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Initiation of antiretroviral therapy at higher nadir CD4+ T-cell counts is associated with reduced arterial stiffness in HIV-infected individuals

Jennifer E. HO^a, Steven G. DEEKS^b, Frederick M. HECHT^b, Yu XIE^a, Amanda SCHNELL^a, Jeffrey N. MARTIN^{b,c}, Peter GANZ^a, and Priscilla Y. HSUE^a

^a Division of Cardiology, San Francisco General Hospital, University of California, San Francisco, California, USA

^b Division of Positive Health Program of the Department of Medicine, San Francisco General Hospital, University of California, San Francisco, California, USA

^c Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA

Introduction

HIV infection is associated with increased rates of cardiovascular disease [1–5]. The etiology of premature atherosclerosis is potentially due to the viral infection itself, to host immune responses or to the use of highly active antiretroviral treatment (HAART) [1]. Paradoxically, while long-term exposure to protease inhibitors and abacavir use are associated with increased risk of cardiovascular events [1,6,7], interruption of therapy (as compared to continuous therapy) may be associated with increased risk of cardiovascular events [8]. Also, short term treatment with HAART in antiretroviral-naïve improves brachial artery reactivity in one study [9]. These observations suggest that under certain conditions, HAART may reduce cardiovascular risk. It remains unknown, however, whether earlier initiation of HAART, before CD4+ T-cell counts fall below 350 cells/μl, reduces cardiovascular risk.

Arterial stiffness is a simple and reproducible measure of subclinical atherosclerotic disease. The central aortic pressure within the larger arteries - including the brachial and femoral arteries - consists of a forward wave generated during ventricular systole, followed by a reflected wave from the periphery. With increasing arterial stiffness, this reflected wave arrives earlier, augmenting pressure during late systole [10]. This can be measured as the ratio of the reflected wave to the pulse pressure (“augmentation index”, or AIx@75). Arterial stiffness can also be assessed by measuring the velocity of the initial pulse wave propagation between two sites (PWV) [11]. These surrogate measures of atherosclerosis have been linked to cardiovascular mortality in non-infected populations [12].

Address for correspondence and reprints: Priscilla Y. Hsue MD, Room 5G1, Division of Cardiology, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110. Telephone: (415) 206-8257; fax: (415) 206-5100; phsue@medsfgh.ucsf.edu.

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HIV-infected patients appear to have increased arterial stiffness when compared with age- and sex-matched uninfected controls; however the effect of HAART on vascular parameters is not well understood [13,14]. We hypothesized that earlier initiation of HAART at higher CD4+ T-cell count thresholds is associated with improved cardiovascular risk as measured by arterial stiffness when compared with delayed initiation at lower CD4+ T-cell counts.

Methods

Study Design

We conducted a cross-sectional study of HIV-infected men who were consecutively recruited from two ongoing prospective cohort studies at San Francisco General Hospital that have previously been described: the SCOPE study [15], and the Options Project [16,17]. The SCOPE study recruits subjects with chronic HIV infection while the Options cohort recruits subjects with acute or early HIV infection. Neither cohort selects individuals based on cardiovascular disease. From both cohorts, we identified patients who initiated HAART and who achieved and maintained an undetectable viral load for at least one year. Participants were recruited during their periodic follow-up appointments in a convenience sample of consecutive volunteers.

Study Participants

Subjects were recruited if they were HIV-infected men on stable HAART (defined as continuous treatment with 3 or more antiretroviral drugs including either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor) for at least 1 year with undetectable plasma HIV RNA levels. All subjects must have been in normal sinus rhythm at the time of their inclusion in this substudy. Subjects with known cardiovascular disease were excluded. The University of California, San Francisco Committee on Human Research approved the study, and all subjects provided written informed consent.

Data Collection

Subjects underwent an in-depth assessment, including a detailed interview and structured questionnaire covering socio-demographic characteristics, HIV disease history, other co-morbid conditions, health-related behaviors, medication exposure, and family history. Laboratory evaluation included serum creatinine, HIV-associated measures including CD4+ T-cell count, HIV RNA level, and markers of inflammation including high-sensitivity C-reactive protein (hs-CRP). HIV RNA levels were measured using branched chain DNA method (Quantiplex HIV RNA, Chiron Version 3.0; Chiron Corporation, Emeryville, California, USA), and hs-CRP was measured using the CardioPhase hs-CRP assay [18].

