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Pulse Wave Velocity in Early-Treated Children living with Perinatal HIV infection is similar to Uninfected Children: a longitudinal study

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Abstract

Introduction: HIV is associated with accelerated cardiovascular disease, due to HIV-associated metabolic abnormalities, antiretroviral therapy (ART), and HIV itself. Carotid-femoral pulse wave velocity (PWV) is the non-invasive gold standard measurement of arterial stiffness, and associated with incident vascular events in adults. It is unclear if arterial stiffness is accelerated in children living with perinatal HIV (CHIV) who initiate ART early in life. We compared the longitudinal trajectory of PWV in CHIV to children unexposed to HIV. A secondary comparison compared HIV exposed uninfected children (CHEU) to unexposed children.

Methods: 465 children (141 CHIV, 160 CHEU, 164 unexposed) previously in the Children with HIV Early ART (CHER) and P1060 trials were followed annually at Tygerberg Children's

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Authors' Contributions

All authors meet criteria for authorship. CD, SI, FV, SB contributed to the conception and design. CD, FV and KO contributed to the statistical analysis. CD drafted the initial manuscript. SI, FV, KO, SB, MC provided substantive edits to the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

Hospital, South Africa between 2014 and 2020. CHIV initiated ART in infancy or early childhood, with excellent ART adherence and largely sustained viral suppression. The primary outcome was PWV, measured using the Vicorder system, and evaluated using linear mixed effects models.

Results: Median (IQR) age at first PWV measurement was 8.64 (7.7–9.1) years, and median follow-up time 2.9 (1.6–4.0) years. Adjusted analyses showed no significant mean difference in PWV in CHIV and CHEU compared to unexposed (CHIV:0.101 m/s, 95%CI −0.012 to 0.214; CHEU:0.068 m/s, 95%CI −0.047 to 0.183), after adjusting for gender, age, ethnicity, mean arterial pressure, resting average heart rate and family history of cardiovascular disease.

Conclusions: Early-treated CHIV with sustained viral suppression have similar PWV to unexposed children. Excellent adherence and early ART initiation may protect against cardiovascular disease.

Keywords

HIV; Children; antiretroviral therapy; ART; metabolic syndrome; pulse wave velocity; PWV; cardiovascular risk

Introduction

Children and adults with HIV are at substantial risk of cardiovascular events (1), driven by multiple factors including HIV-associated metabolic abnormalities (2), antiretroviral therapy (ART) exposure (3), and HIV infection itself (4,5). For children living with perinatal HIV (CHIV), early ART initiation irrespective of CD4 or clinical HIV disease is now standard-of-care globally. It is unclear to what extent cardiovascular disease in CHIV is avoided by early ART initiation.

Our cohort, with minimal HIV disease and preserved CD4 counts, represents the largest homogenous group of children starting ART soon after birth, having participated in the Children with HIV Early antiRetroviral (CHER) (6,7) or IMPAACT 1060 clinical trials (8). Longitudinal data from this unique cohort offers a rare window into the likely future of the world's early-treated children. Unlike their predecessors, early-treated CHIV have largely been spared cumulative organ damage from HIV and multiple infections. However, they still face many decades of cumulative ART exposure and HIV-associated immune activation (9).

Pulse wave velocity (PWV), specifically carotid-femoral PWV, is currently considered the non-invasive gold standard measurement of arterial stiffness (10). PWV is highly associated with the degree of atherosclerosis as reduced elasticity leads to faster propagation of the arterial pulse wave. PWV is a potent predictor of incident cardiovascular events in adults without known cardiovascular disease (11–13). Data from cross-sectional pediatric PWV in CHIV report both no difference and significant increase compared to controls (14–17). There are no known longitudinal, controlled studies examining PWV apart from one unpublished study without a control group (18).

We include two groups from the same local communities as the CHIVs: HIV unexposed children (the control group), and children HIV exposed but uninfected (CHEU) (through vertical transmission prevention programmes). CHEU also experience intermediate

morbidity (19) between CHIV and unexposed children, suggesting immune dysfunction early in life. This allows us to compare groups in a population with high background rates of obesity, cardiovascular disease and diabetes (20).

We compared PWV longitudinal trajectory in CHIV to unexposed children. A secondary comparison compared CHEU to unexposed children.

