

## Review article

# The effect of perinatal HIV and antiretroviral therapy on vascular structure and function in young people: A systematic review and meta-analysis

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## ABSTRACT

**Background and aims:** Perinatal HIV infection (PHIV) and prolonged use of antiretroviral therapy (ART) may increase the likelihood of developing subclinical vascular dysfunction at an early age. We conducted a systematic review to assess the effect of PHIV and ART on intima-media thickness (IMT), arterial stiffness and endothelial function in individuals aged 6–25 years.

**Methods:** Medline, Embase and Web of Science were searched, and studies screened by two independent reviewers. We performed a meta-analysis on selected studies reporting on IMT.

**Results:** A total of 680 studies were retrieved from the databases, with 21 studies deemed eligible for qualitative analysis. There were few studies assessing IMT, arterial stiffness and endothelial function. More than half of the studies found either increased IMT, stiffer arteries or impaired endothelial function in PHIV compared to uninfected controls. A minority of the studies reported that the two groups had similar vascular parameters, a conflicting finding. There was a lack of standardisation for IMT assessment and reporting in numerous studies. In a meta-analysis of seven studies with matching methodologies, IMT was higher in PHIV compared to uninfected controls, (mean difference, 0.05 (0.01–0.09;  $p = 0.01$ ) but heterogeneity between the studies was substantial ( $I^2$ , 96.7%;  $p < 0.001$ ).

**Conclusions:** PHIV may affect vascular structure and function. Existing studies are generally small, often contradictory, and predominantly cross-sectional in design. Further studies are required to understand vascular health in PHIV to identify cardiovascular disease risk and improve interventional strategies aimed at prevention and treatment of early vascular changes in this population.

## 1. Introduction

Antiretroviral therapy (ART) has greatly improved survival of individuals with HIV, including children and adolescents with perinatally-acquired HIV (PHIV), most of whom are surviving to adulthood. As a result, the paradigm of HIV morbidity and mortality has shifted to long-term comorbidities associated with HIV infection and its treatment [1]. Exposure to HIV during the perinatal or early childhood period, a critical time of development and growth, may predispose to life trajectories of ill-health such as cardiovascular disease. Longstanding HIV infection and prolonged use of ART may accelerate subclinical vascular damage and the process of atherogenesis [2]. Atherosclerosis is a chronic arterial wall disease with a long asymptomatic (i.e., subclinical) phase and is a

trigger of many cardiovascular events including myocardial infarction and stroke [3,4].

Although young people rarely experience cardiovascular events, adverse processes leading to vascular alterations reportedly begin in early childhood and typically manifest in later adulthood [5,6]. HIV-associated endothelial dysfunction occurs through disruption of several mechanisms that maintain vascular homeostasis [7,8]. In addition, long-term use of certain ART classes, for example, protease inhibitor (PI)-based regimens are reportedly associated with endothelial dysfunction due to considerable dyslipidaemia [9].

Vascular health indicators including intima media thickness (IMT), arterial stiffness and endothelial function are established surrogate markers for extent, severity, and progression of vascular damage and

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can be assessed non-invasively using different methods [10–12]. Endothelial dysfunction is an important early stage of atherogenesis and generally contributes to the progression and clinical manifestation of atherosclerosis [13]. Impaired endothelial function precedes structural atherosclerotic changes and can predict overt CVD. Arterial stiffness is an independent predictor of CVD events and is closely linked to hypertension, coronary artery disease, stroke, and heart failure [14,15]. Increased arterial stiffness is an indicator of organ damage, and cardiovascular risk factors may contribute to accelerations in this adverse vascular remodelling. Thus, adequate awareness of individual risk profile is important for adoption of preventive strategies [16]. While assessment of the endothelium and arterial stiffness are an indication of functional health of the vascular system, structural characteristics including intima-media thickness (IMT) complement the overall assessment of CVD risk [17]. Carotid IMT is considered a marker for early atherosclerotic changes within the arterial wall, and therefore often serves as a surrogate endpoint in clinical trials [18]. Together, these surrogate vascular markers could be used for screening for early signs of vascular disease in PHIV which may enable risk stratification and early intervention to mitigate future cardiovascular events and complications. The main objective of this study was to systematically review studies that have assessed vascular structure and/or function (IMT, arterial stiffness and endothelial function) in people aged 6–25 years with PHIV who were taking ART or were ART-naïve to identify gaps in knowledge and inform the direction of future research.