Pulse Wave Tonometry

Subjects were examined in a supine position at a room temperature of $22\pm1^{\circ}\text{C}$. No caffeine ingestion or cigarette smoking was allowed 2 hours prior to the examination. All subjects were studied after resting at least 5 minutes. Blood pressure (BP) was taken as the average of 3 consecutive readings obtained on the right arm by a manual sphygmomanometer. Arterial stiffness was assessed noninvasively using the SphygmoCor System (AtCor Medical, Australia). For pulse wave analysis, peripheral pressure waveforms were recorded from the right radial artery using applanation tonometry. After 10 sequential waveforms had been acquired, a validated generalized transfer function was used to generate the corresponding central aortic pressure waveform, from which the augmentation index was obtained (AIx), which was calculated as the ratio between augmentation pressure and pulse pressure. Because AIx is influenced by heart rate, an index normalized for heart rate of 75 bpm (AIx@75) was calculated using the general transformation function used by Wilkinson

et al [19]. Larger values of $AIx@75$ indicate increased wave reflection from the periphery or early return of the reflected wave as a result of increased arterial stiffness.

Pulse wave velocity (PWV) was then obtained using ECG-gated pulse waveforms over the common carotid and femoral arteries. PWV was calculated as the distance between recording sites measured over the surface of the body, divided by the time interval between the feet of the pressure waves. All measurements were performed by a single observer (J.E.H.). Intra-observer reproducibility measurements were performed on 16 randomly selected subjects, who underwent 2 separate pulse wave analysis measurements on the same day. The intra-class correlation coefficient for reported outcome variables was excellent and ranged between 93–94%.

Statistical Analyses

Baseline characteristics and main outcome variables were summarized using medians and inter-quartile ranges. Pearson correlation coefficients were calculated to assess the correlation between nadir CD4+ T-cell counts and measures of arterial stiffness. Because PWV was highly right-skewed and the most appropriate transformation was inverse PWV, the transformed variable was used to calculate the correlation coefficient. The association between clinical and HIV-related predictors and the outcome of arterial stiffness was assessed using univariate linear regression models. Clinical predictors included age, systolic and diastolic BP, the use of antihypertensive medications, diabetes mellitus, hypercholesterolemia, cigarette smoking (ever use), family history of premature coronary heart disease, and current intravenous (IV) drug use. HIV-related predictors included HIV duration, current CD4+ T-cell count, nadir CD4+ T-cell count, and duration and type of HAART. HIV duration was defined as the time period from diagnosis of acute HIV infection in the Options cohort, and as the time period from diagnosis of HIV infection in the SCOPE cohort. Nadir CD4+ T-cell count was dichotomized into < 350 versus ≥ 350 cells/ μ l *a priori* as this is the most common threshold used to define when to start antiretroviral therapy [20–22]. Laboratory parameters considered included hs-CRP, which was log-transformed to account for non-normality. Estimated glomerular filtration rate (eGFR) was calculated based on serum creatinine [23]. Separate analyses were performed using nadir CD4+ T-cell count as a continuous variable. The use and duration of protease inhibitors and abacavir were examined in secondary analyses. In order to compare the relative strength of each of the predictors, standardized regression coefficients were used for continuous variables in order to represent the associated change in the outcome variable per standard deviation change in the predictor variable. A multivariate linear regression model was then constructed using backwards selection, with retention at a significance level of $p < 0.10$. Because PWV was highly right-skewed, generalized linear models using maximum likelihood optimization were constructed to assess the association between clinical and HIV-related predictors and PWV. A gamma distribution of the outcome variable was assumed, and the link function used was identity. Bootstrap percentile confidence intervals were constructed based on 200 replications with replacement. All statistical analyses were performed using the STATA statistical software package version 10.1 (College Station, TX).

Results

Clinical, HIV-related Characteristics, and Measures of Arterial Stiffness

We studied 80 HIV-infected men (26 from the Options cohort, and 54 from the SCOPE cohort). The median age was 47 years and many participants had traditional cardiovascular risk factors including hypertension and hypercholesterolemia (see Table 1). All subjects had an undetectable plasma HIV RNA level on the day of the examination.