Methods

Setting and design

We followed children at the Family Centre for Research with Ubuntu (FAMCRU) (Stellenbosch University and Tygerberg Children's Hospital) from March 2014 to March 2020. The study was approved by Stellenbosch University's Health Research Ethics Committee (Federal Wide Assurance Number: 00001372; Institutional Review Board Number: IRB0005239; Project approval number N12/11/076). Ongoing approval included annual data and participant safety review.

Children were previously in the Children with HIV Early antiRetroviral (CHER) and IMPAACT 1060 clinical trials (6–8) along with CHEU and unexposed controls from the same communities. The CHER trial compared early time limited ART to deferred ART from 6–12 weeks of age. First-line ART was lopinavir-ritonavir, zidovudine and lamivudine. The IMPAACT P1060 trial compared nevirapine to lopinavir-ritonavir as a third antiretroviral with zidovudine and lamivudine in CHIV between 6 months and 3 years of age.

Children were scheduled for at least annual routine appointments (CHEU and unexposed); CHIV were seen 3-monthly for clinical care and had largely sustained viral suppression, preserved CD4 and minimal clinical HIV disease. Cardiometabolic metrics were measured annually, including PWV and Manual blood pressure, BP (average of 3 measurements after minimum 15 minute rest using a manual sphygmomanometer).

PWV measurements

PWV was measured using the Vicorder system (21), an automated and operator-independent device, allowing far greater reliability and repeatability than its counterparts for measuring PWV. A change in PWV indicates a change in aortic elasticity, a sensitive functional indicator of subclinical atherosclerosis (22). The function of the aorta is to receive the punch of pressure that exits the heart; to accommodate some of the pressure by stretching; and then to return that pressure slowly to the column of blood, thus converting quick turbulent flow into healthy (slower) laminar flow. When elasticity is lost as the aorta cannot efficiently absorb the impulse energy, excess energy is retained as velocity. Thus, PWV varies according to the stiffness of the arterial wall: the stiffer the arterial wall, the greater the pulse wave propagation velocity.

PWV measurements were performed following the manufacturer instructions. With children lying supine, one cuff was placed on the neck over the right common carotid artery and the other around the upper right thigh over the femoral artery. The cuffs were then inflated to the set value, and carotid and femoral pulse waves were recorded in cycles of 3.5 seconds.

The time delay between arrival of the pulse wave at the external carotid artery and then the femoral artery was automatically calculated. This transit time represents the time taken to travel a fixed length of the aorta and proximal femoral artery. The velocity of the pulse wave is calculated as distance (d) divided by transit time (t) (PWV = d/t). To accommodate the small inherent variation in transit time from respiration and movement, each child had at least 100 measurements per visit, with the median transit time (t) used to calculate PWV. During the measurement process, children typically fell asleep.

The distance travelled by the pulse wave was estimated by surface anatomy measurements using a non-stretchable tape measure. In growing children, the method of estimating distance must be very precise, as aorta length changes with growth. Currently there is no consensus on how to accurately determine the real path of the arterial tree in children. To date, only one anatomical study has provided guidance on which surface anatomy measurements most accurately represent the distance travelled by the intra-luminal pulse wave: Witbooi et. al. (23) measured true intra-arterial path lengths using multi-planar reformation imaging software for 3-dimensional reconstructions of 483 children scanned at different ages, and compared each to their own surface anatomy measurements using the same 3D reconstruction. They showed that the most accurate determination of distance travelled by the pulse wave is by taking the distance from the suprasternal notch (SSN) to the umbilicus, through the mid-inguinal crease to the femoral PWV recording site, and then subtracting an adjusted surface anatomy distance between the suprasternal notch and the angle of the mandible (PWV recording site in the neck), adjusted using the formula y=4.791+(1.0534*x). This translates into the following formula: (with all measurements in cm):

$$d = (SSN - umb) + (umb - il) + (il - fem) - \{[(SSN - car) * 10 * 1.0534) + 4.791]/10\}$$

where d: distance travelled by pulse wave; SSN: suprasternal notch; umb: umbilicus; il: inguinal ligament; fem: femoral cuff; car: carotid cuff

We used the above validated distance estimation method for our analysis. In addition, we conducted sensitivity analyses using formulae previously used to estimate distance travelled, specifically: {(SSN-umb) + (umb-fem) − (SSN-car)} (24,25) and {(car-fem) − (SSN-car)} (14).