## 2. Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

### 2.1. Search strategy

Searches were made in MEDLINE, EMBASE and WEB of SCIENCES databases for studies reporting on the effect of PHIV and ART on IMT or arterial stiffness or endothelial dysfunction in young people. The search strategy was adapted for each database and included the following key terms: “human immunodeficiency virus” “HIV” or “antiretroviral viral therapy” or “ART” and “intima medial thickness” or “IMT” or “arterial stiffness” or “vascular stiffness” or “endothelial dysfunction” or “endothelial function” and “child” or “children” or “adolescent” or “young people” or “youth”. Appropriate Boolean operators and truncation were used on synonyms. Bibliographic references of key papers retrieved and included in the systematic review were searched manually. We included all studies from inception to March 2022.

### 2.2. Study selection criteria

The following eligibility criteria was used:

- ages 6–25 years
- perinatally-acquired HIV infection
- studies evaluating the effect of HIV and/or ART on IMT or arterial stiffness or endothelial function in young people with PHIV.
- outcome variables of the vascular measures reported as mean  $\pm$  standard deviation (SD) or median (interquartile range (IQR))
- observational studies (prospective cohort, cross sectional, or case-control designs)
- articles published in English.

Studies were excluded for the following reasons:

- duplicate publications
- including older age groups without younger age sub-groups

- having a heterogenous HIV group including both PHIV and other methods of transmission without disaggregation of data by methods of HIV transmission.

### 2.3. Data collection and statistical analysis

Two reviewers (EDM and STC) independently screened and extracted data from the studies. Detailed characteristics of the studies including design and study population were extracted using a tailored data extraction form. Any resulting disagreement was resolved by consensus. Continuous measures for IMT, arterial stiffness and endothelial function were extracted as main outcomes from the studies. These continuous measures were presented as mean (standard deviation), median (interquartile range) or median (ranges). A meta-analysis of mean differences and corresponding 95% confidence intervals was performed comparing IMT in PHIV and uninfected controls. For studies which reported IMT median (IQR), an appropriate mean (SD) was estimated using published formulas and a calculator by Shi et al. and Luo et al. [20–23] The mean differences were pooled using a random effects model to account for between-study heterogeneity in the overall effect estimate. Heterogeneity between studies was assessed using the  $I^2$  statistic. The potential for publication bias was evaluated by visual inspection of the funnel plot, Begg’s and Egger’s tests and finally using non-parametric trim and fill method to adjust analysis for the effect of publication bias [24]. A  $p$ -value  $\leq 0.05$  was considered as statistically significant. Quality of the studies was assessed using Institute of the National Heart, Lung, and Blood institute (NHLBI) Quality Assessment Tool [25].

## 3. Results

A total of 683 studies were retrieved from the databases and manually from references, with 21 studies ultimately deemed eligible for qualitative analysis (Fig. 1). The global distribution of the studies was as follows: SSA ( $n = 5$ ); Europe ( $n = 9$ ); America ( $n = 4$ ) and Asia ( $n = 3$ ). All studies were cross-sectional. The sample sizes were relatively small and varied from 24 to 431 participants. The mean (standard deviation) age for PHIV group was 13.7 (3.1) years, range (8.4–20) years and for the uninfected controls, 13.1 (5.2) years, range (2.6–25) years. Study findings were typically reported by HIV status while five studies disaggregated their results by ART exposure (Table 1 and Table 2) [26–29].

### 3.1. Intima media thickness

IMT was the most studied surrogate vascular marker in 13 studies. Measurements were performed at different anatomic sites, but mainly bilateral common carotid artery (CCA). Two studies included the internal carotid artery (ICA) [46,45], and a further two studies reported measurements of right CCA only [37,44]. Bonnet et al. did not specify the measured side of the CCA [29]. Eight studies reported a significantly increased IMT in individuals with PHIV compared to uninfected controls [28,35–37,41,42,44,45]. Four studies reported contrasting findings of similar IMT between PHIV and uninfected controls [29,46,33,40]. One study did not have a comparator group and reported that more than two-thirds of children with PHIV had abnormal IMT [32]. We conducted a meta-analysis comparing IMT between PHIV and uninfected controls using studies assessing carotid IMT on the far walls as recommended in official guidelines [47]. In the seven studies containing data suitable for meta-analysis, IMT was higher in PHIV compared to uninfected controls, (mean difference, 0.05 mm (95% CI, 0.01–0.09;  $p = 0.01$ ) (Fig. 2). Heterogeneity between the studies was substantial ( $I^2$ , 96.7%;  $p < 0.001$ ). There was no evidence of publication bias using both Begg’s test ( $p = 0.368$ ) and Egger’s test ( $p = 0.230$ ). However, visual inspection of the funnel plot showed asymmetry but the overall effect size following adjustment for the effect of publication bias remained unchanged (mean

