-blind trial of TDF or placebo with optimized background regimen for 48 weeks in HIV-infected adolescents 12–17 years old [24]. Eighty-one subjects were treated with TDF for a median duration of 96 weeks. No subjects discontinued TDF because of an adverse event, and there were no TDF-associated renal toxicity, except for one subject who took 11 TDF tablets as a suicide attempt (but continued TDF without interruption and subsequently recovered).

While these recent studies are reassuring that TDF-associated renal toxicity is relatively rare, a new prodrug of TFV, tenofovir alafenamide (TAF), has been developed with less renal toxicity and excellent potency which will likely replace TDF for most or all of its currently recommended indications [25, 26]. Tenofovir alafenamide accumulates intracellularly where it is subsequently converted to the active TFV. Because of TAF's selective intracellular accumulation of TFV (as opposed to TDF that is converted to TFV mostly in the plasma), the renal exposure to TFV is decreased, leading to less potential toxicity [25]. In fact, administration in TAF resulted in >90% lower concentrations of TFV in the plasma compared to TDF [27]. When TAF was given as elvitegravir/cobicistat/emtricitabine/TAF to treatment-naïve adolescents, there were no cases of proximal renal tubulopathy [28] or decreases in urine β -2 microglobulin, a biomarker for renal inflammation [29].

Cardiac Function and Cardiovascular Disease Risk

HIV-Infected Patients

Cardiac complications like pericarditis, dilated cardiomyopathy, and pulmonary artery hypertension were common early in the HIV epidemic, but are rarely seen today with the advent of cART. However, even in the context of viral suppression, HIV-infected individuals are at an increased risk of atherosclerotic cardiovascular disease (CVD) and major adverse cardiovascular events such as myocardial infarction (MI) and ischemic stroke [30, 31]. In fact, CVD has become a leading cause of morbidity and mortality in HIV [32]. Even in HIV-infected children and young adults, there is evidence of increased CVD risk compared to their uninfected counterparts [33–35], although the pathogenesis and long-term outcomes are less understood in this younger patient population.

The etiology of the increased CVD risk in HIV is very complex with contributing factors from traditional risk factors, metabolic dysfunction, direct vascular effects of HIV, and

immune activation and inflammation from chronic infection [36]. Early epidemiologic studies associated ARVs, particularly PIs, with an increased risk of MI [37]; however, modern cART regimens exhibit less toxicity relative to their predecessors. Despite their improvement, cART medications themselves may still have an impact on CVD risk, although the current consensus is that ART has a net cardiovascular benefit [38].

In general, studies on cardiac function and/or CVD risk in HIV-infected youth are sparse, particularly those that investigate the contribution of cART. Recently, several studies have utilized novel techniques to evaluate cardiac function and CVD risk not previously investigated in HIV-infected youth. For example, Sainz, *et al.* [39] examined ventricular function cross-sectionally in a cohort of 64 HIV-infected children and adolescents (all but two were on ART and 64% had an undetectable HIV-1 RNA level) and 58 healthy controls using conventional echocardiography along with tissue Doppler imaging and strain analysis by speckle tracking. Speckle-tracking echocardiography may provide a “more sensitive, load-independent and angle-independent measure that allows functional analysis of the myocardium and ability to detect cardiac dysfunction at an early stage.”

The authors found that both ejection fraction and fractional shortening, measures of left ventricular (LV) systolic performance, were lower in the HIV-infected group vs. the controls, with four HIV-infected subjects demonstrating evidence of LV systolic dysfunction. Adjusted LV end-systolic diameter was also increased in the HIV-infected subjects, but all values were within normal range. Likewise, all other parameters, including measurements of systolic and diastolic function, systolic pulmonary pressure, and speckle-tracking analyses, which included longitudinal LV and LV rotational motion, did not differ between groups and were within normal ranges. After adjustment, no associations were found between HIV infection and the study parameters except for a lower ejection fraction, fractional shortening, and LV end-systolic diameter. There were also no associations between measured parameters and HIV-related variables including duration of PI or non-nucleoside reverse transcriptase inhibitor (NNRTI) use.