Confounders and interactions

Confounders were selected using a conceptual causal inference approach, represented by a directed acyclic graph ([DAG], Supplementary Figure 1). Gender was included as the only *a priori* confounder; age, heart rate and mean arterial pressure were included as potential time-varying confounders; whilst ethnicity, family history of cardiovascular disease and diabetes were included as potential fixed confounders. Mean arterial pressure was calculated as mean diastolic blood pressure)*2/3 + mean systolic blood pressure*1/3 (26). Family history of cardiovascular disease and diabetes were represented as binary (yes/no) categorical variables. Ethnicity was divided into two categories – “Black” and “Cape Mixed”. The Cape Mixed ancestry group is a South African population group with Khoi, San, Malay,

European and African ancestry, unique to the Western Cape (27,28). Traditional risk factors of subclinical vascular disease such as obesity and blood lipids were excluded as are strongly influenced by HIV status in our resource-limited context (29,30), and may lie on the causal pathway (see DAG, Supplementary Figure 1). Likewise, height and Tanner stage were deemed to be on the causal pathway, based on multi-predictor analysis showing a significant effect of HIV group on both height and Tanner stage in our cohort. Interaction effects considered for inclusion were age by HIV group and gender by HIV group.

Inclusion and Exclusion criteria

All children previously enrolled in either the CHER or IMPAACT 1060 clinical trial at Tygerberg Children's Hospital and still in care were selected for inclusion. Information on cardiometabolic indicators was collected at routine annual clinic appointments. Due to resource limitations, loss to follow up and missed clinic appointments, this was not always possible, thus children had varying numbers of data and timepoints.

Statistical Analysis

We compared baseline characteristics between groups using the Chi-squared test for categorical variables and the F-test for normal quantitative variables. Age and cardiovascular measures at the first PWV measurement were compared. Descriptive analyses included a graph of the mean PWV by HIV group as a function of children's age.

In HIV group comparisons, the primary comparison was between CHIV and unexposed children, with significance declared at level α=0.05. The secondary comparison was between CHEU and unexposed children.

The primary outcome was PWV, modelled as a function of HIV status and age using linear mixed effects models with child-specific random effects. Single-predictor analysis explored the association between PWV and each variable of interest using a linear mixed model with random intercepts for each variable. Multi-predictor analysis was conducted as detailed below.

We chose to evaluate random slope with age given the strong association between age and PWV (24,31). We considered two random effects structures: random intercept only and random intercept and random age slope, and chose the model with minimum Akaike information criterion (AIC) from a restricted maximum likelihood (REML) fit (32). The mean model included the HIV group (3 levels), gender, and age, as variables of interest; interaction effects were included if significant at 0.05 level. Potential confounders were included if significant at 0.20 level using the likelihood ratio test (LRT) in backward stepwise model selection. Confounders varying with time included age, heart rate and mean arterial pressure. We also fitted the polynomials age-squared and age-cubed as part of the mean model. These variables were tested for significance using the LRT, and were removed if not significant at 0.05 level. The final model was re-fitted using REML.

Statistical analysis was performed using RStudio (33). Since ethnicity and history of cardiovascular disease differed across HIV groups, in sensitivity analyses we checked if inclusion changed the coefficient of interest by >10%.

Results

Characteristics of children

Of 485 children, 20 (4%) were excluded because of no PWV measurements over the follow-up period. Therefore, 465 children (141 CHIV, 160 CHEU, and 164 unexposed) with median age 8.64 years at enrolment and 50% female, were analysed. Children had recorded PWV measurements between the ages of 6.3 years and 15.6 years old. There were 1634 PWV measurements over the study period, with a median of 3 (IQR 2, 5) measurements per child (CHIV: 5; CHEU and unexposed children: 3). The median (IQR) follow-up time was 4.9 (IQR 3.9, 5.9) years among CHIV; 2.0 (1.0, 2.9) years among CHEU; and 2.9 (1.3, 3.0) years among unexposed children.

