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Cardiometabolic Complications in youth with perinatally acquired HIV in the era of antiretroviral therapy

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Abstract

Purpose of Review: Antiretroviral therapy (ART) scale-up has dramatically reduced rates of pediatric HIV mortality and morbidity. Children living with perinatally acquired HIV (PHIV) are now expected to live through adolescence and well into adulthood, such that adolescents now represent the largest growing population living with HIV. This review aims to discuss the prevalence and mechanisms for cardiometabolic co-morbidities in the setting of newer ART regimens and the research gaps that remain.

Recent Findings: Data highlight the continued risks of subclinical cardiometabolic complications in PHIV in the setting of newer ART. Novel techniques in imaging and omics may help identify early cardiometabolic abnormalities in this young population and potentially identify early changes in the mechanistic pathways related to these changes.

Summary: Further studies to determine risk and management strategies of the cardiometabolic effects in PHIV adolescents, beyond ART, are warranted. Focus should be on prevention of these complications in youth to avoid new epidemic of diabetes and cardiovascular disease when these youth become aging adults.

Keywords

cardiovascular; metabolic; pediatric; youth; HIV; ART

INTRODUCTION

The World Health Organization (WHO) estimates that over two million children have been infected with HIV, most via perinatal transmission[1]. The majority of individuals who acquired HIV through perinatal transmission are now also heading into adolescence (defined as those people between 10 and 19 years of age[2]) and/or adulthood[3, 4]. Wide access to antiretroviral therapy (ART) has transformed HIV from a fatal condition into a chronic disease leading to increases non-AIDS events such as cardiovascular disease (CVD)

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and metabolic complications. These conditions are becoming major causes of mortality and morbidity in adults living with HIV[5, 6]. The available knowledge about CVD and metabolic disease in the setting of contemporary ART is from adult studies, however recent findings suggest that children, despite ART, continue to be susceptible to subclinical cardiovascular and metabolic complications at an early age. In addition, findings in children suggest that there are unique differences in HIV and ART exposure (in-utero) and treatment during periods of critical development that may exacerbate co-morbidities in this population compared to adults.

Cardiovascular complications (Table 1)

Cardiomyopathy

Cardiomyopathy was one of the leading causes of death in children in the pre-ART era, typically manifested as severe dilated cardiomyopathy and has since decreased in the setting of ART[7]. Exposure to Nucleoside reverse transcriptase inhibitors (NRTIs, in particular thymidine NRTIs) has been associated with mitochondrial toxicity which can lead to cardiomyopathy. While incidence of cardiomyopathy among PHIV children has decreased since the mid-1990s, reports have suggested a higher incidence in children previously exposed to zalcitabine (ddC), and continued or new exposure to zidovudine (AZT) was associated with a higher rate of cardiomyopathy[8].

Adult HIV studies suggest a shift in the pathophysiology of HIV-associated cardiomyopathy which has become more multifactorial including viral associated mechanisms, ART toxicity, inflammation, ectopic adiposity, and nutritional causes[9]. In addition, ART has been increasingly associated from a phenotype of left ventricular systolic dysfunction to left ventricular diastolic dysfunction in adults. Results from the Characterization of Heart Function on Atiretroviral Therapy (CHART) study in adults, a multicentral cross-sectional case-control study of treated and virally suppressed HIV+ adults is the first comprehensive study of virally suppressed HIV+ adults treated with contemporary ART[10]. When comparing participants with and without diastolic dysfunction, with normal ejection fraction and no valvular disease, there was no difference in active ART including NRTI, NNRTI , protease inhibitor,or integrase strand transfer inhibitor (INSTI) use, however prior history of NRTIs was higher in participants with dysfunction. Although commonly adults living with HIV are experiencing comorbidities including hypertension, obesity, and metabolic syndrome likely associated with inflammation and contributing to cardiac dysfunction, the CHART study findings highlight that prior exposure to toxic drugs associated with mitochondrial dysfunction may continue to contribute to myocardial fibrosis and dysfunction well into adulthood.

Conduction and Functional Cardiac Abnormalities

An 11 year follow up of children on HIV (n=74, ages 3-16 years), compared to children followed in the pre-ART era (n=140), clearly demonstrates improvement in cardiac structure and function on ART[11] supporting that symptomatic cardiac disease are now rare compared to the pre-ART era. Overtime, however, children on ART in this study had

a consistent decrease in contractility. Studies of children on ART have reported cardiac conduction and functional abnormalities using EKG and echocardiography.

Children with HIV enrolled in the Pediatric HIV/AIDS Cohort Study (PHACS), a prospective cohort study at 14 US research sites, had higher left ventricular mass, volume and lower function as well as higher biomarkers of inflammation and myocardial injury (high-sensitivity cardiac troponin) compared to HIV-exposed uninfected children (HEUs) [12]. Studies in sub-Saharan Africa, where the vast majority of children with PHIV reside, have also found echocardiographic abnormalities. In a study in Uganda, the prevalence of cardiac abnormalities in 285 children living with HIV on ART, most of whom virally suppressed, was 14%, with the most common detected abnormality being T-wave changes and pericardial disease[13]. On the other hand, a study in Zimbabwe, 83 (42%) of children aged 6-16 years had an echocardiographic abnormality, 78% were virally suppressed (VL< 400 copies/mL) and the most common finding was LV diastolic dysfunction (23% of participants)[14]. This cohort was followed for 18 months, only a minority of cardiac abnormality were transient (6%), and there was an overall increase in mean z scores for LV, left atrium, right septum and LV posterior wall diameters over 18 months, however, the majority of participants remained asymptomatic[15]. In addition, no HIV-related factors (CD4 count, viral load, duration on ART, age at ART initiation or type of ART) were associated with incidences of cardiac abnormalities. Differences in techniques and cohorts likely explain the wide prevalence estimates of cardiac abnormalities in children and adolescents on ART in these studies.

A recent large cross sectional cohort study in young Kenyans (n=653, mean age of 14 years), used newer ultrasound-based imaging techniques which have increased sensitivity to detect myocardial dysfunction using strain technology and myocardial performance index (MPI) [16]. In this study, 28% met criteria for early cardiac dysfunction. Myocardial dysfunction was associated with markers of systemic inflammation, HIV-RNA level and history of AZT exposure. Using proteomics profiling, in a substudy of this cohort, proteins associated with cardiac remodeling, inflammation, and metabolism were higher in those with an abnormal MPI index[17]. This suggests that similar pathways as in adults with HIV-related CVD may be dysregulated in children and adolescents with subclinical cardiac dysfunction. These findings highlight that children on contemporary less toxic ART continue to have a wide spectrum of subclinical cardiac abnormalities.