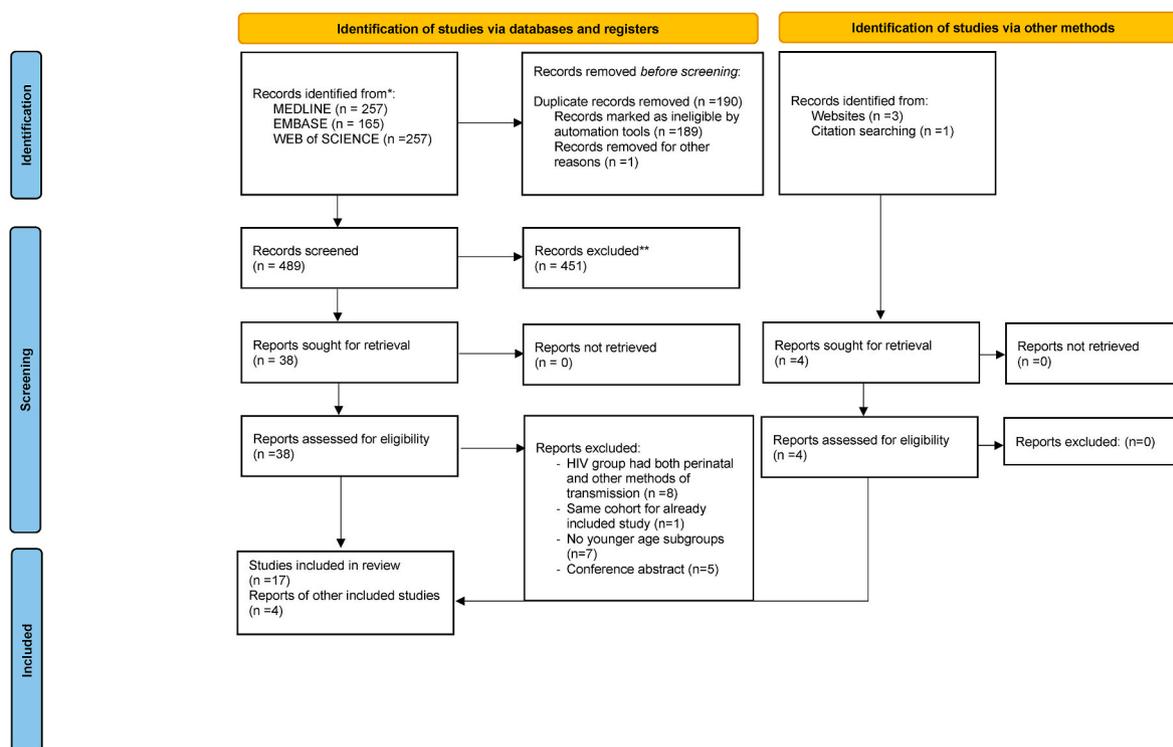


Fig. 1. PRISMA flow diagram for studies included.

difference, 0.05 (95% CI, 0.02–0.09) (Supplementary Figure 1).

Results comparing ART regimens were contradictory. Idris et al., reported that ART-naïve participants had increased IMT compared to both ART-exposed and uninfected controls while participants who were ART-exposed had similar IMT to uninfected controls [26]. Another study found that participants treated with a PI-regimen had thicker IMT compared to non-PI and ART-naïve counterparts [28]. Gleason et al., found similar IMT between groups of different ART regimens including PI and those who were ART-naïve [27].