At baseline (Table 1), CHIV on average had their first PWV measurement at a younger age than CHEU and unexposed children. PWV showed a statistically significant difference between groups at baseline ($p=0.014$), possibly owing to differences in age. Likewise, mean arterial pressure showed a statistically significant difference between groups at baseline ($p<0.001$), again potentially owing to differences in age. Unexposed children had more prevalent family history of cardiovascular disease than CHIV ($p=0.031$). The proportion of Cape Mixed ethnicity vs Black children differed across the 3 groups ($p<0.001$). Supplementary Figure 2 shows the proportion of CHIV with viral suppression over time (mean 92% children virally suppressed).

Single-predictor analysis

The unadjusted progression of PWV by age is shown in Supplementary figure 3. In single-predictor analysis (Table 2), neither CHIV nor CHEU showed a significant association with PWV (CHIV: 0.020, 95% CI −0.078 to 0.118 and CHEU: 0.071, 95% CI −0.028 to 0.171). Age, resting average heart rate and mean arterial pressure showed a significant association with PWV.

Multi-predictor analysis

The mixed effects model (Table 2) showed no significant difference between CHIV and unexposed children (0.101, 95% CI −0.012 to 0.214, $p = 0.080$), after adjusting for gender, age, age squared, ethnicity, resting average heart rate, family history of cardiovascular disease and mean arterial pressure. Likewise, no significant difference was found between CHEU and unexposed children (0.068, 95% CI −0.047 to 0.183, $p = 0.244$). Both age and age squared were significant, indicating a curved relationship between PWV and age (Figure 1), after adjusting for all other variables. The best fitting correlation structure was random intercept only. Ethnicity and family history of cardiovascular disease changed the coefficient of interest by >10%, and were included in the model. Sensitivity analyses using alternative methods for calculating distance produced similar results.

Discussion

Statement of principal findings

After adjusting for gender, age, age squared, ethnicity, resting average heart rate, family history of cardiovascular disease and mean arterial pressure, there was no significant difference in PWV between groups regardless of HIV exposure. However, as the CHIV confidence interval is wide, we cannot exclude a small but clinically significant difference in PWV between groups.

Public Health Relevance

Prior to 2007, WHO guidelines recommended delaying ART initiation in infants with perinatally-acquired HIV until necessitated by advancing HIV disease. The CHER trial changed this treatment approach (6,7), and since 2008/2009 all ART programs globally recommend immediate ART for infants with perinatally-acquired HIV, irrespective of immunological or clinical evidence of HIV disease. Previous generations of CHIV had extensive organ damage from opportunistic infections, with their outcomes distorted by survivor bias. The current CHIV generation entering puberty were spared the organ damage from repeated infections, but have accumulated extensive ART exposures. Being the oldest homogenous group of early-treated African CHIV, our cohort provides a unique window onto the future of the current African generation of early-treated CHIV.

Comparison with other studies

Our results are in line with cross-sectional studies showing no difference in arterial stiffness measured by PWV in CHIV vs. controls (14–16,34). Charakida et al. (17) found a significant cross-sectional difference in PWV between 83 CHIVs (mean age 11 years) and 59 healthy controls ($p<0.05$); however, in contrast to our CHIV cohort 35 (42%) of CHIVs were not receiving ART, and 20 on ART (42%) had severe HIV disease (CDC Stage C) (median duration of ART 4.9 years), implying more opportunistic infections and HIV exposure than our cohort.

As part of longitudinal follow-up in the CHAPAS-3 antiretroviral strategy trial in Uganda and Zambia (34), PWV in ART-experienced children increased over the 96 week period ($p<0.001$) (single-predictor analysis), an increase not fully explained by the increasing age. However, compared to the CHAPAS-3 trial, our period of follow-up was significantly longer (4.9 years vs. 2 years), and our cohort started ART substantially earlier in childhood with a high proportion of viral suppression over time, thereby avoiding early-life immune damage, and potentially less chronic inflammation and persistent immune activation.