Similarly, three recent studies have investigated the use of pulse wave velocity (PWV), measure of large artery elasticity and stiffness, which is strongly correlated with both cardiovascular events and all-cause mortality in the general adult population [40]. Within HIV-infected adults, higher PWV appears to be a reliable marker of subclinical vascular disease [41]. There has been only one published study to date investigating PWV in HIV-infected children [42]. In this study, the investigators evaluated 48 HIV-infected children on ART, 35 ART-naïve children, and 59 controls. While there was no difference between ART-naïve children and controls, there was a significantly increased PWV in HIV-infected children on ART compared to those who were not on ART. This study did not, however, evaluate the ART-treated subjects separately compared to the controls, and there were limited data presented on these subjects' specific ART regimens and virologic status.

The three recent studies investigated the impact of ART on PWV in HIV-infected children and young adults to a greater extent than the previous study [43–45]. In the first study, Eckard, *et al.* evaluated PWV in 101 HIV-infected children and young adults all on cART with an HIV-1 RNA level <1000 copies/mL (median age of 20 years, 49% perinatally-

infected). The authors found no difference in PWV between the HIV-infected group and 86 healthy controls that matched by age, race, sex, and body mass index. These results are consistent with another recent study investigating carotid intima-media thickness (cIMT), a surrogate marker of subclinical atherosclerosis, in 100 children from Thailand aged 12–20 years all with treated asymptomatic HIV infection (90% with an HIV-1 RNA <1000 copies/mL) [46]. Here, there was also no difference between the HIV-infected subjects and the 50 age-matched healthy controls.

In these aforementioned studies, 11% and 18%, respectively, were on LPV/r at the time of study entry. Lopinavir/ritonavir has previously been associated with dyslipidemia and an increased risk of myocardial infarction in HIV-infected adults [47]. In the second study that investigated PWV [44], the authors found that PWV was statistically higher in HIV-infected children in Ethiopia who were on LPV/r compared to those who were ART-naïve or on the NNRTIs, EFV and NVP. The third study evaluated both PWV and cIMT at baseline and over 96 weeks in ART-naïve HIV-infected children about to initiate cART and in HIV-infected children already stable on cART for 2 years from Uganda and Zambia. At baseline, when the HIV-infected, ART-naïve subjects (N=208) were compared to 209 matched uninfected controls (who only had a single assessment), both cIMT and PWV were worse in the HIV-infected group. After 96 weeks of ART, the authors saw significant improvement in both PWV and cIMT among the HIV-infected subjects. On the other hand, while there was a trend toward a difference between the ART-experienced group (N=75) and a matched uninfected control group (N=75) in cIMT (P=0.09), there was no statistically significant difference in PWV (P=0.57). Over 96 weeks, the ART-experienced, HIV-infected subjects had an improvement in cIMT, but a worsening in PWV that the authors attributed to the increasing age of the study participants. There were no significant differences between the different NRTIs that subjects were on (ABC vs. ZDV vs. d4T).

Thus, taken together, these three studies validate the use of newer ARVs with less toxicity and side effects and emphasize the current goal of long-term virologic suppression with cART to decelerate disease progression and minimize the risk of co-morbidities like CVD. In addition, the studies that investigated PWV lend support to the use of this technique to estimate CVD risk in HIV-infected children and young adults. Pulse wave velocity has several advantages over other modalities, including that the procedure is non-invasive and relatively short. It also does not require contrast or radiation, and the machine offers portability and minimal technician training. However, further studies, particularly additional longitudinal trials, are needed to fully investigate PWV in this younger population.

