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# Non-communicable diseases in adolescents with perinatally-acquired HIV-1 infection in high- and low-income settings

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## Abstract

**Purpose of review—**Perinatally HIV-infected adolescents may be at increased risk of non-infectious co-morbidities later in life. This review summarizes recent advances in the understanding of non-communicable diseases (NCD) among HIV-infected adolescents in high-income and lower-middle-income countries, and identifies key questions that remain unanswered. We review atherosclerotic vascular disease (AVD), chronic bone disease (CBD), chronic kidney disease (CKD), and chronic lung disease (CLD).

**Recent findings—**Persistent immune activation and inflammation underlie the pathogenesis of AVD, highlighting the importance of treatment adherence and maintenance of viral suppression, and the need to evaluate interventions to decrease risk. Tenofovir disoproxil fumarate (TDF) and trials of vitamin D supplementation have been the focus of recent studies of CBD with limited studies to date evaluating tenofovir alafenamide as an alternative to TDF for decreasing risk for bone and renal adverse effects among HIV-infected adolescents. Recent studies of CKD have focused primarily on estimating prevalence in different settings while studies of CLD are limited.

**Summary—**As perinatally HIV-infected children age into adolescence and adulthood with effective long-term ART, it is necessary to continue to evaluate their risks for non-infectious co-morbidities and complications, understand mechanisms underlying their risks, and identify and evaluate interventions specifically in this population.

### Keywords

perinatally-acquired HIV; adolescents; non-communicable diseases

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**Conflicts of interest**

The authors have no conflicts of interest.

## Introduction

Perinatally-infected children and adolescents will be exposed to more decades of antiretroviral therapy (ART) than adults. Additionally, being infected perinatally when the immune system is not yet matured, may lead to different long-term sequelae compared to behaviourally-infected adolescents and adults. In particular, the damage done to immune regulatory mechanisms may result in more severe non-infectious consequences later in life. This review summarizes recent advances in the understanding of non-communicable diseases (NCD) among adolescents with perinatally-acquired HIV, and identifies some key questions that remain unanswered. We review atherosclerotic vascular disease, chronic bone disease, chronic kidney disease, and chronic lung disease, as these co-morbidities are the primary focus of recent publications among HIV-infected adolescents.

### Atherosclerotic vascular disease (AVD)

Prior to ART, cardiomyopathy was the most concerning HIV-related cardiac problem [1]. Following effective ART, there remains excess AVD risk contributed by HIV infection and/or ART in perinatally-infected adolescents, both in high-income countries (HIC) [2] and lower-middle-income countries (LMIC) [3–5]. Metabolic syndrome is similarly increased independent of traditional risk factors, both in HIC [6–8**] and LMIC [9–10] with prevalence estimates of 2-7%. Prevalence of any lipid or glucose metabolic abnormality could be up to 99% [9].

**Etiology and pathogenesis/mechanisms—**Multiple etiologies have been implicated in HIV-related AVD. ART adverse drug effects contribute to etiology via dyslipidemia (although less so with newer 2$^{nd}$- and 3$^{rd}$-generation drugs), both in HIC [8**, 11] and in LMIC [12]. There is also sizeable contribution from low level HIV [13–14] and CMV [15] replication, which fuel chronic inflammatory and immune activation processes. Bacterial translocation is well-known to activate the inflammasome, a component of the innate immune system that induces production of pro-inflammatory cytokines in response to microbes [16]. In addition, dysbiosis, or alterations in the gut microbiome, in itself likely also plays an underappreciated role in chronic immune activation and risk of cardiovascular events [17].

Multiple immune cell types are implicated in chronic immune activation, especially monocytes and CD8 T-cells (i.e. cytotoxic T cell, CTL). Monocyte activation is associated with extensive pro-inflammatory biomarker expression (particularly IL-6, hsCRP, cystatin C) with consequent inflammatory endothelial damage that in turn allows circulating low-density lipoprotein (LDL) cholesterol particles entry into the intima where they become oxidized (oxLDL) [18**]. Monocyte activation, accompanied by elevated monocyte-specific markers (e.g., sCD14, sCD163, MCP-1), also promotes monocyte migration into the intima of large arteries where, in the presence of large amounts of oxLDL, they become dysfunctional foam cells [19].

Persistent CD8 T-cell activation (as defined by CD38 and HLA-DR expression by flow cytometry) has been shown in young adults with early-acquired HIV to be associated with coronary plaque and CD8 T-cell exhaustion and senescence [20–21]. With prolonged HIV

suppression, the number and function of regulatory CD4+ CD25+ T-cells (Tregs) is also reduced (ie opposite to the pattern seen in advanced HIV disease), leading to unbridled helper CD4 T-cell activity and consequent persistent inappropriate immune activation [22]. Resultant inflammation causes or aggravates peripheral insulin resistance, leading to pro-atherogenic dyslipidemia [6, 23–24] with increased production of both oxLDL and oxidized high-density lipoprotein (oxHDL), which themselves have a broad-based inflammatory effect [25]. Inflammation also contributes to increased coagulability (reflected in elevated D-dimer) [26].

Finally, traditional AVD risk factors continue to play a major role among adolescents, particularly diet and obesity [8**]. Renal dysfunction also remains a potent risk factor, both via hypertension and other mechanisms [27–28**].

**Therapeutics—**Suppressive ART is a potent, albeit incomplete, suppressor of inflammation driven by HIV replication. In addition, statins have lipid-lowering effects in adults [29–30] and are beginning to be evaluated in children with one recent Phase I/II trial finding improvements in lipid parameters among children with ART-associated dyslipidemia with atorvastatin use but also possible toxicity concerns in younger children [31**]. Vitamin D supplementation was also evaluated as a potential mediator of AVD risk in HIV-infected children but contrary to expectations may increase carotid intima-media thickness and be detrimental to vascular health [32].

Traditional risk factor control remains paramount, particularly diet [8**] and exercise [8**, 33]. Cautious use of antihypertensives may also have a place in decreasing AVD risk where essential hypertension related to metabolic syndrome is diagnosed [34].

**Surveillance + monitoring—**Given the long delay between pathogenesis and clinical events among youth, surrogate endpoints have been used to facilitate recognition of early abnormalities. One that can be directly measured by pulse wave velocity is arterial wall stiffness [35]. Carotid intima-media thickness has also been utilized as an indicator of early AVD where available [3]. Endothelial dysfunction which predates atherosclerosis [36] can be monitored by augmentation index and reactive hyperemic index using digital pulse amplitude tonometry [18**], while anthropometric metrics may be a useful surrogate screen for AVD risk factors (i.e., dyslipidemia and/or insulin resistance), particularly in low-resource settings [37].

**Unanswered questions and foci for future research—**Given the significant role of persistent immune activation on AVD, there is a need to comprehensively evaluate mechanisms by which such inappropriate immune activation is perpetuated, specifically in well-suppressed patients. In the immune deficient state, gut epithelial cells are damaged, allowing translocation of gut bacteria and large molecular weight bacterial components (eg lipopolysaccharide, LPS). In the immune replete state following long-standing viral suppression, the degree of translocation of bacterial antigens is similar to the general population [38], presumably reflecting that normal epithelial integrity is restored and that some gut-associated lymphoid tissue function has returned. The persistent immune activation seen in individuals with long-standing viral suppression thus requires additional

explanation. The answer may involve the recently elucidated zonulin system [39]. Zonulin is a paracrine messenger released in a controlled way by gut columnar epithelial cells that causes temporary and reversible relaxation of intercellular tight junctions, intentionally allowing small (~600 to 1000 Daltons) antigenic fragments of dietary origin to enter the lamina propria where they are taken up by antigen presenting cells and presented to naïve CD8 T lymphocytes to induce immune tolerance and thereby prevent food allergies and intolerances [40]. Since zonulin is produced by *intact* gut epithelial cells, it is not surprising that in the immediate post-AIDS recovery period, serum zonulin is low and the deficit in zonulin is proportional to the extent of gut epithelium damage [41]. Once immune recovery is complete, zonulin becomes a marker of tight junction porosity, as in the pre-AIDS state. However, even when viral suppression is maintained for a long period, previous HIV-induced damage to regulatory T cells does not recover fully. This may allow CD4 T helper cells to respond in an inappropriate, unbridled fashion to the routine antigen stimulation supplied continuously by the zonulin system and may contribute in varying degree to persistent low-grade immune activation. Of relevance, a zonulin blocker (larazotide acetate) is now entering phase 3 clinical trials for celiac disease [42] and may have a role in similar conditions driven by low-grade persistent immune activation.

Although statins are believed to have an anti-inflammatory effect in adults [29–30], their use in children for this purpose may be limited by muscle-related toxicities (myalgia, myopathies). There is a place for a cautious anti-inflammatory statin trial in older adolescents, keeping in mind that the clinical benefit of statins' anti-inflammatory action remains uncertain. Newer experimental anti-inflammatory agents trialled in adults include newer monoclonal antibodies to inflammatory cytokines, CCR5 blockade [43–44] and tissue factor blockade [45]. If shown to be effective, these modalities could also be cautiously investigated in youth. In addition, omega-3 fatty acids and aspirin may have some benefit.

The efficacy of statins in treating persistent dyslipidemia has been compared to ART switching in adults (specifically protease inhibitor, PI, to efavirenz, EFV), with mixed outcome [30]. However, similar dyslipidemia efficacy trials have not been conducted in adolescents. These may be important given the large cost and toxicity differences between ART switch and statin initiation.

There remains a severe lack of observational data around cardiometabolic vascular morbidity in suppressed youth from LMIC.

## Chronic bone disease (CBD)

CBD risk is increased in perinatally-acquired HIV independent of traditional CBD risk factors [46–49**], possibly leading to premature osteoporosis and fractures.

**Etiology and pathogenesis/mechanisms—**ART and persistent low-grade immune activation are believed to play the largest roles in pathogenesis of HIV-related CBD. The most notorious ART drug associated with bone turnover dysregulation is tenofovir disoproxil fumarate (TDF) [50]. The extent of TDF toxicity on bone mineral density (BMD) is assumed to be greater in children and adolescents undergoing a skeletal growth spurt; however a small longitudinal study did not find evidence of this [51**]. While the

mechanism by which TDF directly affects bone loss is still uncertain, TDF causes renal tubular dysfunction resulting in inappropriate phosphaturia as a late feature [52]. Low phosphate in turn stimulates parathyroid hormone release [53]. Although this should increase vitamin D hydroxylation and activation, TDF interferes with vitamin D activation in the kidney, further stimulating secondary hyperparathyroidism [46, 48, 54]. Excessive parathyroid hormone activity inappropriately increases osteoclast and decreases osteoblast differentiation resulting in increased bone resorption and reduced formation of new bone matrix. Comorbid renal tubular disease of any kind (whether related to HIV or not) remains a potent contributor. Also implicated in the pathogenesis of osteopenia are thymidine nucleoside reverse transcriptase inhibitors (NRTI) [55] and boosted PI exposure [47**, 49].

The likely role of inflammatory pathways is supported by the observation that immune reconstitution immediately following ART initiation is associated with short-term bone loss [56]. Persistent inappropriate CD8 T-cell and monocyte/macrophage activation beyond the period of immune reconstitution have also been associated with low BMD, although the mechanism is unclear [57–58]. Some studies suggest that T-cell activation is more potently associated with low BMD than macrophage activation [59], while other data refute the assertion that T-cell activation plays a significant role [60].

Interestingly, low BMD has recently been linked to disordered fat metabolism, possibly reflecting the common origin and interchangeability of bone and fat progenitor cells [61].

**Therapeutics—**The primary therapeutic tool against persistent immune activation remains consistent and uninterrupted HIV viral suppression by ART [11].

Although Vitamin D activity is a component of low BMD pathogenesis, there is conflicting evidence around the efficacy of routine vitamin D supplementation; some studies suggest efficacy [62–63] while others do not [64]. This may reflect varying degrees of pre-existing vitamin D deficiency or repletion in different study populations. It should be borne in mind that excessive vitamin D supplementation may be detrimental to vascular health [32]. Calcium supplementation has not been evaluated among HIV-infected adolescents to improve BMD.

TDF's bone and renal toxicity have severely limited its use in paediatrics. Industry-sponsored trials suggest that these toxicities might be avoided by using tenofovir alafenamide (TAF) instead of TDF [65–66]. Confirmatory studies are needed. Abacavir, a more widely available and cheaper nucleoside reverse transcriptase inhibitor, may also be an alternative to TDF among children. Switching from a PI to EFV may also have a role in preventing PI-related BMD reductions [47**].

**Surveillance + monitoring—**While dual energy x-ray absorptiometry (DXA) is the gold standard for measuring BMD, this modality is not commonly available outside of tertiary centres. In addition, BMD change is a late feature of bone disease and, therefore, bone turnover markers and parathyroid hormone monitoring may be more appropriate surveillance measures. Serum bone-specific alkaline phosphatase and C-terminal collagen crosslinks (a collagen degradation product released during bone resorption) directly measure

metabolic bone turnover but the clinical utility of these measures to monitor BMD in young HIV-infected children is uncertain and they are prohibitively expensive if utilized on a large scale [67]. It is unclear whether BMD assessment by calcaneal quantitative ultrasound has a place in routine surveillance; some studies find it helpful [68] and others not [69]. Delayed bone age (by plain radiography) is associated with reduced BMD (by DXA) and may be useful as a crude screening tool in individuals whose epiphyses have not yet fused [70]. A novel recent study has suggested that anthropometric measures may provide simple and widely-available surveillance for low BMD in adolescents on ART in LMIC [71]. Bioelectrical impedance does not appear to be useful as a surveillance method for BMD [72].

**Unanswered questions + foci for future research—**Mechanism(s) by which HIV independently accelerates CBD in perinatally-infected adolescents will be important to elucidate. This may lead to novel (and effective) immune therapies to control persistent inappropriate immune responses in the virologically suppressed state.

The toxicity of TDF is thought to be far more pronounced in individuals undergoing skeletal bone growth. Whether switching from TDF to TAF in growing adolescents obviates that toxicity would likely require serial DXA scans and, to date, this has not been performed. Dipyridamole, which appears to prevent TDF-induced bone toxicity in adults, has not been tested in adolescents [53].

The therapeutic benefit of calcium supplementation in HIV-related bone disease has not been investigated in adolescents. Bisphosphonates given together with calcium have shown temporary BMD benefit in HIV-infected adults, although the effect is not durable beyond cessation of bisphosphonate exposure [73–74]. A trial of alendronate in HIV-infected adolescents 11-24 years of age (NCT00921557) has recently been completed and results are eagerly awaited.

There is a severe lack of observational data around bone health and morbidity in virologically suppressed youth from LMIC.

## Chronic kidney disease (CKD)

CKD risk is increased in perinatally-acquired HIV independent of traditional CKD risk factors [75–80]. Prevalence of persistent renal dysfunction associated with TDF was 14% in HIV+ Thai adolescents [75].

**Etiology and pathogenesis/mechanisms—**As with chronic bone disease, the antiretroviral most strongly associated with CKD, particularly proximal renal tubular dysfunction, is TDF [55, 75]. A recent study implicates boosted PIs, although specific drugs are not mentioned [75].

In the combination ART era, the prevalence of classical HIV-associated nephropathy (HIVAN) has declined substantially and HIV-associated immune complex kidney disease (HIVICK) has become the predominant renal syndrome in virologically suppressed individuals. HIV-induced activation and dysfunction of B cells results in

hypergammaglobulinemia and monoclonal gammopathy that largely persists despite effective ART. This may lead to excess circulating antibody-antigen complexes that accumulate in the glomerular basement membrane and continuously trigger local inflammatory responses [81]. In addition, with immune recovery, it has been proposed that basic fibroblast growth factor (FGF-2) and vascular endothelial growth factor A may react to accumulations of HIV Tat protein trapped in the glomerular basement membrane, contributing to glomerular injury and excessive permeability to small proteins such as albumin [82], leading to microalbuminuria characteristic of HIVICK. Interestingly, HIV may be found persistently in renal tissue despite sustained viral suppression [83]. There may therefore be a direct viral effect on renal epithelial cells, although this is poorly characterized. While the APOL-1 renal risk allele (common in children of African descent) increases risk of HIVAN-associated focal segmental glomerulosclerosis in HIV+ youth [84], it does not appear to increase risk of HIVICK [85]. Traditional CKD risk factors (especially hypertension and type 2 diabetes) would also contribute substantially to both tubular and glomerular renal deterioration in suppressed youth and should be viewed in a serious light [28**].

**Therapeutics—**The primary therapeutic tool against persistent immune activation and consequent CKD remains consistent and uninterrupted HIV viral suppression by ART [11], avoiding TDF. Although angiotensin converting enzyme inhibitors are given empirically for HIVICK-associated microalbuminuria, the effectiveness of this intervention has not been investigated. Control of traditional risk factors, particularly hypertension, remains paramount [28**].

**Surveillance + monitoring—**While albumin-creatinine ratio is a commonly used screening test for microalbuminuria, detection of beta-2-microglobulin in urine (in the absence of haematological malignancy) may be a useful marker of renal tubular function, particularly among those using TDF [86]. Note that protein-creatinine ratio is non-specific since it cannot differentiate glomerular protein leak from inflammation of lower urinary tract due to urethritis or bladder trauma, prostatitis, or normal seminal fluid. However, it may be a useful marker of tubular disease where urine albumin measurement is not available. Glucosuria and phosphaturia (in the absence of an alternative explanation) are specific to renal tubular injury [87]. An elevated ratio of tubular maximum phosphate reabsorption to glomerular filtration rate (TMP/GFR) confirms inappropriate phosphate wasting by the kidney.

Change in glomerular filtration rate is a late feature and suggests advanced renal disease. Where this is suspected, serum cystatin C may be a more accurate and more sensitive measure of glomerular filtration rate than creatinine. However, serum cystatin C is an acute phase reactant and may be elevated during acute viral or bacterial infection or in inflammatory conditions [88].

**Unanswered questions + foci for future research—**Mechanism(s) by which HIV independently accelerates CKD in perinatally-infected adolescents will be important to elucidate. This may lead to novel (and effective) immune therapies to control persistent inappropriate immune responses in the virologically suppressed state. The effectiveness of

angiotensin converting enzyme inhibitors for HIVICK-associated microalbuminuria requires investigation. There remains a severe lack of observational data around renal health and morbidity in suppressed youth from LMIC.

## Chronic lung disease (CLD)

While there are few studies evaluating CLD among HIV-infected adolescents, CLD risk is increased in perinatally-acquired HIV [89–91]. Prevalence of abnormal spirometry was 24-38% in HIV+ adolescents in Zimbabwe and Malawi respectively [90, 91].

**Etiology and pathogenesis/mechanisms—**A common pathology contributing to CLD in perinatally-infected adolescents is small-airway bronchiectasis following repeated pneumonias (especially tuberculosis and lymphocytic interstitial pneumonitis) prior to immune reconstitution, resulting in permanent distortion of lung tissue by cicatrix (scarring) [91]. Th1 /Th2 imbalance may increase the risk of atypical asthma that is poorly-responsive to standard asthma therapies and may be a precursor to adult chronic obstructive pulmonary disease [92]. Obliterative bronchiolitis may be more common than previously recognized, present in 43% of ART-treated adolescents meeting a clinical case definition of chronic lung disease (defined as chronic cough for ≥1 month in the absence of tuberculosis; resting tachypnea or dyspnea; or desaturation with exercise)[93]. This lesion is a final common pathway of various insults and is not specific to HIV.

There may be a direct viral effect on HIV-infected pulmonary epithelial cells, although this is poorly characterized. This idea has been purported based on the finding that HIV may be found persistently in a variety of tissue sites despite sustained viral suppression [83].

**Therapeutics—**No recent data are available to support a particular therapeutic approach other than strictly maintaining HIV viral suppression and diligent bronchiectasis and reactive airways disease care.

**Surveillance + monitoring—**Spirometry is the gold standard surveillance method, however this modality is not widely available outside of tertiary centres, particularly in LMIC [89–92]. Exercise tolerance testing is a low-tech (yet sensitive) alternative screen for functional respiratory decline [89–90].

**Unanswered questions + foci for future research—**It is unknown whether infants receiving early ART, who are largely spared repeated lung infections, will remain at risk of CLD in adolescence.

Mechanism(s) by which HIV independently accelerates CLD in virologically suppressed perinatally-infected adolescents will be important to elucidate. This may lead to novel (and effective) immune therapies to control persistent inappropriate immune responses in the suppressed state.

## Conclusion

As perinatally HIV-infected children age into adolescence and adulthood with effective long-term ART, it is necessary to evaluate their risks for non-infectious co-morbidities and complications, understand mechanisms underlying their risks, and identify and evaluate interventions specifically in this population. There are many studies of AVD risk among HIV-infected adolescents though studies of interventions to reduce risk are relatively limited compared to adults. TDF and trials of vitamin D supplementation have been the focus of recent studies of CBD with few studies to date evaluating TAF as an alternative to TDF for decreasing risk for both bone and renal adverse effects among adolescents. Recent studies of CKD have focused primarily on estimating prevalence in LMIC settings while studies of CLD are limited.

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**Key Points**

- There are many studies of AVD risk among HIV-infected adolescents though studies of interventions to reduce risk are relatively limited compared to adults.
- Few studies to date have compared TAF to TDF for risk of bone or renal adverse effects among HIV-infected adolescents.
- Recent studies of CKD have focused primarily on estimating prevalence in LMIC settings while studies of CLD are limited.