Subclinical Vascular Disease

Increasingly, data in non-HIV adult and pediatric populations have shown that surrogate markers of subclinical vascular diseases, such as carotid intima-medial thickness (IMT), a structural measure, and pulse wave velocity (PWV), a functional measure, are predictive of important clinical outcomes, such as myocardial infarction and strokes[18–20]. There are reports on IMT between PHIV and HIV-children in higher resource settings[21–26] and only three cross sectional studies have measured arterial stiffness with PWV in pediatric HIV[27–29]. There are conflicting results in these reports with some studies highlighting evidence of subclinical vascular disease in PHIV and others showing no difference between the groups. This is again likely due to sample size, the participants and HIV-children varied

widely in age, ART use, viremia and varying anatomic sites used to measure IMT and PWV. A recent pooled analysis of >2000 HIV-infected and uninfected individuals in the US found that children and youth living with HIV had greater IMT thickness even after controlling for demographics and CVD risk factors[30]; moreover, HIV infection itself appeared to be the main risk factor for increased carotid artery thickening in this population. Amongst these studies, only a few recent studies have assessed IMT and PWV in African children[29, 31, 32]. Ethiopian children 6-17 years of age on efavirenz and LPV/r had increased PWV and IMT compared to those on nevirapine, however there was no uninfected control group for comparison. In Ugandan children 10-18 years of age (n=197), with PHIV children being mostly virally suppressed (86% with VL < 50 copies/mL), we reported no difference in arterial stiffness as measured by PWV but found that PHIV in Uganda have slightly thicker IMT compared to age- and sex-matched uninfected adolescents. Similar to our findings, reported differences in IMT in children with HIV in prior studies had ranged from 0.02-0.15 mm. We also found no differences in IMT or PWV between sexes or by ART regimen.

Direct evaluation of the coronary vessel using novel MRI techniques in a small cohort of mostly PHIV young adults (86 PHIV%, mean age 22 years old) compared to uninfected controls demonstrated a significant increase in coronary vessel wall thickness without associated increases in coronary plaque or stenosis, as measured by CT scan, in HIV+ compared to controls. In addition, smoking and history of stavudine use were associated with coronary wall thickness[33]. This suggests that similarly to cardiac function, newer and more sensitivity techniques may demonstrate that children and adolescents with HIV on lifelong ART have high rates of early vascular disease with the potential to develop into cardiovascular disease events early in life.

Endothelial Dysfunction

Changes in the endothelium are one of the earliest alterations of the vessel wall which occur prior to atherosclerosis[34]. Forearm flow-mediated vasodilation (FMD) has classically been used to assess peripheral endothelial dysfunction[35] and is predictive of long term cardiovascular events[36]. Its results, however, can vary during measurement and FMD has poor reproducibility[37]. Recently, we and others have conducted studies in children and young adults with HIV[38–40] using Peripheral Arterial Tonometry (endoPAT) which measures vascular function in an automatic and non-invasive manner. These studies have highlighted evidence of endothelial dysfunction in perinatally acquired HIV compared to uninfected controls[38, 39] that does not appear to be associated with immune status or current ART type used (specifically protease inhibitor vs others).

Metabolic Complications

Alteration in adipose tissue and potential mechanisms (Table 2)

Lipoatrophy and lipodystrophy, caused by thymidine analogue NRTIs and d-drugs like ddI and ddC, were historically common early in the HIV epidemic[41, 42]. Reassuringly, low prevalence of mild lipodystrophy have been reported on newer ART regimen, even those including AZT[43, 44], however, children previously treated with stavudine still have a greater risk for lipoatrophy[43]. Obesity is increased in people living with HIV[45, 46]

and continued abnormalities in fat distribution remain an issue despite contemporary ART [47]. The few studies that have quantified body mass composition in youth with HIV with standardized imaging have also suggested increased fat and specifically trunk fat, compared to uninfected youth[48–51]. In PHACS[49], HIV-infected children who had ever used stavudine, didanosine or zidovudine had a lower percentage of extremity fat, and higher percentage of trunk fat and in a longitudinal study from children in South Africa and the Netherlands[52], history of stavudine was also associated with lower subcutaneous fat. These findings suggest that, similarly to adult studies, previous exposure to thymidine NRTIs, may result in ongoing adiposity alteration in a cumulative, time-dependent manner.

Despite having similar total body fat percentage, alterations in regional fat distribution as measured by dual-energy x-ray absorptiometry (DXA) are detectable in perinatally infected youth compared to HIV-youth, with greater trunk fat and decreased leg fat and differences that appear to accelerate over time[53]. The little data that exist on the longitudinal changes in body composition in YLHIV also suggest that young PHIV females demonstrate greater gains in trunk fat and total percent body fat over a 7 year period compared to uninfected controls[50].

INSTI use has become more widespread for pediatric and adolescent ART. The most promising and affordable INSTI, DTG, has recently moved to the position of preferred first line drug regimen on the World Health Organization HIV treatment guidelines for adults and older children[1] and has just been approved for use in young infants[54]. Recent data from large cohort studies suggest that adults living with HIV on an INSTI-based regimen, have significant weight gain and metabolic complications [55–58]. There are only a few reports on the effect of dolutegravir (DTG) or other INSTIs on anthropometric changes in children. In a retrospective analysis of a longitudinal observational cohort known as the DC Cohort, among 117 youth with HIV (57% PHIV) we have shown an increase in the rate of BMI-z score post-INSTI initiation predominantly in those perinatally infected[59]. In an observational longitudinal study in Italy, 12 participants transitioning to a DTG-based regimen, changes in body composition, as measured by DXA scan were detected, including a significant increase in trunk fat, but not changes in BMI, total body or limbs fat[60]. Data on randomized trials in children on INSTI are very limited; recent findings presented from the multicenter ODYSSEY trial, an open label randomized trial where children were randomized to DTG, suggest a slight but significant increase in weight, height and BMI(1kg, 0.7cm, 0.3kg/m^2 respectively) at week 96 compared to standard of care (PI or NNRTI based ART)[61].

Although overall changes in body weight can have significant effects on cardiometabolic complications, the location of fat accumulation is important. Trunk/visceral fat is known to be associated with cardiovascular disease risk (CVD) in adults[62, 63] raising concern that with survival extending into adulthood, these findings suggest that alterations in regional fat are likely to continue to be significant and may contribute to cardiometabolic complications.

The mechanisms for alteration of body composition in children and adolescents with PHIV are unclear and likely multifactorial. Specifically ART, viremia, mitochondrial dysfunction, alteration of intestinal integrity and the resultant translocation of microbial products from

the intestinal lumen may all play a role[62, 64–66]. Mitochondrial function and substrate utilization are perturbed in PHIV when compared to HIV-exposed uninfected youth, additionally, HIV modified the relationship between BMI and complex I suggesting that despite having a lower BMI, PHIV may be unable to utilize substrates efficiently[67]. Even in the era of non-thymidine NRTI-containing regimens, HIV+ adults randomized to regimens containing either abacavir or tenofovir demonstrate a significant decrease in fat mitochondrial DNA[68]. In addition, in subjects receiving TDF, abnormalities in oxidative phosphorylation enzymes were correlated with larger total and visceral adiposity, raising concern for children and adolescents on life-long ART who already had mitochondrial injury due to prior toxic drugs.