HIV-Exposed, Uninfected Infants

There have been several recent and notable studies investigating cardiac function in ART-exposed, HEU infants [48–51]. While most studies failed to show any evidence of gross cardiac toxicity by echocardiography between children exposed to ART *in utero* and those who were not exposed, a number of subclinical findings are quite concerning. For example, several studies demonstrated that *in utero* ART exposure may be associated with some degree of LV diastolic dysfunction, changes in LV shortening fraction, lower stress-velocity z-scores, and posterior wall thickening. One particularly alarming study showed a higher

risk of congenital heart disease, particularly ventricular septal defects, among female subjects exposed to ZDV *in utero* [51]. The long-term implications of these findings are yet unclear, but the possibility that cardiac contractility may eventually be compromised in some of these HEU patients should be considered and closely monitored.

Bone Toxicity

HIV-infected adults exhibit an increased risk of osteoporosis and fractures [52, 53]. Bone health appears to be compromised in HIV-infected children and adolescents too, although the long-term ramifications are largely unknown. Bone toxicity is particularly concerning in this younger population, however, as bone mass acquisition occurs during this period of rapid growth, and the effects of chronic HIV infection and exposure to ART accumulate over many decades. There are limited data on the effects of specific ARVs and how to optimize ARVs to improve bone outcomes in children.

Role of Specific Antiretrovirals

Initiation of any ARV appears to cause a decrease in bone mineral density (BMD); however, TDF is associated with greater bone loss than other ARVs. Its use, however, is widespread because of its excellent efficacy for maintaining virological suppression. Recently, Aurpibul, *et al* [20] conducted a prospective, open-label study in HIV-infected children where 40 were started on a TDF-containing regimen, and 40 age-, gender- and CD4-matched controls received a TDF-sparing regimen. Lumbar spine (LS) bone mineral density (BMD) z-scores decreased significantly over 96 weeks in children receiving TDF, but remained unchanged in the TDF-sparing group. Most of this decrease occurred over the first 24 weeks of the study, then remained stable thereafter. At week 96, there was no significant difference in the prevalence of LS BMD z-scores ≤ -2.0 between the two groups.

The final results of the Gilead 321 extension study were also recently published, which included HIV-infected subjects ages 12–17 years receiving TDF for a median duration of 96 weeks [24]. Results varied depending on the body part and what bone mineral density (BMD) measurement was reported. Although both LS and total body less head (TBLH) BMD increased over time, age-adjusted LS and TBLH BMD z-scores declined significantly over 96 and 192 weeks, respectively. However, height-age-adjusted LS BMD z-scores were unchanged from baseline to week 96 and showed significant increases from week 144. Moreover, although height-age-adjusted TB BMD z-scores decreased from baseline to week 48, median changes after this were not significantly different from baseline.

Similarly, long-term safety data from Gilead 352 were recently presented [54], which included children aged 2–15 years in a phase 3, randomized, open-label non-inferiority study comparing switching to TDF vs. continuing on d4T or ZDV [21]. Bone data presented were limited, but TB, TBLH, and LS height-age-adjusted BMD z-scores stayed the same or improved slightly over 336 weeks. Results from both Gilead studies, though, must be interpreted cautiously, as data are limited by a lack of comparator and small sample sizes. Longer-term studies are needed to fully assess the clinical impact of TDF on bone.

However, as described previously, TAF, Gilead's second generation TDF pro-drug, may replace TDF over time. Thus far, data have only been presented in a small number of HIV-infected ART-naïve adolescents, but showed minimal change in height-adjusted BMD z-scores over 24 weeks [55]. Forty-eight week follow-up data were also recently presented [56]. Minimal impact was seen here too with average increases in BMD and no change in height-adjusted z-scores.

While TDF is mostly commonly associated with bone loss, other ARVs play a role as well. For example, in a secondary objective of a randomized clinical trial, the authors evaluated whether changing ARVs from LPV/r to EFV was associated with beneficial outcomes in terms of bone development. Two-hundred twenty-two HIV-infected children were evaluated 1–4 years (mean 2.1 years) after randomization, which included staying on LPV/r vs. switching to EFV. The bone mineral content (BMC) z-score was -0.49 in the EFV group vs. -1.07 in the LPV/r group, which remained significant ($P < 0.001$) after adjustment for potential confounding variables. These results suggest that considering bone toxicity when selecting cART regimens could have an impact on long-term bone health in HIV-infected children and young adults.