### 3.2. Arterial stiffness

Arterial stiffness was assessed through pulse wave velocity (PWV) by six studies [27,36,38,43,30,31]. Higher PWV in PHIV compared to uninfected controls was reported in two studies suggesting stiffer arteries [38,43]. However, Dirajlal-Fargo et al. and Mellin et al., found no difference in arterial stiffness between PHIV group and uninfected controls [36,30]. One study did not have a comparator group and found that a fifth of children with PHIV had abnormal PWV [31]. According to Gleason et al., participants who were taking efavirenz and ritonavir-boosted lopinavir (LPV/r) had stiffer arteries (higher PWV) compared to those receiving nevirapine. PWV was also higher for LPV/r group compared to those who were ART-naïve [27]. Charakida et al., found higher PWV in those treated with ART compared to those who were ART-naïve and no differences were observed between those who were taking PI and non-PI regimens [43].

### 3.3. Endothelial function

A total of six studies investigated endothelial function by measuring either reactive hyperaemic index (RHI) in two studies or flow-mediated dilation (FMD) of the brachial artery in 4 studies [27–29,32,34,39]. Overall, four studies consistently reported impaired endothelial function (either lower RHI or FMD) in PHIV group compared to uninfected controls [28,29,34,39]. Castaldi et al., reported that 45% of children with PHIV had abnormal FMD [32]. ART-treated participants had

similar endothelial function to those ART-naïve as reported by two studies [27,29]. However, Gleason et al. found no difference in endothelial function among different ART regimens compared to non-treated HIV [27].

## 4. Discussion

This review summarises the available evidence on vascular structure and function in young people with PHIV. We found inconsistent reports from the studies, mainly with regards to effect of PHIV on IMT and arterial stiffness. A significantly thicker IMT and increased arterial stiffness in PHIV compared to uninfected controls was reported by some, while fewer studies found similar IMT or arterial stiffness between the groups. Data on endothelial function was limited and consisted of FMD and RHI, which are non-interchangeable techniques.

### 4.1. Effect of PHIV on vascular structure and function

There was non-standardisation of measurement sites for IMT, with some studies reporting an average of bilateral measurements of CCA while others reported for one side only, mainly right CCA which may have contributed to the conflicting results [26,35–37,44,33]. IMT ultrasound, the main technique used by studies in this review is highly operator-dependent and the different populations studied may further explain the varying results. The meta-analysis findings suggest a difference in IMT between PHIV and uninfected controls. However, these results need to be interpreted with caution due to the substantial heterogeneity between the studies. We also cannot rule out the possibility that the wall thickening observed in other studies may have been non-atherosclerotic compensatory remodelling as an adaptive response to blood flow and intraluminal pressure, which have been shown to associate with mild increases in IMT [48–50]. In a recent study from members of our group, increases in IMT among healthy young people were found to predominantly relate to increased blood pressure secondary to lean tissue mass i.e. as young people grow, their arteries and wall thickness increases accordingly, further supporting the