We measured neither carotid intimal medial thickness (cIMT) nor flow mediated dilation, alternative measures of premature atherosclerosis and cardiovascular disease (CVD). Indeed, several studies have shown increased cIMT in CHIV than controls (35–38). However, many of those early studies were in CHIV who initiated ART later on in childhood (35–38), and low CD4 nadir is related to increased cIMT (37). In contrast and in line with our findings, two longitudinal studies showed an improvement in cIMT over time in CHIV (34,39) related to duration on ART (40), suggesting that immune restoration and viral suppression may

protect against CVD. Similarly, a more recent cross-sectional study in Zimbabwe showed that CHIV on ART from an early age have similar cIMT to uninfected children (41).

Strengths and limitations of the study

Strengths of our study include the prospective design and longitudinal nature, the regular follow-up of early-treated CHIV and a suitable comparison group. Measurements of PWV were highly accurate, given that each child had at least 100 measurements during each PWV recording. In addition, we adjusted the calculation of PWV obtained from the Vicorder system to more accurately reflect the distance travelled by the pulse wave in children (Witbooi et. al. (23)), thereby overcoming shortcomings of the Vicorder system (42).

Several limitations should be considered. There are differences in the number of outcome measurements per child, indicating some missingness in PWV. This could result from travel in and out of the province with family (common in our context), and in unexposed children not attending study visits when they are feeling healthy. In addition, CHIV had more measurements than CHEU and unexposed children, given they were seen more regularly for clinical support. However, mixed effects models are robust in dealing with missing data and imbalanced follow-up times.

Generalisability

These findings are generalisable to CHIV in sub-Saharan Africa, where 88% of the world's CHIV reside (43). Our data may not extrapolate to African immigrants living in developed countries, whose environment and exposures are different.

Our CHIV have been in care for a long time and received timely interventions when viral rebound or other poor clinical outcomes (such as opportunistic infections) occurred and therefore our results are only generalisable to children with a good standard of care, consistent ART maintenance and early ART initiation. Also, as very early treatment close to birth is now the norm, new paediatric cohorts with even earlier ART initiation must be studied.

Our dataset contained children with study visits ranging between 6 and 15 years old and from Tanner Stage 1 to Tanner Stage 5. However, as the median age at last visit was 12.4 (IQR 10.8, 13.5) years, at the last PWV measurement only 9% had reached Tanner Stages 4 or 5. Therefore, our findings are from the pre-pubertal and early pubertal period. Further research is necessary to evaluate PWV at the end of puberty in this population. The need for continued follow-up and evaluation is critical based on 1) evidence that longitudinal PWV trajectories climb during the transition from youth to young adulthood and show significant ethnic and sex differences (44) and 2) the transition to integrase inhibitor ART treatment in sub-Saharan Africa given evidence of an early onset increased incidence of cardiovascular disease in the first 2 years of integrase inhibitor exposure, after controlling for known cardiovascular disease risk factors (45).