Bone Health in HIV-Exposed Infants

Although TDF use during pregnancy has increased in recent years, concern remains about bone health in HEU infants exposed to TDF *in utero*. For example, a large study compared BMC in 69 TDF-exposed infants to that of 74 TDF-unexposed infants [57]. Bone mineral content was measured by dual energy x-ray absorptiometry (DXA) in the whole skeleton at a mean age of 4–5 weeks. The unadjusted comparison showed a 7.8g difference between exposure groups, with higher BMC in the TDF-unexposed infants. After adjustment for maternal age at delivery, tobacco use during pregnancy, infant race, gestational age, length, age at DXA scan, and clinical site, the difference between exposure groups decreased to 5.5g. Interestingly, when the analysis was repeated considering BMC less head, the difference between the two groups was no longer present.

In a sub-study of the IMPAACT PROMISE trial, the authors tried to further investigate the previous study's finding that TDF may affect BMC in HEU infants [58]. They sought to compare BMC by 28 days of life in newborns who had been exposed *in utero* to one of three randomized maternal ART regimens. There was no adverse infant BMC effect linked to maternal TDF use. Interestingly, however, this study suggested that LPV/r-containing regimens appear to adversely affect newborn bone mineralization.

Conclusions

There is little question that ART has revolutionized not only the treatment of HIV infection, allowing HIV-infected youth to live decades longer than before, but it has also dramatically decreased the risk of mother-to-child transmission of HIV. However, the long-term effects of ART exposure must be considered. From these recent studies (and many previous ones), it is clear that ART use does cause subclinical manifestations that may affect these individuals' long-term quality of life. Optimizing ART regimens that offer the least amount of toxicity, while maintaining virologic suppression is crucial to minimize the risk of these long-term

complications. Likewise, long-term, continued research is urgently needed in this vulnerable population.

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References

1. Bwakura-Dangarembizi M, Musiime V, Szubert AJ, et al. Prevalence of lipodystrophy and metabolic abnormalities in HIV-infected African children after 3 years on first-line antiretroviral therapy. *The Pediatric infectious disease journal*. 2015; 34(2):e23–31. [PubMed: 25068287]
2. Mulenga V, Musiime V, Kekitiinwa A, et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *The Lancet Infectious diseases*. 2016; 16(2):169–179. [PubMed: 26481928]
3. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new (policy brief). [<http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en/>]
4. Blazquez D, Ramos-Amador JT, Sainz T, et al. Lipid and glucose alterations in perinatally-acquired HIV-infected adolescents and young adults. *BMC infectious diseases*. 2015; 15:119. [PubMed: 25880777]
5. Jao J, Kirmse B, Yu C, et al. Lower Preprandial Insulin and Altered Fuel Use in HIV/Antiretroviral-Exposed Infants in Cameroon. *The Journal of clinical endocrinology and metabolism*. 2015; 100(9):3260–3269. [PubMed: 26133363]
6. Moren C, Noguera-Julian A, Garrabou G, et al. Mitochondrial disturbances in HIV pregnancies. *Aids*. 2015; 29(1):5–12. [PubMed: 25268887]
7. Noguera-Julian A, Moren C, Rovira N, et al. Decreased Mitochondrial Function Among Healthy Infants Exposed to Antiretrovirals During Gestation, Delivery and the Neonatal Period. *The Pediatric infectious disease journal*. 2015; 34(12):1349–1354. [PubMed: 26372453]
8. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet*. 1999; 354(9184):1084–1089. [PubMed: 10509500]
9. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS*. 2003; 17(12):1769–1785. [PubMed: 12891063]
10. Poirier MC, Divi RL, 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(2):175–183. [PubMed: 12794551]
11. Shiramizu B, Shikuma KM, Kamemoto L, et al. Placenta and cord blood mitochondrial DNA toxicity in HIV-infected women receiving nucleoside reverse transcriptase inhibitors during pregnancy. *J Acquir Immune Defic Syndr*. 2003; 32(4):370–374. [PubMed: 12640193]
12. Divi RL, Walker VE, Wade NA, et al. Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir. *AIDS*. 2004; 18(7):1013–1021. [PubMed: 15096804]
13. Brogly SB, Ylitalo N, Mofenson LM, et al. In utero nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. *AIDS*. 2007; 21(8):929–938. [PubMed: 17457086]
14. Aldrovandi GM, Chu C, Shearer WT, et al. Antiretroviral exposure and lymphocyte mtDNA content among uninfected infants of HIV-1-infected women. *Pediatrics*. 2009; 124(6):e1189–1197. [PubMed: 19933732]
15. Ross AC, Leong T, Avery A, et al. Effects of in utero antiretroviral exposure on mitochondrial DNA levels, mitochondrial function and oxidative stress. *HIV medicine*. 2012; 13(2):98–106. [PubMed: 22103263]