Of the 80 individuals, 15 started HAART with a CD4 nadir ≥ 350 cells/ μ l and 65 started HAART with a CD4 nadir below this threshold. As expected, participants with a nadir CD4+ T-cell count < 350 cells/ μ l had significantly longer HIV duration and a lower proximal CD4+ T cell count than participants with a nadir ≥ 350 ($p < 0.001$ for both).

Effect of CD4 Nadir on Arterial Function

The derived central median systolic BP based on the arterial waveform was 108 mmHg (IQR 102-116) in those with a nadir < 350 and 102 mmHg (IQR 94-111) in those with nadir ≥ 350 ($p = 0.02$). Those with nadir CD4+ T-cell counts < 350 had higher Aix@75 (17% (IQR 10-22) versus 4% (IQR -8-12), $p < 0.001$), and higher PWV (5.5 m/s (IQR 4.9-6.3) versus 5.0 (IQR 4.5-5.3), $p = 0.009$) compared with those with nadir CD4+ T-cell counts ≥ 350 , indicating increased arterial stiffness.

Impact of Clinical and HIV-related Parameters on Augmentation Index (Aix@75)

In univariate analyses, clinical predictors of Aix@75 included age ($p < 0.001$), systolic and diastolic BP ($p = 0.05$ and $p < 0.001$), the use of antihypertensive medications ($p = 0.003$), and tobacco use ($p = 0.02$) (Table 2). Significant HIV-related predictors of arterial stiffness included HIV duration, nadir CD4+ T-cell count < 350 , and duration of protease inhibitor use. Notably, a nadir CD4+ T-cell count < 350 was associated with a 12.2% increase in Aix@75 (95% CI 6.7–17.8, $p < 0.001$). The correlation between nadir CD4+ T-cell count and Aix@75 is represented in Figure 1a. Each 1 standard deviation (SD) increase in HIV disease duration was associated with a 3% increase in Aix@75 (95% CI 1.0–5.5, $p = 0.006$), and a 1 SD increase in protease inhibitor duration was associated with a 2.5% increase in Aix@75 (95% CI 0.0–4.9, $p = 0.05$).

After adjustment for clinical and HIV-related predictors in a multivariate model, age, diastolic BP, antihypertensive medication treatment, smoking, and nadir CD4+ T-cell count remained significant predictors of arterial stiffness (Table 2). Specifically, a nadir CD4+ T-cell count < 350 was independently associated with a 7.3% increase in Aix@75 (95% CI 2.6–11.9, $p = 0.003$) compared with a nadir CD4+ T-cell count ≥ 350 cells/ μ l. When analyzed as a continuous variable, nadir CD4+ T-cell count was a significant predictor of Aix@75 in unadjusted analyses, and remained significant predictor after adjustment for other clinical and HIV-related parameters. Each 1 SD decrease in nadir CD4+ T-cell count was associated with a 2.3% increase in Aix@75 (95% CI 0.4–4.2, $p = 0.02$).

Impact of Clinical and HIV-related Parameters on Pulse Wave Velocity (PWV)

Univariate predictors of PWV included age ($p < 0.001$), the use of antihypertensive medications ($p = 0.02$), diabetes mellitus ($p < 0.001$), current IV drug use ($p = 0.001$), and nadir CD4 count < 350 ($p < 0.001$) (Table 3). In particular, a nadir CD4+ T-cell count < 350 was associated with a 0.83 m/s increase in PWV (95% CI 0.36–1.29, $p < 0.001$) compared with a nadir CD4+ T-cell count ≥ 350 . After adjustment for both clinical and HIV-related covariates, the effect of current IV drug use was attenuated. In contrast, increasing age, higher systolic BP, and a history of diabetes mellitus all remained significant predictors of PWV. Lastly, a nadir CD4+ T-cell count < 350 cells/ μ l was independently associated with a 0.58 m/s increase in PWV (95% CI 0.15–1.01, $p = 0.008$). The correlation between nadir CD4+ T-cell count versus PWV is presented in Figure 1b. When analyzed as a continuous variable, nadir CD4+ T-cell was no longer a significant predictor of PWV. Of note, duration of antiretroviral therapy or exposure to protease inhibitors did not appear to be associated with arterial stiffness in adjusted analyses. Neither current abacavir use, nor duration of abacavir use were associated with arterial stiffness as measured by PWV in both unadjusted and adjusted analyses ($p = 0.12$ and $p = 0.46$, respectively). We did not detect any association

between log-transformed hs-CRP levels or estimated GFR and measures of arterial stiffness in univariate or multivariate analyses.