Alteration of intestinal integrity and the resultant translocation of microbial products from the intestinal lumen may also play a role in ectopic fat accumulation[62, 64]. In obesity and diabetes, translocation of bacterial products has been shown to promote systemic and adipose tissue inflammation and lead to expansion of visceral adipose tissue and insulin resistance[69]. We have previously shown in a randomized clinical trial of ART initiation in adults, that intestinal fatty acid binding protein (IFAB-P), a marker of intestinal barrier dysfunction, independently predicted increases in total and visceral abdominal fat at 96 weeks after ART[64]. In cross sectional studies, we have also shown evidence of disturbances in intestinal integrity and translocation in children despite viral suppression[70, 71], supporting the fact that ART does not fully restore the gut barrier even in younger populations. In PHACS, we also investigated the role of gut dysfunction on body composition as measured by DXA in youth with HIV (n=261). We found that markers of intestinal integrity and microbial translocation were associated with percent body fat at baseline and 2 years later, even after adjusting for demographic confounders, and ART exposure[72]. We hypothesize that gut dysbiosis, and alteration in intestinal barrier could lead to expansion of visceral fat, and contribute to upregulation of cytokines produced by inflamed adipose tissue.

Insulin Resistance

Insulin resistance is the decreased ability of insulin to stimulate the use of glucose driving increased production of insulin. Several recent pediatric studies both in US and sub-Saharan Africa have measured insulin resistance using the homeostatic assessment of insulin resistance (HOMA-IR)[65, 73–84]. Overall, these studies highlight that despite low or normal BMI and viral suppression on ART, PHIV have derangements in glucose metabolism. Some studies indicated higher prevalence of insulin resistance[83, 84] compared to uninfected children (exposed or unexposed to HIV) while others did not[76, 77], which may be due to a different HOMA-IR cut off value to define insulin resistance. HOMA-IR in PHIV has been independently associated with anthropometric measures[73, 76, 77, 84]. Although prior use of Abacavir was associated with HOMA-IR in South-African adolescents[76], Ugandan children from the Children with HIV in Africa-Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens (CHAPAS-3) trial randomized to zidovudine (AZT), stavudine (D4T) or abacavir (ABC) based regimens, HOMA-IR significantly increased in all groups at 48 weeks, however there was no difference between the groups[83].

Despite these controversial results, these findings raise the concern that PHIV adolescents, who will require decades of therapy, may develop persistent elevated levels of insulin which may lead to a high incidence of diabetes overtime. In addition, a rise in insulin resistance during puberty has been noted[85, 86] and may be potentiated in PHIV[87].

Dyslipidemia

The prevalence of dyslipidemia has ranged widely in HIV+ children and adolescents depending on the definition. Newer ART appear to present more favorable lipid profiles, specifically studies in children transitioning to newer protease inhibitors (ATV/r or DRV/r) report reductions in total cholesterol and or triglycerides [88, 89]. Similarly, findings from the ODYSSEY trial have found a significant decline in total cholesterol and triglycerides over 96 weeks in the DTG arm compared to PI or NNRTI-based regimen[61].

Dyslipidemia is traditionally assessed with high abundance-lipids. These basic lipid panels provide insufficient characterization and insight as to the fundamental metabolic perturbations in HIV infection, and their relationship to both inflammation and CVD risk[90]. New methods have been developed that allow for a finer characterization of these elements. ‘Lipidomics’ is a branch of metabolomics that applies to studying lipid metabolism on a broad scale Lipidomics in HIV is still in its infancy. Altered lipid classes have been associated with HIV infection in adults[91]. In a small sub-cohort of 20 HIV+ youth and 20 HIV− in Uganda, we measured concentrations of serum lipids and fatty acid compositions by direct infusion-tandem mass spectrometry[92]. A total of 13 lipid classes constituting 850 different lipid species were identified. The lipidome of PHIV was significantly different from HIV−. Main differences were observed in increased concentrations of cholesterol esters (CE), ceramides (CER), phosphatidylcholines (PC), sphingomyelins (SM) and lactosylceramides (LCER) containing saturated fatty acids (SaFA) in PHIV compared to HIV−. Specifically, lipid species known to be associated with CVD, were increased in HIV, including ceramides. When comparing serum fatty acids concentrations in PHIV to those in HIV+ adults on ART[93], or adults with inflammatory conditions such as nonalcoholic fatty liver disease[94], we find that levels of SaFA are nearly two fold higher in PHIV, suggesting that this population likely has a unique lipidomic signature.

It is important to note however that the majority of lipid studies in PHIV or in adults living with HIV were conducted without assessment of nutritional factors that can substantially affect lipid levels and composition.

Conclusions

Our understanding of the trajectory of cardiometabolic complications in children and adolescents with HIV is sorely lacking. PHIV on ART with viral suppression still show evidence of subclinical cardiac and metabolic disease. The exposure of HIV and ART in utero, the decades of ART therapy, the lasting effects of older toxic ART with mitochondrial toxicity and the long term sub-optimal adherence known to occur with prolonged ART use, heighten concern that sequelae of HIV and ART in children and adolescents may be more frequent and potentially more devastating than in adults. Better understanding of the CVD

and metabolic risks and their effects on other organ dysfunction in PHIV is crucial, as it is often easier to limit or even reverse arterial and metabolic injury at an early stage.

As youth worldwide are aging towards adulthood, this special population deserves special consideration and longitudinal studies of prevalence, incidence and pathogenesis are needed and should include resource-limited settings where most of the pediatric HIV population currently reside. Similarly a better understanding of the contribution of nutritional factors, both macro and micronutrients, to these cardiometabolic abnormalities is urgently needed. We need to work together across specialties, to gain a clear understanding of the long term cardiometabolic risk in youth with HIV and the mechanisms behind these comorbidities, in order to guide future preventive and therapeutic interventions.

REFERENCES

Papers of particular interest, published recently, have been highlighted as: • Of importance •• Of major importance