**Table 1**  
Study Characteristics for vascular markers by HIV status.

Author	Year	Design	Country	Sample size		Age (y)		Sex distribution (%)		ART (%)	Marker (assessment method)	Site measured	Measurement		Main findings	Study quality
				HIV+	HIV-	HIV+	HIV-	HIV+ Female (Males)	HIV- Female (Males)				HIV+	HIV-		
Mellin [30]	2022	CS	UK	213	65	18 (16–20)	18 (16–21)	60 (40)	69 (31)	100	PWV (Vicorder)	Carotid-femoral artery	6.15 (0.83)	5.93 (0.70)	PWV was similar between the groups	Good
Dobe [31]	2021	CS	Mozambique	77		10 (8.6–12)		45 (55)		100	PWV (Vicorder)	Aorto-femoral artery	−0.1 (−1.5 to −2.4) <sup>a</sup>		22% had abnormal PWV	Fair
Castaldi [32]	2021	CS	Italy	52		20.9 (5.7)		50 (50)		100	IMT (Far wall) FMD	Bilateral CCA Brachial artery	0.54 (0.12) 9.4 (4.7)		73% had higher cIMT; 45% had abnormal FMD	Fair
Majonga [33]	2020	CS	Zimbabwe	117	75	11.9 (2.6)	10.7 (2.4)	47 (53)	45 (55)	100	IMT (Far wall)	Bilateral CCA	0.40 (0.05)	0.40 (0.04)	IMT was similar between HIV+ & HIV- groups	Good
Mahtab [34]	2020	CS	South Africa	431	93	14.1 (12.8–15.5)	13.9 (12.1–15.3)	49 (51)	57 (43)	100	RHI (EndoPAT device)	Both hands	1.36 (1.09, 1.70)	1.52 (1.23, 1.92)	HIV + group had endothelial dysfunction (lower RHI) compared to HIV- group	Good
Marsico [35]	2019	CS	Italy	29	29	13 (9–18)	13.6 (9.9–19)	55 (45)	55 (45)	100	IMT (wall not specified)	Bilateral CCA	0.77 (0.15)	0.51 (0.11)	IMT was thicker in HIV + group compared to HIV- group	Fair
Dirajlal- Fargo [36]	2019	CS	Uganda	101	96	12.9 (11.5–14.7)	12.7 (11.1–14.3)	53 (47)	52 (48)	100	IMT (Far wall) PWV (Vicorder)	Bilateral CCA Carotid-femoral artery	IMT 1.05 NR	1.02 NR	IMT was thicker in HIV + group compared to HIV- group; Arterial stiffness (PWV) was similar between groups	Good
De Lima [37]	2018	CS	Brazil	65	65	12.2 (2.1)	12.1 (1.8)	54 (46)	54 (46)	83.1	IMT (Far wall)	Right CCA	0.526 (0.1)	0.490 (0.0)	IMT was thicker in HIV + group compared to HIV- group	Good
Kuilder [38]	2017	CS	Indonesia	51	52	8.4 (3.0)	8.9 (2.7)	49 (51)	56 (44)	100	PWV (Oscillometric arteriography system)	Aorta	6.28 (1.13)	6.13 (0.67)	Increased arterial stiffness (higher PWV) in HIV + group compared to HIV- group.	Fair
Dirajlal- Fargo [39]	2017	CS	USA	18	48	18 (12–21) <sup>b</sup>	22 (29–26)	67 (33)	34 (66)	100	RHI (Peripheral arterial tonometry)	Both hands	1.34 (1.20, 1.42) <sup>b</sup>	1.52 (1.27, 1.80)	HIV + group had endothelial dysfunction (lower RHI) compared to HIV- group	Fair
Sainz [40]	2014	CS	Spain	64	30	14.2 (4.9)	14.1 (5.5)	68 (32)	54 (46)	100	IMT (Far wall)	Bilateral CCA	0.433 (0.02)	0.427 (0.02)	IMT was similar between HIV+ & HIV- groups	Fair
Chanthong <sup>58</sup>	2014	CS	Thailand	100	50	15.5 (12–20.4)‡	16.1 (12.1–19.4)	44 (56)	52 (48)	100	IMT (Near and Far wall)	Bilateral CCA & ICA (far and near wall)	CCA 0.373 (0.284–0.451)‡ ICA 0.350 (0.260–0.513)	0.371 (0.324–0.446)‡ 0.355 (0.302–0.452)	IMT was similar between HIV+ & HIV- groups	Good
Di Biagio [41]	2013	CS	Italy	40	27	16.3 (4.7)	17.7 (4.6)	52 (48)	41 (59)	97.5	IMT (Far wall)	Bilateral CCA	0.450 (0.088)	0.407 (0.079)	IMT was thicker in HIV + group compared to HIV- group	Fair
Vigano [42]	2010	CS	Italy	23	19	20 (2)	20 (1)	48 (52)	47 (53)	100	IMT (Far wall)	Bilateral CCA	0.50 (0.1)	0.40 (0.1)	IMT was thicker in HIV + group compared to HIV- group	Fair

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Table 1 (continued)