Discussion

HIV infected persons have a higher risk of developing cardiovascular disease compared with age-matched uninfected persons [1,2,24]. The mechanism for this increase is unknown, but is almost certainly multi-factorial. Prior work from our group and others suggest that uncontrolled viral replication (and its effect on biomarkers of inflammation) appear to be causally associated with this increased risk [3,24,25]. Among treated patients, certain drugs such as the protease inhibitor class and perhaps abacavir are also associated with increased risk of disease [1,6,7]. The relative degree of immunodeficiency—as defined by nadir and recent CD4+ T cell counts—may also be associated with cardiovascular risk. Here, we performed a detailed assessment of arterial stiffness by pulse wave analysis and tonometry. Arterial stiffness has been associated with all-cause mortality, cardiovascular mortality [12], coronary artery disease [26], and stroke [27] in HIV uninfected persons. As expected, age, blood pressure, and antihypertensive medication use were associated with increased arterial stiffness in our population. We also found that the peripheral CD4+ T cell count was a strong and consistent predictor of both PWV and arterial stiffness. This association appeared to be independent of other important clinical factors that are known to influence measures of arterial stiffness, such as age, BP, and diabetes mellitus. More importantly, the relationship between nadir CD4+ T-cell count and arterial stiffness was independent of other HIV-associated characteristics, including HIV duration, the use of protease inhibitors, and current CD4+ T-cell count.

Among long-term treated patients, there is a growing body of evidence that suggests the degree of prior or residual immunodeficiency while on therapy is associated with the short-term risk of cardiovascular disease. In our earlier studies, we found that a nadir CD4+ T-cell count ≤ 200 cells/ μ l was associated with carotid intima-medial thickness [24] while other studies have failed to detect an effect [28,29]. The discrepancies between study results may be due to differences in methods of assessment of carotid artery IMT [30]. Some studies have also suggested that the on-therapy CD4+ T-cell count is independently associated with an increased risk of cardiovascular disease [31–33]. These observations suggest that for unclear reasons, persistent immunodeficiency during HAART has negative cardiovascular consequences. Given the manner in which treatment has been historically administered, the vast majority of individuals in these cohorts had chronic infection at the time they started HAART, and most had a CD4 nadir below 350 cells/ μ l. These studies were hence unable to determine whether earlier initiation of HAART is associated with better cardiovascular outcomes than delayed initiation of HAART. Defining with more precision the role of prior or current immunodeficiency in driving heart disease could prove to be informative for the ongoing debate as to when to start combination antiretroviral therapy [34]. Our data show that advanced immunodeficiency as represented by a nadir CD4+ T-cell count < 350 cells/ μ l is independently associated with increased arterial stiffness. While it is not possible to conclude from our cross-sectional study that earlier initiation of antiretroviral therapy may help reduce cardiovascular risk, our study results provide important initial evidence that might support the further pursuit of prospective studies addressing this question.

Prior studies of arterial stiffness in the HIV population have focused mainly on case-control study designs demonstrating increased (i.e. worse) arterial stiffness in HIV-infected subjects when compared with non-infected controls [13,14,35]. HIV-specific disease characteristics that have been associated with arterial stiffness include HAART duration [29], concomitant impaired glucose tolerance [36], and HIV disease duration [37]. However, prior studies were limited in the number of HIV-infected participants enrolled, which diminished the ability to

explore the impact of HIV-specific disease characteristics on arterial stiffness in detail. Van Vonderen et al compared carotid intima-medial thickness (IMT), arterial stiffness and other markers of endothelial function in 37 HAART-naïve men after randomization to 2 different HAART regimens. Compared with baseline measurements, carotid IMT and femoral arterial stiffness worsened after 24 months of HAART, whereas serum markers of endothelial function improved [28]. Of note, worsening arterial stiffness in this study was observed only in the femoral artery, and assessment of systemic arterial stiffness by AIx did not change over the treatment course. In a second study by the same group, 77 HIV-infected men (55 on HAART and 22 treatment-naïve individuals) were found to have similar PWV compared with non-infected controls, although the effect of nadir CD4+ T-cell count on PWV in HIV-infected individuals was not reported [38].