1. Organization TWH. Fact Sheet HIV/AIDS. 2019.
2. Age limits and adolescents. Paediatrics & child health. 2003;8(9):577–8. [PubMed: 20019831]
3. Centers for Disease Control and Prevention. HIV Surveillance Report. 2017.
4. Flynn PM, Abrams EJ. Growing up with perinatal HIV. AIDS (London, England). 2019;33(4):597–603.
5. Paula AA, Schechter M, Tuboi SH, Faulhaber JC, Luz PM, Veloso VG, et al. Continuous Increase of Cardiovascular Diseases, Diabetes, and Non-HIV Related Cancers as Causes of Death in HIV-Infected Individuals in Brazil: An Analysis of Nationwide Data. PloS one. 2014;9(4):e94636. [PubMed: 24728320]
6. Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Gill H, Attali M, Asher I. HIV-associated neurocognitive disorders (HAND). The Israel Medical Association journal : IMAJ. 2015;17(1):54–9. [PubMed: 25739180]
7. Brady MT, Oleske JM, Williams PL, Elgie C, Mofenson LM, Dankner WM, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. Journal of acquired immune deficiency syndromes (1999). 2010;53(1):86–94. [PubMed: 20035164]
8. Patel K, Van Dyke RB, Mittleman MA, Colan SD, Oleske JM, Seage GR 3rd. The impact of HAART on cardiomyopathy among children and adolescents perinatally infected with HIV-1. AIDS (London, England). 2012;26(16):2027–37.
9. Savvoulidis P, Butler J, Kalogeropoulos A. Cardiomyopathy and Heart Failure in Patients With HIV Infection. The Canadian journal of cardiology. 2019;35(3):299–309. [PubMed: 30621958]
10. Butler J, Greene SJ, Shah SH, Shah SJ, Anstrom KJ, Kim RJ, et al. Diastolic Dysfunction in Patients With Human Immunodeficiency Virus Receiving Antiretroviral Therapy: Results From the CHART Study. Journal of cardiac failure. 2020;26(5):371–80. [PubMed: 31682908]
11 (•). Lipshultz SE, Wilkinson JD, Thompson B, Cheng I, Briston DA, Shearer WT, et al. Cardiac Effects of Highly Active Antiretroviral Therapy in Perinatally HIV-Infected Children: The CHAART-2 Study. Journal of the American College of Cardiology. 2017;70(18):2240–7. [PubMed: 29073951] This study compared echocardiograms from ART-exposed children compared to ART unexposed children. Cardiac structure and function improved in PHIV children on ART compared to children in pre-ART area but did decline over time.
12. Wilkinson JD, Williams PL, Yu W, Colan SD, Mendez A, Zachariah JPV, et al. Cardiac and inflammatory biomarkers in perinatally HIV-infected and HIV-exposed uninfected children. AIDS (London, England). 2018;32(10):1267–77.
13. Namuyonga J, Lubega S, Musiime V, Lwabi P, Lubega I. Cardiac Dysfunction Among Ugandan HIV-infected Children on Antiretroviral Therapy. The Pediatric infectious disease journal. 2016;35(3):e85–8. [PubMed: 26569195]

14. Majonga ED, Rehman AM, Simms V, McHugh G, Mujuru HA, Nathoo K, et al. High prevalence of echocardiographic abnormalities in older HIV-infected children taking antiretroviral therapy. AIDS (London, England). 2018;32(18):2739–48.

15 (•). Majonga ED, Rehman AM, McHugh G, Mujuru HA, Nathoo K, Odland JO, et al. Incidence and Progression of Echocardiographic Abnormalities in Older Children with Human Immunodeficiency Virus and Adolescents Taking Antiretroviral Therapy: A Prospective Cohort Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;70(7):1372–8. [PubMed: 31054255] Prospective longitudinal cohort in Zimbabwe of children on ART with echocardiograms at baseline and 18 months after, PHIV on ART have a high incidence of cardiac abnormalities that persist and progress over time.

16 (•). McCrary AW, Nyandiko WM, Ellis AM, Chakraborty H, Muehlbauer MJ, Koech MM, et al. Early cardiac dysfunction in children and young adults with perinatally acquired HIV. AIDS (London, England). 2020;34(4):539–48.In a large cohort in Kenya (n=643) with a mean age of 14 yo, echocardiogram was performed to assess for early cardiac dysfunction as measured by left ventricular strain and myocardial performance index. 28% of children had early cardiac dysfunction. AZT exposure was independently association with strain.

17. Andrew McCrary WN, Michasel J Muehlbauer, Ibrahim Daug, Nathan M Thielman, Maggie Nguyen, Shah Svati J., Bloomfield Gerald S., editor Serum Biomarkers Identify Cardiac Dysfunction in Youth Living with HIV. CROI; 2021; Virtual.

18. Terai M, Ohishi M, Ito N, Takagi T, Tatara Y, Kaibe M, et al. Comparison of arterial functional evaluations as a predictor of cardiovascular events in hypertensive patients: the Non-Invasive Atherosclerotic Evaluation in Hypertension (NOAH) study. Hypertension research : official journal of the Japanese Society of Hypertension. 2008;31(6):1135–45. [PubMed: 18716361]

19. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006;113(5):657–63. [PubMed: 16461838]

20. Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, et al. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Circulation journal : official journal of the Japanese Circulation Society. 2005;69(3):259–64. [PubMed: 15731528]

21. McComsey GA, O'Riordan M, Hazen SL, El-Bejjani D, Bhatt S, Brennan ML, et al. Increased carotid intima media thickness and cardiac biomarkers in HIV infected children. AIDS (London, England). 2007;21(8):921–7.

22. Charakida M, Donald AE, Green H, Storry C, Clapson M, Caslake M, et al. Early structural and functional changes of the vasculature in HIV-infected children: impact of disease and antiretroviral therapy. Circulation. 2005;112(1):103–9. [PubMed: 15983247]

23. Sainz T, Alvarez-Fuente M, Navarro ML, Diaz L, Rojo P, Blazquez D, et al. Subclinical Atherosclerosis and Markers of Immune Activation in HIV-Infected Children and Adolescents: The CaroVIH Study. Journal of acquired immune deficiency syndromes (1999). 2014;65(1):42–9. [PubMed: 23982657]

24. Bonnet D, Aggoun Y, Szezepanski I, Bellal N, Blanche S. Arterial stiffness and endothelial dysfunction in HIV-infected children. AIDS (London, England). 2004;18(7):1037–41.

25. Chanthong P, Lapphra K, Saihongthong S, Sricharoenchai S, Wittawatmongkol O, Phongsamart W, et al. Echocardiography and carotid intima-media thickness among asymptomatic HIV-infected adolescents in Thailand. AIDS (London, England). 2014;28(14):2071–9.

26. Marsico F, Lo Vecchio A, Paolillo S, D'Andrea C, De Lucia V, Bruzzese E, et al. Left Ventricular Function, Epicardial Adipose Tissue, and Carotid Intima-Media Thickness in Children and Adolescents With Vertical HIV Infection. Journal of acquired immune deficiency syndromes (1999). 2019;82(5):462–7. [PubMed: 31714424]

27. Charakida M, Loukogeorgakis SP, Okorie MI, Masi S, Halcox JP, Deanfield JE, et al. Increased arterial stiffness in HIV-infected children: risk factors and antiretroviral therapy. Antiviral therapy. 2009;14(8):1075–9. [PubMed: 20032537]

28. Eckard AR, Raggi P, Ruff JH, O'Riordan MA, Rosebush JC, Labbato D, et al. Arterial stiffness in HIV-infected youth and associations with HIV-related variables. Virulence. 2017;8(7):1265–73. [PubMed: 28324675]

29. Gleason RL Jr., Caulk AW, Seifu D, Rosebush JC, Shapiro AM, Schwartz MH, et al. Efavirenz and ritonavir-boosted lopinavir use exhibited elevated markers of atherosclerosis across age groups in people living with HIV in Ethiopia. Journal of biomechanics. 2016;49(13):2584–92. [PubMed: 27270208]

30(••). Hanna DB, Guo M, Buzkova P, Miller TL, Post WS, Stein JH, et al. HIV Infection and Carotid Artery Intima-media Thickness: Pooled Analyses Across 5 Cohorts of the NHLBI HIV-CVD Collaborative. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(2):249–56. [PubMed: 27118787] Through a NHLBI research consortium, this study analyzed IMT measurements from 5 studies and >2000 HIV+ individuals, including 221 6–29 yo HIV+ and 58 HIV−. There was higher IMT in this group when compared to uninfected participants and the increase in IMT in HIV+ was strengthened when limited to PHIV.