Author	Year	Design	Country	Sample size		Age (y)		Sex distribution (%)		ART (%)	Marker (assessment method)	Site measured	Measurement		Main findings	Study quality
				HIV+	HIV-	HIV+	HIV-	HIV+ Female (Males)	HIV- Female (Males)				HIV+	HIV-		
Charakida [43]	2009	CS	UK	83	59	11 (3.1)	12 (2.8)	43 (57)	53 (47)	58	PWV (SphygmoCor system)	Radial and carotid artery	7.5 (1.3)	7.0 (1.1)	Increased arterial stiffness (higher PWV) in HIV + group compared to HIV- group	Good
Giuliano [44]	2008	CC	Brazil	83	83	10.8 (2.6)	10.7 (2.9)	53 (47)	47 (53)	88	IMT (Far wall)	Right CCA	0.48 (0.455–0.518)	0.426 (0.415–0.453)	IMT was thicker in HIV + group compared to HIV- group	Fair
Mcomsey [45]	2007	CS	USA	31	31	9 (2–20) ‡	9 (2–20)	65 (35)	68 (32)	96.7	IMT (Near and Far wall)	Bilateral CCA & ICA	R-ICA: 0.45 (0.30–0.70) R-CCA: 0.50 (0.40–0.65) L-ICA: 0.50 (0.30–0.73) L-CCA: 0.50 (0.40–0.70)	R-ICA: 0.40 (0.25–0.55) R-CCA: 0.45 (0.25–0.60) L-ICA: 0.43 (0.23–0.55) L-CCA: 0.48 (0.25–0.65)	IMT was thicker in HIV + group compared to HIV- group	Good
Charakida [28]	2005	CS	UK	83	59	11 (3.1)	12 (2.8)	43 (57)	53 (47)	67	IMT (Far wall) FMD	Bilateral CCA Brachial artery	IMT: 0.6 (0.07) FMD: 7.9 (4.9)	IMT: 0.47 (0.06) FMD: 9.4 (5.8)	IMT was thicker in HIV + group compared to HIV- group; HIV + group had endothelial dysfunction (lower FMD) compared to HIV- group	Good
Bonnet [29]	2004	CS	France	49	24	13.5 (3.5–19) ‡	12 (5–17)	47 (53)	46 (54)	69	IMT (Far wall) FMD	Right CCA Brachial artery	IMT: 0.47 (0.008)* FMD: 5.3 (0.3)	IMT: 0.49 (0.002)* FMD: 6.9 (0.4)	IMT was similar between HIV+ & HIV- groups; HIV + group had endothelial dysfunction (lower FMD) compared to HIV- group	Good

CS, cross-sectional study; CC, case-control; HIV+, HIV-infected; HIV-, HIV-uninfected; IMT, intima-media thickness; PWV, pulse wave velocity; FMD, flow mediated dilation; RHI, reactive hyperaemic index; R, right; L, left; CCA, common carotid artery; ICA, internal carotid artery; NR, not reported; NVP, nevirapine; EFV, efavirenz; LPV/r, Lopinavir/ritonavir; PI, protease inhibitor; USA, United States of America; UK, United Kingdom. Measures reported as mean (standard deviation) or median (interquartile range) unless stated. Units of measurements are as follows, IMT (mm); PWV (m/s) and FMD (%), unless stated.

<sup>a</sup> Reported values are z-scores.

<sup>b</sup> Reported measures for HIV group are only for those perinatally-infected with HIV, median (interquartile range). ‡ Median (range) is reported. \*IMT reported as mean (Standard error).