The pathophysiologic mechanism by which immunodeficiency may mediate arterial stiffness and cardiovascular risk remains unclear. In the SMART study, elevations in IL-6 and D-dimer were strongly associated with all-cause mortality, suggesting that interruption of HAART may result in higher levels of HIV-associated inflammation [25]. In our study, there was no correlation with hs-CRP and the degree of arterial stiffness, however this may have been due to insufficient power to detect differences between participants.

Chronic activation of the immune system in HIV infection may be due to microbial translocation in the gastrointestinal tract, leading to elevated levels of circulating microbial products such as lipopolysaccharide, which may activate immune and inflammatory pathways [39]. It is known that residual microbial translocation during suppressive HAART is associated with the degree of immune reconstitution, as reflected by CD4+ T-cell count recovery [40]. It has also been shown that initiation of HAART at CD4+ T-cell nadir ≤ 350 is associated with incomplete reconstitution of T-cell subsets and T-cell activation [41]. It is thus possible that the relationship between nadir CD4+ T-cell counts and arterial stiffness may be mediated via microbial translocation, which in turn may activate inflammatory pathways, leading to premature atherosclerosis.

Our study has many limitations common to cross-sectional studies. Although our study demonstrates a strong association between nadir CD4+ T-cell count and measures of arterial stiffness, it was a cross-sectional observational study, and is therefore subject to potential selection biases and limitations in establishing cause-effect relationships. Our data argue for early use of antiretroviral therapy, however we were unable to analyze whether treatment initiation during the acute versus chronic phases of HIV infection (and potential associated differences in lifestyle or behavioral factors), affected cardiovascular risk, independent of nadir CD4+ T-cell count, due to limited number of individuals who started HAART during acute infection.

In addition, while a nadir CD4 T-cell count above 350 appeared to be associated with improved cardiovascular risk in our study, it is unclear from our data whether this relationship extends beyond a CD4+ T-cell count of 500 cells/ μ l, as few participants met these criteria. Thus, whether earlier initiation of HAART at a CD4+ T-cell count of 500 rather than 350 cells/ μ l may impact cardiovascular risk is unclear. It is also unclear from our study whether it is exposure to HIV replication or low CD4+ T-cell counts or both were driving vascular dysfunction. However, because nadir but not current CD4+ T-cell count in persons with undetectable viral load predicted arterial stiffness suggests that duration of untreated HIV or exposure to viremia may be more important than persistent depressed CD4+ T-cell counts. Finally, we failed to detect consistent associations between diabetes mellitus, smoking, and our two vascular outcome measures. This may be due to the limited number of individuals with clinical diabetes mellitus. Also, a recent systematic review examining cardiovascular risk factors associated with PWV reported that only 6 of 44

studies reported an association between smoking and PWV [42], thus the lack of association between these parameters in our study is not surprising. Finally, given that arterial stiffness is a surrogate and not direct measure of atherosclerosis, the ultimate clinical significance of our findings is unclear. Prior studies have shown a 5 m/s increase in PWV to be associated with a 2-fold greater odds of all-cause mortality in hypertensive patients [12], and each quartile increase in AIx was associated with a 2-fold greater odds of coronary artery disease [26]. Whether or not our findings of increased AIx@75 or increased PWV in association with nadir CD4+ T-cell counts < 350 translate into clinically significant outcomes is unclear and will require further study.

Despite these limitations, the strengths of this study are that participants were recruited from two unique ongoing longitudinal cohorts which included individuals who were treated with HAART both early and late in the course of their HIV infection, and were thus were extremely well-characterized with respect to their clinical and HIV-related parameters. Our study is the largest study examining arterial stiffness to date, and may provide important initial evidence to prompt longitudinal studies addressing whether early initiation of HAART may have any impact on cardiovascular risk.

In conclusion, among treated HIV-infected individuals, increased arterial stiffness was independently associated with both traditional cardiovascular risk factors including age and diabetes, as well as a low nadir CD4 count. While inferences drawn from our findings must be interpreted with caution due to the cross-sectional nature of our study, our data may provide initial evidence that earlier initiation of antiretroviral therapy before low CD4 counts occur may be a means of reducing cardiovascular risk among individuals with HIV infection. Prospective studies are needed to evaluate potential beneficial effects of HAART initiation at higher CD4 T-cell counts on cardiovascular risk.