Conclusion

This study demonstrates that CHIV with sustained viral suppression who initiate ART in infancy do not have significantly different PWV compared to uninfected controls. Excellent adherence and early ART initiation may protect against cardiovascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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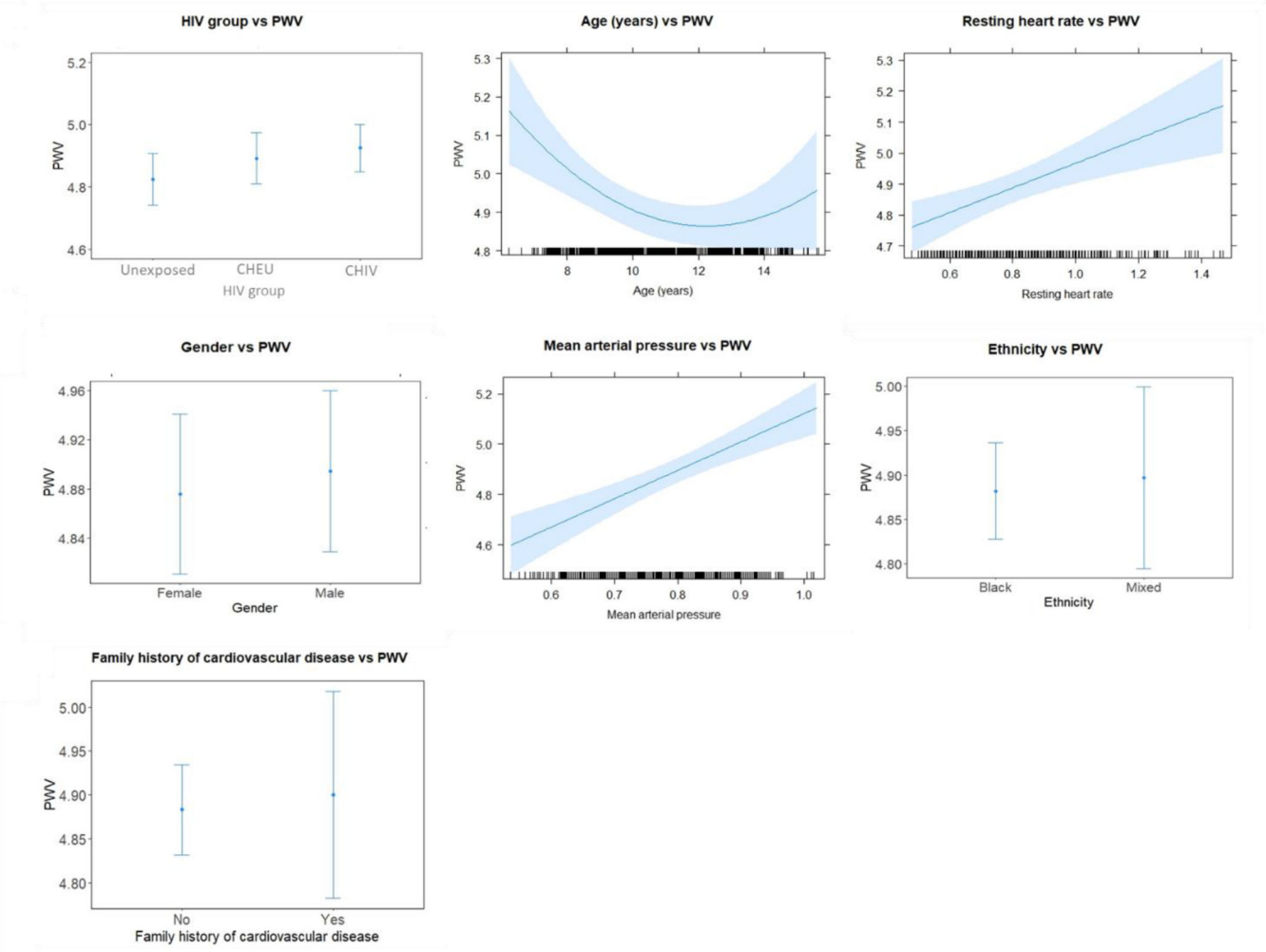

Figure 1:

Effect display for each variable on longitudinal PWV from linear mixed model

Each figure is a graphical depiction of the terms from the linear mixed model after adjusting for gender, age, age squared, resting average heart rate, mean arterial pressure, ethnicity and family history of cardiovascular disease (Table 2). The figures have been constructed using the *Effects* package in R, and therefore the analysis only reflects the fixed effects of the model (not random effects), and assumes that other variables in the model are constant and take on their average values. 95% Confidence intervals are shown, with standard errors computed from the covariance matrix of the fitted regression coefficients. Unexposed: Children who are HIV unexposed; CHEU: Children who are HIV exposed uninfected; CHIV: Children living with perinatally-acquired HIV; PWV: Pulse wave velocity

Table 1:

Baseline characteristics of the cohort, by HIV group. Age and cardiovascular measures at entry are as at first PWV measurement. Median (IQR) or n (%), and p-values (Chi-squared/ F-test) are reported.