**Table 2**  
Vascular markers by ART exposure.

Author	Year	Design	Country	Sample size		Age (years)		Marker	Site measured	Measurements‡		Main findings	Study quality
				ART	No-ART	ART	No-ART			ART	No-ART		
Idris [26]	2016	CS	Indonesia	58	56	5.7 (0.6–12.2)	4 (0.4–11.5)	IMT (Far wall)	Right CCA	0.397 (0.07)	0.449 (0.07)	No-ART group had thicker cIMT than ART group and HIV- group; ART group had similar cIMT with HIV- group	Good
Gleason [27]	2016	CS	Ethiopia	186	45	<b>NVP</b> 11 (9–14) <b>EFV</b> 13 (10–15) <b>LPV/r</b> 13 (11–15)	11 (9–14)	IMT (Near and Far wall) FMD PWV (SphygmoCor System)	Bilateral CCA Brachial artery Site unspecified	<b>NVP</b> IMT 0.45 (0.42–0.50) FMD 8.3 (4.5–12.4) PWV 4.5 (4.2–5.2) <b>EFV</b> IMT 0.45 (0.43–0.48) FMD 6.4 (4.1–10) PWV 4.7 (4.3–5.3) <b>LPV/r</b> IMT 0.47 (0.45–0.50) FMD 9.6 (5.0–12.2) PWV 5.2 (4.6–5.9)	IMT 0.45 (0.42–0.47) FMD 8.6 (5.4–13.6) PWV 4.6 (4.1–5.0)	Increased arterial stiffness (higher PWV) for EFV and LPV/r groups; Increased arterial stiffness (higher PWV) for LPV/r compared to no- ART group; Endothelial function (FMD) and IMT were similar across all treatment groups and No-ART group	Good
Charakida [43]	2009	CS	UK	48	35	11.3 (3.2)	10.3 (2.5)	PWV (SphygmoCor system)	Brachial artery	7.8 (1.5)	7.2 (0.9)	Increased arterial stiffness (higher PWV) in ART group compared to No-ART group; Similar PWV for PI vs non-PI.	Good
Bonnet [29]	2004	CS	France	34	15	13.5 (6–18)‡	10.5 (3.5–19.5) ‡	IMT (far wall) FMD	Right CCA Brachial artery	IMT 0.7 (0.009) FMD 5.3 (0.4)	0.47 (0.016) 5.2 (0.5)	Endothelial function (FMD) and IMT were similar between ART and No-ART groups.	Good
Charakida [28]	2005	CS	UK	56	27	<b>PI</b> 11.1 (3.5) <b>Non-PI</b> 11.5 (3.0)	10.3 (2.5)	IMT (far wall) FMD	Bilateral CCA Brachial artery	IMT <b>PI</b> 0.62 (0.07) <b>Non-PI</b> 0.58 (0.06) FMD <b>PI</b> 6.3 (5.4) <b>Non-PI</b> 8.1 (5.9)	IMT 0.58 (0.06) FMD 9.9 (5.7)	IMT was thicker in PI-treated compared to both non-PI and No-ART groups. Endothelial dysfunction (lower FMD) in PI treated compared to both non-PI and No-ART groups	Good

CS, cross-sectional study; IMT, intima-media thickness (mm); PWV, pulse wave velocity (m/s); FMD, flow mediated dilation (%); R, right; L, left; CCA, common carotid artery; NVP, nevirapine; EFV, efavirenz; LPV/r, Lopinavir/ritonavir; PI, protease inhibitor; UK, United Kingdom.

‡ Measures reported as mean (standard deviation) or median (interquartile range) unless stated; † median (range) is reported for all measure.

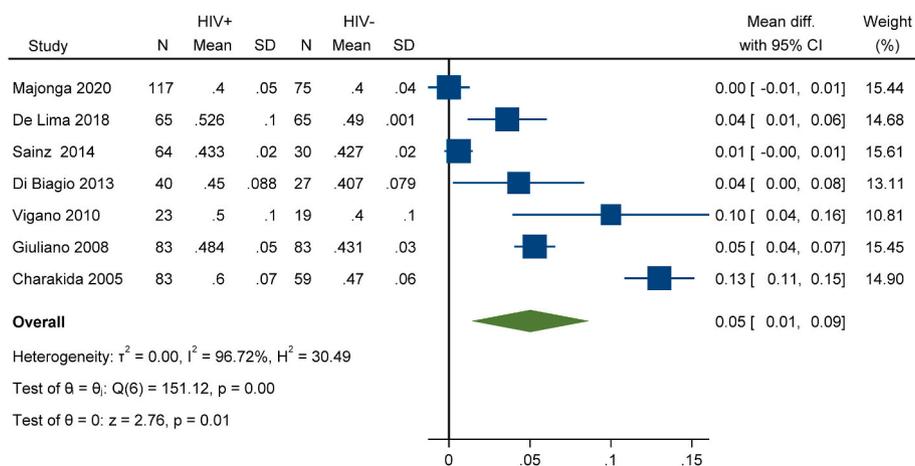


Fig. 2. Forest plot for IMT in children with PHIV and HIV-negative controls.

Forest plot showing IMT comparison between PHIV and uninfected groups. Mean difference between PHIV and uninfected controls was significant (0.05 mm; 95% CI, 0.02 to 0.09;  $p = 0.01$ ).

non-pathological thickening of the walls [49]. A noteworthy observation from the studies contained within the current meta-analysis, however, is the lack of difference in blood pressure observed between PHIV and uninfected controls. As such, increased IMT in the context of PHIV may indeed represent a pathological response to different underlying drivers. Therefore, assessment of IMT likely remains important as a graded marker of cardiovascular risk in this population. Interestingly, this same meta-analysis also demonstrates a progressive attenuation towards the null when comparing PHIV to controls in newer studies - the reasons for which are unclear. Advances in treatments, epidemiological transitions in populations being studied, and technological advancements in assessing IMT may all contribute in some way.