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Figure 1. Correlation between nadir CD4+ T-cell count and measures of arterial stiffness as assessed by a) augmentation index normalized for a heart rate of 75 bpm ($r=-0.37$, $p=0.0009$, and b) carotid-femoral pulse wave velocity (for transformed PWV, $r=0.25$, $p=0.03$)

Table 1

Baseline Clinical and HIV Disease Characteristics by Nadir CD4+ T-cell count

	Nadir CD4 < 350 cells/μl (n=65) Median (IQR)	Nadir CD4 ≥ 350 cells/μl (n=15) Median (IQR)	p-value
Clinical characteristics:			
Age (years)	<u>48 (43–54)</u>	<u>44 (39–50)</u>	<u>0.06</u>
Systolic BP (mmHg)	<u>120 (114–128)</u>	<u>116 (108–123)</u>	<u>0.17</u>
Diastolic BP (mmHg)	<u>72 (68–80)</u>	<u>70 (62–74)</u>	<u>0.07</u>
Heart rate (bpm)	<u>65 (56–70)</u>	<u>59 (53–67)</u>	<u>0.09</u>
Hypertension (%)	<u>39</u>	<u>20</u>	<u>0.18</u>
Hypercholesterolemia (%)	<u>3</u>	<u>0</u>	<u>0.49</u>
Diabetes (%)	<u>43</u>	<u>53</u>	<u>0.47</u>
Tobacco use - ever (%)	<u>60</u>	<u>53</u>	<u>0.47</u>
Family history of CHD (%)	<u>19</u>	<u>20</u>	<u>0.91</u>
Current IV drug use (%)	<u>2</u>	<u>0</u>	<u>0.63</u>
Medications:			
Anti-hypertensive (%)	<u>31</u>	<u>13</u>	<u>0.39</u>
Cholesterol lowering (%)	<u>20</u>	<u>31</u>	<u>0.53</u>
HIV disease characteristics:			
Estimated Disease duration (years)	<u>17 (8–20)</u>	<u>6 (4–8)</u>	<u><0.001</u>
Current CD4 T-cell count (cells/ul)	<u>459 (316–621)</u>	<u>785 (684–1190)</u>	<u><0.001</u>
Nadir CD4 T-cell count (cells/ul)	<u>85 (14–216)</u>	<u>494 (400–540)</u>	<u><0.001</u>
Duration of HAART (years)	<u>7 (3–10)</u>	<u>5 (3–7)</u>	<u>0.66</u>
Duration of protease inhibitor (years)	<u>4 (0–9)</u>	<u>2 (0–4)</u>	<u>0.07</u>
History of opportunistic infections (%)	<u>17</u>	<u>7</u>	<u>0.32</u>
HCV co-infection (%)	<u>11</u>	<u>0</u>	<u>0.18</u>
Laboratory parameters:			
hs-CRP (mg/L)	<u>1.8 (0.9–3.1)</u>	<u>1.7 (0.5–2.0)</u>	<u>0.62</u>
eGFR (ml/min)	<u>110 (97–124)</u>	<u>114 (96–132)</u>	<u>0.79</u>

IQR, inter-quartile range; BP, blood pressure; CHD, coronary heart disease; IV, intravenous; HAART, highly active antiretroviral therapy; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

Table 2

Clinical and HIV-related predictors of Augmentation Index (AIx@75) (N=80)

	Univariate Model		Multivariate Model ^b Adjusted for clinical and HIV-related covariates	
	Beta ^a (95% CI)	p-value	Beta (95% CI)	p-value
Clinical history				
Age	5.2 (3.1–7.3)	<0.001	3.8 (2.0–5.6)	<0.001
Systolic BP	2.4 (0.1–4.7)	0.05		
Diastolic BP	4.0 (1.8–6.2)	0.001	3.4 (1.7–5.2)	<0.001
Antihypertensive medication use	7.8 (2.8–12.7)	0.003	4.5 (0.6–8.5)	0.03
Diabetes mellitus	4.5 (–11.0–19.9)	0.56		
Hypercholesterolemia	2.6 (–2.1–7.4)	0.27		
Tobacco use - ever	5.6 (1.0–10.3)	0.02	4.5 (0.9–8.0)	0.01
Family history of CHD	–2.5 (–8.7–3.6)	0.42		
Current IV drug use	2.1 (–19.6–23.7)	0.85		
HIV-related history				
HIV duration	3.2 (1.0–5.5)	0.006		
Current CD4+ T-cell count	–2.3 (–46–0.1)	0.06		
Nadir CD4+ T-cell count < 350	12.2 (6.7–17.8)	<0.001	7.3 (2.6–11.9)	0.003
HAART duration	1.4 (–1.1–3.9)	0.26		
PI duration	2.5 (0.0–4.9)	0.05		
Laboratory parameters				
hs-CRP	–0.17 (–2.26–1.92)	0.87		
eGFR	0.30 (–11.65–1.26)	0.96		