16. Madrid L, Noguera-Julian A, Falcon-Neyra L, et al. Microbial translocation and T cell activation are not associated in chronic HIV-infected children. *Aids*. 2014; 28(13):1989–1992. [PubMed: 25259707]
17. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis*. 2010; 51(5):496–505. [PubMed: 20673002]
18. Fortuny C, Deya-Martinez A, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. *Pediatr Infect Dis J*. 2015; 34(5 Suppl 1):S36–43. [PubMed: 25629891]
19. Hall AM. Update on tenofovir toxicity in the kidney. *Pediatr Nephrol*. 2013; 28(7):1011–1023. [PubMed: 22878694]
- 20. Aupibul L, Cressey TR, Sricharoenchai S, et al. Efficacy, safety and pharmacokinetics of tenofovir disoproxil fumarate in virologic-suppressed HIV-infected children using weight-band dosing. *The Pediatric infectious disease journal*. 2015; 34(4):392–397. This prospective study evaluated TDF use in HIV-infected children who were already virologically-suppressed on a cART regimen. There was no evidence of significant renal or bone adverse events over a 96 week period. [PubMed: 25760566]
21. Saez-Llorens X, Castano E, Rathore M, et al. A randomized, open-label study of the safety and efficacy of switching stavudine or zidovudine to tenofovir disoproxil fumarate in HIV-1-infected children with virologic suppression. *The Pediatric infectious disease journal*. 2015; 34(4):376–382. [PubMed: 25760565]
22. Saez-Llorens, X.; Deville, J.; Mirza, A., et al. Long term safety and efficacy of Tenofovir DF therapy in HIV-infected children through week 336. 22nd Conference on Retroviruses and Opportunistic Infections; Seattle, WA. 2015;
- 23. Andrade-Fuentes K, Mata-Marin JA, Lopez-De Leon JJ, Manjarrez-Tellez B, Ramirez JL, Gaytan-Martinez J. Proximal renal tubular dysfunction related to antiretroviral therapy among HIV-infected patients in an HIV clinic in Mexico. *AIDS Patient Care STDS*. 2015; 29(4):181–185. This is an observational study looking at renal tubule dysfunction in children on ABC- versus TDF-containing regimens. Children in the TDF group had more evidence of renal dysfunction when they were also taking a PI. [PubMed: 25101526]
24. Della Negra M, De Carvalho AP, De Aquino MZ, et al. Long-term efficacy and safety of tenofovir disoproxil fumarate in HIV-1-infected adolescents failing antiretroviral therapy: the final results of study GS-US-104-0321. *The Pediatric infectious disease journal*. 2015; 34(4):398–405. [PubMed: 25599284]
25. Ray AS, Fordyce MW, Hitchcock MJ. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. *Antiviral research*. 2016; 125:63–70. [PubMed: 26640223]
26. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015; 385(9987): 2606–2615. [PubMed: 25890673]
27. Genvoya full prescribing information. [www.genvoya.com]
28. Gaur, A.; Kizito, H.; Chakraborty, R., et al. Safety and Efficacy of E/C/F/TAF in HIV-1-Infected Treatment Naïve Adolescents. Conference on Retroviruses and Opportunistic Infections; Boston, MA: CROI; 2016.
29. Kizito, H.; Gaur, A.; Prasitsuebsai, W., et al. Safety, Efficacy and Pharmacokinetics of the Integrase Inhibitor-Based E/C/F/TAF single tablet regimen in Treatment Naïve HIV-Infected Adolescents Through 24 Weeks of Treatment. Conference on Retroviruses and Opportunistic Infections; Seattle, WA: CROI; 2015.
30. Freiberg MS, Chang CC, Kuller LH, et al. HIV Infection and the Risk of Acute Myocardial Infarction. *JAMA internal medicine*. 2013:1–9.
31. Sico JJ, Chang CC, So-Armah K, et al. HIV status and the risk of ischemic stroke among men. *Neurology*. 2015; 84(19):1933–1940. [PubMed: 25862803]