31 (•). Dirajlal-Fargo S, Albar Z, Bowman E, Labbato D, Sattar A, Karungi C, et al. Subclinical Vascular Disease in Children With Human Immunodeficiency Virus in Uganda Is Associated With Intestinal Barrier Dysfunction. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(12):3025–32. [PubMed: 31807748] In a cross sectional study, Ugandan PHIV, virally suppressed on ART, had evidence of higher IMT compared to HIV-which was independently associated with alteration in gut barrier.

32. Majonga ED, Chiesa ST, McHugh G, Mujuru H, Nathoo K, Odland JO, et al. Carotid intima media thickness in older children and adolescents with HIV taking antiretroviral therapy. Medicine. 2020;99(17):e19554. [PubMed: 32332603]

33. Abd-Elmoniem KZ, Unsal AB, Eshera S, Matta JR, Muldoon N, McAreavey D, et al. Increased coronary vessel wall thickness in HIV-infected young adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59(12):1779–86. [PubMed: 25159580]

34. Poredos P Endothelial dysfunction in the pathogenesis of atherosclerosis. International angiology : a journal of the International Union of Angiology. 2002;21(2):109–16. [PubMed: 12110769]

35. Widlansky ME, Gokce N, Keaney JF Jr., Vita JA. The clinical implications of endothelial dysfunction. Journal of the American College of Cardiology. 2003;42(7):1149–60. [PubMed: 14522472]

36. Gokce N, Keaney JF Jr., Hunter LM, Watkins MT, Nedeljkovic ZS, Menzoian JO, et al. Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. Journal of the American College of Cardiology. 2003;41(10):1769–75. [PubMed: 12767663]

37. Hijmering ML, Stroes ES, Pasterkamp G, Sierevogel M, Banga JD, Rabelink TJ. Variability of flow mediated dilation: consequences for clinical application. Atherosclerosis. 2001;157(2):369–73. [PubMed: 11472736]

38. Mahtab S, Zar HJ, Ntusi NAB, Joubert S, Asafu-Agyei NAA, Luff NJ, et al. Endothelial Dysfunction in South African Youth Living With Perinatally Acquired Human Immunodeficiency Virus on Antiretroviral Therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(10):e672–e9. [PubMed: 32285090]

39. Dirajlal-Fargo S, Sattar A, Kulkarni M, Bowman E, Funderburg N, McComsey GA. HIV-positive youth who are perinatally infected have impaired endothelial function. AIDS (London, England). 2017;31(14):1917–24.

40. Bush KNV, Teel JL, Watts JA, Gore RS, Alvarado G, Harper NL, et al. Association of Endothelial Dysfunction and Antiretroviral Therapy in Early HIV Infection. JAMA Network Open. 2019;2(10):e1913615–e. [PubMed: 31626317]

41. Domingo P, Estrada V, López-Aldeguer J, Villaroya F, Martínez E. Fat redistribution syndromes associated with HIV-1 infection and combination antiretroviral therapy. AIDS reviews. 2012;14(2):112–23. [PubMed: 22627607]

42. Mallon PW, Miller J, Cooper DA, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. AIDS (London, England). 2003;17(7):971–9.

43. Cames C, Pascal L, Ba A, Mbodj H, Ouattara B, Diallo NF, et al. Low prevalence of lipodystrophy in HIV-infected Senegalese children on long-term antiretroviral treatment: the

ANRS 12279 MAGGSEN Pediatric Cohort Study. BMC infectious diseases. 2018;18(1):374. [PubMed: 30081838]

44. Bwakura-Dangarembizi M, Musiime V, Szubert AJ, Prendergast AJ, Gomo ZA, Thomason MJ, 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]
45. Crum-Cianflone N, Roediger MP, Eberly L, Headd M, Marconi V, Ganesan A, et al. Increasing rates of obesity among HIV-infected persons during the HIV epidemic. PloS one. 2010;5(4):e10106. [PubMed: 20419086]
46. Crum-Cianflone N, Tejidor R, Medina S, Barahona I, Ganesan A. Obesity among patients with HIV: the latest epidemic. AIDS patient care and STDs. 2008;22(12):925–30. [PubMed: 19072098]
47. Koethe JR, Lagathu C, Lake JE, Domingo P, Calmy A, Falutz J, et al. HIV and antiretroviral therapy-related fat alterations. Nature reviews Disease primers. 2020;6(1):48.
48. Jacobson DL, Lindsey JC, Coull BA, Mulligan K, Bhagwat P, Aldrovandi GM. The Association of Fat and Lean Tissue With Whole Body and Spine Bone Mineral Density Is Modified by HIV Status and Sex in Children and Youth. The Pediatric infectious disease journal. 2018;37(1):71–7. [PubMed: 28817419]
49. Jacobson DL, Patel K, Siberry GK, Van Dyke RB, DiMeglio LA, Geffner ME, et al. Body fat distribution in perinatally HIV-infected and HIV-exposed but uninfected children in the era of highly active antiretroviral therapy: outcomes from the Pediatric HIV/AIDS Cohort Study. The American journal of clinical nutrition. 2011;94(6):1485–95. [PubMed: 22049166]
50(••). Sharma TS, Somarriba G, Arheart KL, Neri D, Mathew MS, Graham PL, et al. Longitudinal Changes in Body Composition by Dual-energy Radiograph Absorptiometry Among Perinatally HIV-infected and HIV-uninfected Youth: Increased Risk of Adiposity Among HIV-infected Female Youth. The Pediatric infectious disease journal. 2018;37(10):1002–7. [PubMed: 29474262] PHIV on ART and HIV-controls were prospectively enrolled and DXA scans were obtained in a longitudinal fashion over a median of 2.5 years, PHIV females had significant increases in total percent body and trunk fat compared to HIV-females and PHIV males.
51. Aurpibul L, Namwongprom S, Sudjaritruk T, Ounjaijean S. Metabolic syndrome, biochemical markers, and body composition in youth living with perinatal HIV infection on antiretroviral treatment. PloS one. 2020;15(3):e0230707. [PubMed: 32226033]
52 (•). Cohen S, Innes S, Geelen SP, Wells JC, Smit C, Wolfs TF, et al. Long-Term Changes of Subcutaneous Fat Mass in HIV-Infected Children on Antiretroviral Therapy: A Retrospective Analysis of Longitudinal Data from Two Pediatric HIV-Cohorts. PloS one. 2015;10(7):e0120927. [PubMed: 26148119] 218 PHIV children in South Africa and the Netherlands underwent DXA scans over a period of 3.5 years. Findings highlight ongoing subcutaneous fat loss in PHIV on ART associated with prior stavudine exposure.
53. Arpadi SM, Bethel J, Horlick M, Sarr M, Bamji M, Abrams EJ, et al. Longitudinal changes in regional fat content in HIV-infected children and adolescents. AIDS (London, England). 2009;23(12):1501–9.
54. Food and Drug Administration. FDA News Release: FDA Approves Drug to Treat Infants and Children with HIV 2020 [Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-drug-treat-infants-and-children-hiv.
55. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgan T, Raffanti SP, et al. Greater Weight Gain in Treatment Naive Persons Starting Dolutegravir-Based Antiretroviral Therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019;70(7):1267–74.
56. Sax PE, Erlandson KM, Lake JE, McComsey GA, Orkin C, Esser S, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials [published online ahead of print, 2019 Oct 14]. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019;ciz999.
57. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. The New England journal of medicine. 2019;381(9):803–15. [PubMed: 31339677]