CI, confidence interval; BP, blood pressure; CHD, coronary heart disease; IV, intravenous; HAART, highly active antiretroviral therapy; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

^a Standardized regression coefficients denote change in AIx@75 per standard deviation increase for continuous predictor variables. Standard deviations were as follows: age = 8.3 years, systolic BP = 13 mmHg, diastolic BP = 11 mmHg, HIV duration = 7.3 years, current CD4+ T-cell count = 313 cells/μl, nadir CD4+ T-cell count = 185 cells/μl, HAART duration = 3.7 years, PI duration = 4.3 years, hs-CRP = 7.7 mg/L, eGFR = 25 ml/min

^b Covariates considered in multivariate models included age, systolic and diastolic BP, antihypertensive medication use, diabetes mellitus, hypercholesterolemia, tobacco use (ever), family history of premature coronary heart disease, current IV drug use, HIV duration, current CD4+ T-cell count, nadir CD4+ T-cell count, HAART duration, PI duration, hs-CRP, and eGFR

Table 3

Clinical and HIV-related predictors of PWV (N=80)

	Univariate Model		Multivariate Model ^b Adjusted for clinical and HIV- related covariates	
	Beta ^a (95% CI)	p-value	Beta (95% CI)	p-value
Clinical history				
Age	0.48 (0.23–0.73)	<0.001	0.50 (0.28–0.72)	<0.001
Systolic BP	0.21 (–0.15–0.57)	0.26	0.48 (0.21–0.76)	0.001
Diastolic BP	0.01 (–0.28–0.30)	0.94	–0.31 (–0.56–0.05)	0.02
Antihypertensive medication use	0.73 (0.05–1.42)	0.02	0.44 (–0.04–0.92)	0.08
Diabetes mellitus	2.60 (1.20–4.01)	<0.001	2.25 (0.78–3.73)	0.003
Hypercholesterolemia	0.31 (–0.29–0.90)	0.31		
Tobacco use - ever	0.38 (–0.10–0.86)	0.12		
Family history of CHD	–0.30 (–0.89–0.29)	0.32		
Current IV drug use	0.53 (0.23–0.83)	0.001		
HIV-related history				
HIV duration	0.22 (–0.01–0.44)	0.06		
Current CD4+ T-cell count	–0.22 (–0.45–0.01)	0.06		
Nadir CD4+ T-cell count < 350	0.83 (0.36–1.29)	<0.001	0.41 (0.03–0.79)	0.03
HAART duration	0.18 (–0.15–0.51)	0.28	–0.23 (–0.44–0.02)	0.03
PI duration	0.28 (–0.05–0.61)	0.10		
Laboratory Parameters				
hs-CRP	0.00 (–0.25–0.24)	0.98		
eGFR	0.51 (–0.80–1.83)	0.45		

CI, confidence interval; BP, blood pressure; CHD, coronary heart disease; IV, intravenous; HAART, highly active antiretroviral therapy; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

^a Standardized regression coefficients denote change in PWV per standard deviation increase for continuous predictor variables. Standard deviations were as follows: age = 8.3 years, systolic BP = 13 mmHg, diastolic BP = 11 mmHg, HIV duration = 7.3 years, current CD4+ T-cell count = 313 cells/μl, nadir CD4+ T-cell count = 185 cells/μl, HAART duration = 3.7 years, PI duration = 4.3 years, hs-CRP = 7.7 mg/L, eGFR = 25 ml/min

^b Covariates considered in multivariate models included age, systolic and diastolic BP, anti-hypertensive medication use, diabetes mellitus, hypercholesterolemia, tobacco use (ever), family history of premature coronary heart disease, current IV drug use, HIV duration, current CD4+ T-cell count, nadir CD4+ T-cell count, HAART duration, PI duration, hs-CRP, and eGFR