32. Nou E, Lo J, Hadigan C, Grinspoon SK. Pathophysiology and management of cardiovascular disease in patients with HIV. *Lancet Diabetes Endocrinol.* 2016
33. McComsey GA, O’Riordan M, Hazen SL, et al. Increased carotid intima media thickness and cardiac biomarkers in HIV infected children. *Aids.* 2007; 21(8):921–927. [PubMed: 17457085]
34. Charakida M, Donald AE, Green H, et al. Early structural and functional changes of the vasculature in HIV-infected children: impact of disease and antiretroviral therapy. *Circulation.* 2005; 112(1):103–109. [PubMed: 15983247]
35. Sainz T, Alvarez-Fuente M, Navarro ML, et al. Subclinical atherosclerosis and markers of immune activation in HIV-infected children and adolescents: the CaroVIH Study. *Journal of acquired immune deficiency syndromes.* 2014; 65(1):42–49. [PubMed: 23982657]
36. Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease: time for a better understanding. *Journal of the American College of Cardiology.* 2013; 61(5):511–523. [PubMed: 23369416]
37. Lambert CT, Sandesara PB, Hirsh B, et al. HIV, highly active antiretroviral therapy and the heart: a cellular to epidemiological review. *HIV Med.* 2015
38. Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? *Curr Opin HIV AIDS.* 2014; 9(1):54–62. [PubMed: 24275676]
- 39. Sainz T, Alvarez-Fuente M, Fernandez-Jimenez R, et al. Cardiac function in vertically HIV-infected children and adolescents in the era of highly active antiretroviral therapy. *The Pediatric infectious disease journal.* 2015; 34(5):e125–131. This study showed evidence of subclinical systolic dysfunction in HIV-infected subjects compared to healthy controls, which causes concern for cardiac compromise later in life. [PubMed: 25876103]
40. Choo J, Shin C, Barinas-Mitchell E, et al. Regional pulse wave velocities and their cardiovascular risk factors among healthy middle-aged men: a cross-sectional population-based study. *BMC cardiovascular disorders.* 2014; 14:5. [PubMed: 24410766]
41. Sun D, Wu Y, Yuan Y, Wang Y, Liu W, Yang J. Is the atherosclerotic process accentuated under conditions of HIV infection, antiretroviral therapy, and protease inhibitor exposure? Meta-analysis of the markers of arterial structure and function. *Atherosclerosis.* 2015; 242(1):109–116. [PubMed: 26188532]
42. Charakida M, Loukogeorgakis SP, Okorie MI, et al. Increased arterial stiffness in HIV-infected children: risk factors and antiretroviral therapy. *Antiviral therapy.* 2009; 14(8):1075–1079. [PubMed: 20032537]
43. Eckard, AR.; Rosebush, JC.; O’Riordan, MA., et al. Arterial Stiffness in HIV+ Youth and Associations with HIV-Related Variables. *Conference on Retroviruses and Opportunistic Infections;* 2015; Seattle, Washington. 2015.
44. Rosebush, JC.; Rudolph, LG.; Caulk, A.; Seifu, D.; Eckard, AR.; Taye, W. Preclinical Atherosclerosis in Eastern Africa: Results from a Pediatric Ethiopian Cohort. *Conference on Retroviruses and Opportunistic Infections;* 2014; Boston, Massachusetts. 2014.
45. Kenny, J.; Cook, A.; Mirembe, G., et al. Structural cardiovascular changes are reversible in HIV-infected children in Zambia and Uganda. Abstract 37. 22nd Conference on Retroviruses and Opportunistic Infections; 2015; Seattle, WA. 2015.
46. Chanthong P, Lapphra K, Saihongthong S, et al. Echocardiography and carotid intima-media thickness among asymptomatic HIV-infected adolescents in Thailand. *Aids.* 2014; 28(14):2071–2079. [PubMed: 25265075]
47. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *The New England journal of medicine.* 2007; 356(17):1723–1735. [PubMed: 17460226]
48. Lipshultz SE, Williams PL, Zeldow B, et al. Cardiac effects of in-utero exposure to antiretroviral therapy in HIV-uninfected children born to HIV-infected mothers. *AIDS.* 2015; 29(1):91–100. [PubMed: 25562493]
49. De la Calle M, Rodriguez R, Deiros L, Bartha JL. Fetal cardiac biometry and function in HIV-infected pregnant women exposed to HAART therapy. *Prenat Diagn.* 2015; 35(5):453–455. [PubMed: 25512023]