58. Lamorde M, Atwiine M, Owarwo NC, Ddungu A, Laker EO, Mubiru F, et al. Dolutegravir-associated hyperglycaemia in patients with HIV [published online ahead of print, 2020 Feb 24]. Lancet HIV. 2020;S2352-3018(20)30042-4.

59. Sahera Dirajlal-fargo WLAK, Levy Matthew E., Monroe Anne K., Castel Amanda D., Rakhmanina Natella, editor Effect of Integrase Inhibitors on Weight Gain in Children and Adolescents with HIV. CROI; 2020 03/2020; Virtual.

60. Giacomet V, Lazzarin S, Manzo A, Paradiso L, Maruca K, Barera G, et al. Body Fat Distribution and Metabolic Changes in a Cohort of Adolescents Living With HIV Switched to an Antiretroviral Regimen Containing Dolutegravir. The Pediatric infectious disease journal. 2021;40(5):457–9. [PubMed: 33847293]

61 (•). Turkova A, editor Dolutegravir-based ART is superior to NNRI/PI-based ART in children and adolescents. CROI; 2021; virtual.Findings from ODYSSEY trial, an open label multicountry randomized trial presented at CROI 2021. PHIV randomized to DTG highlighted a slight but significant increase in BMI compared to standard of care.

62. Erlandson KM, Lake JE. Fat Matters: Understanding the Role of Adipose Tissue in Health in HIV Infection. Current HIV/AIDS reports. 2016;13(1):20–30. [PubMed: 26830284]

63. Alexopoulos N, Katritsis D, Raggi P. Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis. Atherosclerosis. 2014;233(1):104–12. [PubMed: 24529130]

64. El Kamari V, Moser C, Hileman CO, Currier JS, Brown TT, Johnston L, et al. Lower Pretreatment Gut Integrity Is Independently Associated With Fat Gain on Antiretroviral Therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019;68(8):1394–401. [PubMed: 30137242]

65. Gojanovich GS, Jacobson DL, Jao J, Russell JS, Van Dyke RB, Libutti DE, et al. Mitochondrial Dysfunction and Insulin Resistance in Pubertal Youth Living with Perinatally Acquired HIV. AIDS research and human retroviruses. 2020;36(9):703–11. [PubMed: 32586116]

66. Hulgan T, Ramsey BS, Koethe JR, Samuels DC, Gerschenson M, Libutti DE, et al. Relationships Between Adipose Mitochondrial Function, Serum Adiponectin, and Insulin Resistance in Persons With HIV After 96 Weeks of Antiretroviral Therapy. Journal of acquired immune deficiency syndromes (1999). 2019;80(3):358–66. [PubMed: 30531304]

67. Jao J, Jacobson DL, Russell JS, Wang J, Yu W, Gojanovich GS, et al. Perinatally acquired HIV infection is associated with abnormal blood mitochondrial function during childhood/adolescence. AIDS (London, England). 2021;Publish Ahead of Print.

68. McComsey GA, Daar ES, O'Riordan M, Collier AC, Kosmiski L, Santana JL, et al. Changes in fat mitochondrial DNA and function in subjects randomized to abacavir-lamivudine or tenofovir DF-emtricitabine with atazanavir-ritonavir or efavirenz: AIDS Clinical Trials Group study A5224s, substudy of A5202. The Journal of infectious diseases. 2013;207(4):604–11. [PubMed: 23204164]

69. Bouter KE, van Raalte DH, Groen AK, Nieuwdorp M. Role of the Gut Microbiome in the Pathogenesis of Obesity and Obesity-Related Metabolic Dysfunction. Gastroenterology. 2017;152(7):1671–8. [PubMed: 28192102]

70. Koay WLA, Lindsey JC, Uprety P, Bwakura-Dangarembizi M, Weinberg A, Levin MJ, et al. Intestinal Integrity Biomarkers in Early Antiretroviral-Treated Perinatally HIV-1-Infected Infants. The Journal of infectious diseases. 2018;218(7):1085–9. [PubMed: 29762690]

71(••). Dirajlal-Fargo S, El-Kamari V, Weiner L, Shan L, Sattar A, Kulkarni M, et al. Altered intestinal permeability and fungal translocation in Ugandan children with HIV. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019.In this cross sectional study performed in Uganda, PHIV had evidence of alteration in intestinal permeability compared to HIV− and HEU children despite viral suppression on ART. In PHIV< these markers correlated with systemic inflammation.

72. Sahera Dirajlal-Fargo DJ, Wendy Yu, Ayesha Mirza, Geffner Mitchell E., Jennifer Jao, McComsey Grace A. , on behalf of the Pediatric HIV/AIDS Cohort Study (PHACS). GUT MARKERS' ASSOCIATIONS WITH BODY FAT IN YOUTH LIVING WITH PERINATALLY-ACQUIRED HIV. Conference of Retroviruses and Opportunistic Infections-2021; Virtual2021.

73. Blázquez D, Ramos-Amador JT, Saínz T, Mellado MJ, García-Ascaso M, De José MI, et al. Lipid and glucose alterations in perinatally-acquired HIV-infected adolescents and young adults. BMC infectious diseases. 2015;15:119. [PubMed: 25880777]

74. Espiau M, Yeste D, Noguera-Julian A, González-Tomé MI, Falcón-Neyra L, Gavilán C, et al. Metabolic Syndrome in Children and Adolescents Living with HIV. The Pediatric infectious disease journal. 2016;35(6):e171–6. [PubMed: 26910591]

75. Espiau M, Yeste D, Noguera-Julian A, Soler-Palacín P, Fortuny C, Ferrer R, et al. Adiponectin, Leptin and Inflammatory Markers in HIV-associated Metabolic Syndrome in Children and Adolescents. The Pediatric infectious disease journal. 2017;36(2):e31–e7. [PubMed: 27832021]

76. Frigati LJ, Jao J, Mahtab S, Asafu Agyei NA, Cotton MF, Myer L, et al. Insulin Resistance in South African Youth Living with Perinatally Acquired HIV Receiving Antiretroviral Therapy. AIDS research and human retroviruses. 2019;35(1):56–62. [PubMed: 30156434]

77. Geffner ME, Patel K, Jacobson DL, Wu J, Miller TL, Hazra R, et al. Changes in insulin sensitivity over time and associated factors in HIV-infected adolescents. AIDS (London, England). 2018;32(5):613–22.

78. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High Prevalence of Dyslipidemia and Insulin Resistance in HIV-infected Prepubertal African Children on Antiretroviral Therapy. The Pediatric infectious disease journal. 2016;35(1):e1–7. [PubMed: 26421804]

79. Paganella MP, Cohen RA, Harris DR, de Souza Kuchenbecker R, Sperhacke RD, Kato SK, et al. Association of Dyslipidemia and Glucose Abnormalities With Antiretroviral Treatment in a Cohort of HIV-Infected Latin American Children. Journal of acquired immune deficiency syndromes (1999). 2017;74(1):e1–e8. [PubMed: 27570910]

80. Santiprabhob J, Chokephaibulkit K, Khantee P, Maleesatharn A, Phonrat B, Phongsamart W, et al. Adipocytokine dysregulation, abnormal glucose metabolism, and lipodystrophy in HIV-infected adolescents receiving protease inhibitors. Cytokine. 2020;136:155145. [PubMed: 32920318]

81. Santiprabhob J, Tanchaweng S, Maturapat S, Maleesatharn A, Lermankul W, Sricharoenchai S, et al. Metabolic Disorders in HIV-Infected Adolescents Receiving Protease Inhibitors. BioMed research international. 2017;2017:7481597. [PubMed: 28293638]

82. Takemoto JK, Miller TL, Wang J, Jacobson DL, Geffner ME, Van Dyke RB, et al. Insulin resistance in HIV-infected youth is associated with decreased mitochondrial respiration. AIDS (London, England). 2017;31(1):15–23.

83. Dirajlal-Fargo S, Musiime V, Cook A, Mirembe G, Kenny J, Jiang Y, et al. Insulin Resistance and Markers of Inflammation in HIV-infected Ugandan Children in the CHAPAS-3 Trial. The Pediatric infectious disease journal. 2017;36(8):761–7. [PubMed: 28067719]

84. Dirajlal-Fargo S, Shan L, Sattar A, Bowman E, Gabriel J, Kulkarni M, et al. Insulin resistance and intestinal integrity in children with and without HIV infection in Uganda. HIV medicine. 2020;21(2):119–27. [PubMed: 31642582]

85. Moran A, Jacobs DR Jr., Steinberger J, Steffen LM, Pankow JS, Hong CP, et al. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. Circulation. 2008;117(18):2361–8. [PubMed: 18427135]

86. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatric research. 2006;60(6):759–63. [PubMed: 17065576]

87. Dimock D, Thomas V, Cushing A, Purdy JB, Worrell C, Kopp JB, et al. Longitudinal assessment of metabolic abnormalities in adolescents and young adults with HIV-infection acquired perinatally or in early childhood. Metabolism: clinical and experimental. 2011;60(6):874–80. [PubMed: 20947103]

88 (•). Jao J, Yu W, Patel K, Miller TL, Karalius B, Geffner ME, et al. Improvement in lipids after switch to boosted atazanavir or darunavir in children/adolescents with perinatally acquired HIV on older protease inhibitors: results from the Pediatric HIV/AIDS Cohort Study. HIV medicine. 2018;19(3):175–83. [PubMed: 29159965] PHIV enrolled in PHACS who switched to ATV/r or DRV/r compared to those who remained on older PI had a more rappid reduction in lipids.

89. Rutstein RM, Samson P, Fenton T, Fletcher CV, Kiser JJ, Mofenson LM, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the Pediatric AIDS Clinical Trials Group Protocol 1020A. The Pediatric infectious disease journal. 2015;34(2):162–7. [PubMed: 25232777]

90. Munger AM, Chow DC, Playford MP, Parikh NI, Gangcuangco LM, Nakamoto BK, et al. Characterization of Lipid Composition and High-Density Lipoprotein Function in HIV-

Infected Individuals on Stable Antiretroviral Regimens. AIDS research and human retroviruses. 2015;31(2):221–8. [PubMed: 25416403]

91. Wong G, Trevillyan JM, Fatou B, Cinel M, Weir JM, Hoy JF, et al. Plasma lipidomic profiling of treated HIV-positive individuals and the implications for cardiovascular risk prediction. PloS one. 2014;9(4):e94810. [PubMed: 24733512]

92 (•). Dirajlal-Fargo S, Sattar A, Yu J, Albar Z, Chaves FC, Riedl K, et al. Lipidome Association with Vascular Disease and Inflammation in HIV+ Ugandan Children. AIDS (London, England). 2021.In this small pilot study, Ugandan PHIV (n=20) compared to HIV-(n=20) had evidence of altered lipidomic panel and increased in lipid species known to be inflammatory and associated with CVD.

93. Bowman ER, Kulkarni M, Gabriel J, Cichon MJ, Riedl K, Belury MA, et al. Altered Lipidome Composition Is Related to Markers of Monocyte and Immune Activation in Antiretroviral Therapy Treated Human Immunodeficiency Virus (HIV) Infection and in Uninfected Persons. Frontiers in immunology. 2019;10:785. [PubMed: 31040846]

94. Puri P, Wiest MM, Cheung O, Mirshahi F, Sargeant C, Min HK, et al. The plasma lipidomic signature of nonalcoholic steatohepatitis. Hepatology (Baltimore, Md). 2009;50(6):1827–38.

95. Taramasso L, Di Biagio A, Bovis F, Forlanini F, Albani E, Papaioannu R, et al. Switching to Integrase Inhibitors Unlinked to Weight Increase in Perinatally HIV-Infected Young Adults and Adolescents: A 10-Year Observational Study. Microorganisms. 2020;8(6):864.

96. al TNe, editor Optimization to dolutegravir-based ART in a cohort of virally suppressed adolescents is associated with an increase in the rate of BMI change and odds of becoming overweight. AIDS 2020; 2020; virtual.