	CHIV (n = 141)	CHEU (n = 160)	Unexposed (n = 164)	p-value
Age at Entry (yr) - median (IQR)	8.19 (7.62, 8.80)	8.81 (7.85, 10.58)	8.81 (8.11, 10.39)	<0.001
Gender:				
Male, n (%)	64 (45)	78 (49)	92 (56)	0.156
Female, n (%)	77 (55)	82 (51)	72 (44)	
Cardiovascular measures at entry				
PWV - median (IQR)	4.93 (4.58, 5.37)	5.08 (4.64, 5.41)	4.86 (4.45, 5.28)	0.014
Mean arterial pressure - median (IQR)	71.56 (66.22, 76.00)	77.67 (71.33, 83.06)	76.44 (70.89, 81.11)	<0.001
Systolic blood pressure – median (IQR)	96.00 (90.00, 102.00)	98.67 (92.67, 104.00)	98.67 (92.67, 102.67)	0.001
Diastolic blood pressure – median (IQR)	58.00 (54.00, 64.67)	68.00 (60.00, 73.17)	64.67 (58.00, 70.67)	<0.001
Heart rate - median (IQR)	82.00 (76.50, 90.00)	84.00 (76.00, 94.50)	84.00 (77.00, 93.00)	0.141
Number of PWV measurements per child – median (IQR)	5.0 (4.0, 6.0)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)	
Family history of diabetes				
Yes, n (%)	34 (24)	35 (22)	42 (26)	0.739
No, n (%)	96 (68)	105 (66)	103 (63)	
Missing, n(%)	11 (8)	20 (12)	19 (12)	
Family history of cardiovascular disease				
Yes, n (%)	13 (9)	18 (11)	30 (18)	0.031
No, n (%)	117 (83)	121 (76)	114 (70)	
Missing, n(%)	11 (8)	21 (13)	20 (12)	
Ethnicity				
Black, n (%)	128 (91)	144 (90)	89 (54)	<0.001
Cape Mixed, n (%)	13 (9)	16 (10)	75 (46)	
Age at ART initiation in months – median (IQR)	4.2 (1.8, 8.4)	NA	NA	NA
Antiretroviral drugs				
Zidovudine, n(%)	141 (100)	NA	NA	NA
Lamivudine, n(%)	141 (100)	NA	NA	NA
Lopinavir/r, n(%)	116 (82)	NA	NA	NA
Nevirapine, n(%)	27 (19)	NA	NA	NA
Efavirenz, n(%)	2 (2)	NA	NA	NA
ART regimen switch required	10 (7.1%)			

Unexposed: HIV Unexposed children; CHEU: HIV exposed uninfected children; CHIV: Children living with perinatally-acquired HIV; NNRTI: Non-nucleoside reverse transcriptase inhibitors; IQR: interquartile range; PWV: pulse wave velocity

[†]Missing values are not included in the inferential analysis.

Table 2:

Association between each HIV group and pulse wave velocity using linear mixed effects model. Unadjusted estimates show single-predictor analysis of each variable on pulse wave velocity. Adjusted results show the mean difference (m/s) (with 95% CI) on pulse wave velocity between the two exposed groups (CHIV and CHEU) and the Unexposed group.

Predictors	Unadjusted Estimate (95% CI)	p-value	Adjusted Estimate (95% CI)	p-value
CHIV (vs Unexposed)	0.020 (−0.078 to 0.118)	0.69	0.101 (−0.012 to 0.214)	0.080
CHEU (vs Unexposed)	0.071 (−0.028 to 0.171)	0.161	0.068 (−0.047 to 0.183)	0.244
Sex: Male	−0.005 (−0.087 to 0.076)	0.894	0.019 (−0.068 to 0.106)	0.672
Age (years)	−0.228 (−1.227 – 0.772)	0.655	−0.205 (−0.339 to −0.070)	0.003
Age square	1.864 (0.915 – 2.813)	<0.001	0.008 (0.002 to 0.015)	0.008
Resting average heart rate (beats per minute*10^-2)	0.426 (0.234 to 0.618)	<0.001	0.397 (0.182 to 0.611)	<0.001
Mean arterial pressure (mmHg*10^-2)	0.687 (0.377 to 0.997)	<0.001	1.127 (0.726 to 1.527)	<0.001
Ethnicity (Cape Malay vs. Black)	0.001 (−0.097 to 0.099)	0.988	0.015 (−0.099 to 0.129)	0.795
Family history of cardiovascular disease	0.031 (−0.092 to 0.154)	0.624	0.017 (−0.108 to 0.142)	0.786
Family history of diabetes	0.072 (−0.024 to 0.168)	0.143	-	-

Results show the adjusted mean differences (in m/s) between HIV groups. The model with random intercept only was optimal.

Unexposed: Children who are HIV unexposed; CHEU: Children who are HIV exposed uninfected; CHIV: Children living with perinatally-acquired HIV; PWV: Pulse wave velocity