- 50. Guerra VC, Leister EC, Williams PL, et al. Long-Term Effects of In Utero Antiretroviral Exposure: Systolic and Diastolic Function in HIV-Exposed Uninfected Youth. *AIDS Res Hum Retroviruses*. 2016 This study showed a higher risk of ventricular septal defects among female subjects exposed in utero to ZDV.
51. Sibiude J, Le Chenadec J, Bonnet D, et al. In utero exposure to zidovudine and heart anomalies in the ANRS French perinatal cohort and the nested PRIMEVA randomized trial. *Clin Infect Dis*. 2015; 61(2):270–280. [PubMed: 25838291]
52. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *Aids*. 2006; 20(17):2165–2174. [PubMed: 17086056]
53. Prieto-Alhambra D, Guerri-Fernandez R, De Vries F, et al. HIV infection and its association with an excess risk of clinical fractures: a nationwide case-control study. *Journal of acquired immune deficiency syndromes*. 2014; 66(1):90–95. [PubMed: 24457634]
54. Saez-Llorens, X.; Deville, JG.; Mirza, A., et al. Long-term safety and efficacy of tenofovir DF therapy in HIV-infected children through week 336. Abstract 954. 22nd Conference on Retroviruses and Opportunistic Infections; 2015; Seattle, Washington. 2015.
55. Kizito, H.; Gaur, A.; Prasitsuebsai, W., et al. Safety, efficacy and pharmacokinetics of the integrase inhibitor-based E/C/F/TAF single-tablet regimen in treatment-naïve HIV-infected adolescents through 24 weeks of treatment. Abstract 953. In. 22nd Conference on Retroviruses and Opportunistic Infections; 2015; Seattle, Washington. 2015.
56. Gaur, A.; Kizito, H.; Chakraborty, R., et al. Safety and efficacy of E/C/F/TAF in HIV-1-infected treatment-naïve adolescents. Abstract 817. In. 23rd Conference on Retroviruses and Opportunistic Infections; 2016; Boston, MA. 2016.
57. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2015; 61(6):996–1003. [PubMed: 26060285]
58. Siberry, G.; Tierney, C.; Stranix-Chibanda, L., et al. Impact of maternal tenofovir use on HIV-exposed newborn bone mineral. Abstract 36. 23rd Conference on Retroviruses and Opportunistic Infections; 2016; Boston, MA. 2016.