PWV is a simple, reproducible technique and a well-recognised surrogate marker for vascular stiffness. Increased pulse wave velocity is associated with increased systolic blood pressure, left ventricular afterload, and decreased myocardial perfusion which ultimately impairs cardiac function [51]. The European Society of Hypertension/Cardiology (ESH/ESC) recommends that PWV in addition to IMT be used to evaluate vascular stiffness in organ damage [52]. There is limited data on PWV in PHIV, and those studies which do exist were found to report often contradictory findings.

Endothelial function was impaired in PHIV compared to uninfected controls and this was consistently reported, albeit fewer studies investigated this. It is important to note that the studies in this review were cross-sectional in design with small sample sizes and thus, the reported findings may be biased and a reflection of the effect of chance. Future study designs should have large sample sizes to allow more accurate mean values and precise estimates of effects.

#### 4.2. Effect of ART on vascular structure and function

Overall, the effect of ART on vascular structure and function was investigated by very few studies (five studies) and again yielded conflicting results [26–29,43]. The role of ART on vascular structure and function in PHIV therefore remains unclear. Furthermore, it is still debatable whether specific ART regimens have greater influence on vascular markers than others. While Gleason et al. found that those taking EFV and LPV/r had stiffer arteries than those ART-naïve [27], Charakida et al. reported similar arterial stiffness regardless of taking PI or non-PI regimen, and thicker IMT in those receiving PI than non-PI regimen [28,43]. One of the well-known complications of ART is dyslipidaemia, characterised by increased levels of triglycerides and low-density lipoprotein cholesterol and a decrease of high density lipoprotein-cholesterol [53]. Deranged lipids profile increases atherogenesis and vascular damage, consequently increasing the risk of

cardiovascular disease [54]. Although there is evidence that some antiretroviral agents have metabolic side effects including dyslipidaemia which increases cardiovascular risk [55], it is also plausible that suppression of HIV viraemia with ART can slow down the progression of vascular damage - perhaps explaining why some vascular markers were similar between those who were receiving ART and uninfected controls [26,27,46,33,40]. There is evidence pointing to an association of PI-based regimens with vascular dysfunction as well as reports of improvements in vascular markers, particularly endothelial function following ART-initiation, regardless of ART-regimen [56]. Together, these findings underscore the need to investigate the effects of specific antiretroviral agents on vascular dysfunction in PHIV rather than attribution of class effect. Vascular alterations in PHIV may be associated with delayed ART-initiation, although this could not be reviewed in the study. Most of the studies did not report on time of HIV diagnosis and/or ART initiation.

#### 4.3. Potential limitations

Limitations of this review are lack of a robust meta-analysis of the different vascular measures as only a few studies were conducted for arterial stiffness and endothelial function assessment. Notably, different tools were used to assess for vascular function, and in some studies different regions were examined [38,30,31,34], which further hindered pooling of results in a meta-analysis. There was substantial heterogeneity of studies included in the meta-analysis. Finally, we only included studies written in English which may have resulted in language bias.

#### 4.4. Research priorities

Although there is evidence of premature subclinical vascular alterations in young people with PHIV, the long-term outcomes of these young people are unclear and somewhat speculative. There is dire need for longitudinal studies of large and well-phenotyped young people with PHIV using gold-standard non-invasive measures for comprehensive risk factor analysis. To date, FMD has been reliably used to examine vascular function and it rapidly changes following treatment. Therefore, FMD can be objectively used to assess the impact of antiretroviral drugs in a much shorter time (i.e., months) than would be required for IMT and other clinical endpoints [57]. In addition, IMT and PWV are more suited for long-term effects and provide complementary important data on cumulative vascular changes over time.

In conclusion, this review shows that despite decades of investigations on effect of HIV and ART on vascular health in young people, we still have a patchwork of small and conflicting studies. A

further systematic approach of vascular function studies is therefore warranted to understand vascular health in PHIV.

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### CRedit authorship contribution statement

**Edith D. Majonga:** Conceptualization, Methodology, Writing – original draft, preparation, Funding acquisition. **Rashida A. Ferrand:** Writing – review & editing. **John E. Deanfield:** Writing – review & editing. **Scott T. Chiesa:** Investigation, Validation, Writing – review & editing.

### Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2022.05.013>.

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