97. Yeoh DK, Campbell AJ, Bowen AC. Increase in Body Mass Index in Children With HIV, Switched to Tenofovir Alafenamide Fumarate or Dolutegravir Containing Antiretroviral Regimens. The Pediatric infectious disease journal. 2021;40(5):e215–e6. [PubMed: 33847305]

Table 1:

Summary of recent reports of cardiovascular complication in pediatric HIV

Author and Year	Country	Population	Age Range (years)	Design	Parameters used	Findings
CONDUCTION AND FUNCTIONAL ABNORMALITIES						
Namuyonga et al, 2016[13]	Uganda	285 PHIV children	1-18	Cross Sectional	• EKG • TT Echocardiogram	• Cardiac abnormalities detected in 14% children • Most common abnormalities: T-wave changes, pericardial disease
Lipshultz et al, 2017[11]	USA	74 HIV+ on ART compared to 140 HIV+ not on ART (conducted from 1990-1997)	3-16	Longitudinal	Serial TT Echocardiograms	• ART + children had more normal LV function and structure than pre-ART children • Cardiac function in ART+ children declined with increased follow up
Wilkinson et al, 2018[12]	USA	Adolescent Master Protocol (AMP) study in the Pediatric HIV/AIDS Cohort Study (PHACS) 246 PHIV Youth 156 HEU	7-16	Cross Sectional	• TT Echocardiogram • Serum TNT	• PHIV had higher biomarker levels associated with lower LV mass and structure
Majonga et al, 2018[14]	Zimbabwe	201 PHIV	6-16	Cross Sectional	TT Echocardiogram	• Abnormalities detected in 42% children • Most common abnormalities: LV diastolic dysfunction, LVH
Majonga et al, 2020[15]	Zimbabwe	197 PHIV	6-16	Longitudinal	TT Echocardiogram at baseline and 18 months later	• RV dilatation persisted at follow up in 92% of participants and LV dysfunction in 88% • 6% of Cardiac abnormalities present at baseline reverted to normal • Overall increase in mean z scores for LV, LA, RV and LV diameters
McCrary et al, 2020[16]	Kenya	643 PHIV	0-26	Cross sectional	TT Echocardiogram Myocardial Performance Index	• PHIV with cardiac dysfunction were older, viremic with exposure to AZT and higher systemic inflammation • MPI was associated with serum inflammatory marker IL6.
VASCULAR DISEASE						
Abd-Elmoniem et al, 2014[33]	USA	35 HIV+ and 11 healthy controls	15-29	Cross Sectional	RCA vessel wall thickness measured by MRI	• Increase in vessel wall thickness in HIV+ • Epicardial fat not increased in HIV+ • Smoking and exposure to D4T associated with vessel thickness
Gleason et al, 2016[29]	Ethiopia	231 PHIV	6-17	Cross sectional	PWV , IMT and FMD	• Children on EFV and LPV/r has increased PWV and IMT compared to those on NVP
Hanna et al, 2016[30]	USA	5 cohorts from NHLBI HIV-CVD Collaborative 58 HIV+ and 221 HIV− controls in pediatric study	6-29	Cross sectional	IMT	• Higher IMT in HIV+ than HIV− in 6-29 age group • Increase in IMT in HIV+ compared to HIV-was strengthened when limited to PHIV

Author and Year	Country	Population	Age Range (years)	Design	Parameters used	Findings
Eckard et al, 2017[28]	USA	101 HIV and 86 healthy controls	8-25	Cross sectional	PWV and IMT	• No difference in PWV between the groups
Dirajlal-Fargo et al, 2020[31]	Uganda	101 PHIV and 96 HIV−	10-18	Cross sectional	IMT and PWV	• Higher IMT in PHIV • IMT independently associated with marker of intestinal permeability in PHIV
Majonga et al, 2020[32]	Zimbabwe	117 PHIV and 75 HIV−	6-16	Cross sectional	IMT	• No difference in IMT between groups
ENDOTHELIAL DYSFUNCTION						
Dirajlal-Fargo et al, 2017[39]	USA	71 HIV+ and 48 HIV-controls	8-30	Cross Sectional	EndoPAT	• Endothelial dysfunction in PHIV compared to behaviorally infected group and control group
Mahtab et al, 2020[38]	South Africa	431 PHIV and 93 HIV− youth			EndoPAT	• PHIV had higher rates of endothelial dysfunction • PI use associated with endothelial dysfunction

Abbreviations: D4t: stavudine; EFV: efavirenz, FMD: Flow mediated dilation; HEU: HIV-exposed uninfected; IMT: intima media thickness; LA: left atrium; LPV/r: ritonavir boosted lopinavir; LV: left ventricle; LVH: left ventricular hypertrophy; MRI: magnetic resonance imaging; MPI: myocardial performance index; NVP: nevirapine; PHIV: perinatally acquired HIV; PI: protease inhibitors; PWV: pulse wave velocity; RA: right atrium; RCA: right coronary artery; RV: right ventricle; TT : transthoracic

Table 2:

Body Composition studies in pediatric and young adults in the setting of newer ART

Author and Year	Country	Population	Age Range (years)	Design	Parameters used	Findings
INTEGRASE INHIBITORS						
Dirajlal-Fargo et al, 2020[59]	USA	51 HIV+	0-24	Retrospective study of children Pre and post INSTI-initiation	BMI	• Higher rates of BMI-for-age z score increase after EVG and DTG initiation compared to pre-INSTI.
Taramasso et al, 2020[95]	Italy	66 HIV+	18-26	Retrospective case-control study, switch to INSTI vs non-INSTI switch	BMI	• PHIV switched to INSTI-based regimen did not experience an excessive weight gain compared to those who did not switch to INSTI
Thivalapill et al, 2020[96]	Eswatini	605 PHIV	12-19	Retrospective observational cohort pre and post DTG	BMI	• adolescents receiving TDF/3TC/DTG had a BMI greater than those receiving ABC/3TC/DTG • After switching to DTG, odds of becoming overweight or obese increased by 1% everyday
Giacomet et al, 2021[60]	Italy	13 HIV+	12-19	Switch from a PI- or NNRTI-based regimens to ABC/3TC/DTG-longitudinal	BMI and DXA	• BMI, triponderal and total % body fat did not change post DTG. • Trunk fat and trunk/body fat ratio increased after 12 months post switch.
Turkova, 2021[61]	Multi-center ODYSSEY trial (Europe, Asia and sub-Saharan Africa)	707 PHIV	3-18	Randomized non-inferiority trial evaluated DTG +2NRTIs vs standard of care (NNRTI or PI-based ART)	BMI	• Slight but significant increase in BMI compared to standard of care.
Yeoh, et al 2021[97]	Australia	8 HIV	13-15	Retrospective cohort study of children switched to a regimen containing DTG	BMI	• Increase in BMI z score 12 months post switch with stabilization in subsequent months
TENOFOVIR ALAFENAMIDE						
Yeoh, et al 2021[97]	Australia	9 HIV	9-14	Retrospective cohort study of children switched to a regimen containing TAF	BMI	• Increase in BMI z score 12 months post switch with stabilization in subsequent months

Abbreviations: 3TC: lamivudine; ABC: abacavir; BMI: body mass index; DTG: dolutegravir; DXA: dual energy x-ray absorptiometry; EVG:elvitegravir; INSTI: Integrase strand transfer inhibitor; NRTI: nucleotide reverse transcriptase inhibitor; NNRTI:non-nucleoside reverse transcriptase inhibitors; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate