Aggregate Risk of Cardiovascular Disease Among Adolescents Perinatally Infected With the Human Immunodeficiency Virus

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Background—Perinatally HIV-infected adolescents may be susceptible to aggregate atherosclerotic cardiovascular disease risk, as measured by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) coronary arteries and abdominal aorta risk scores, as a result of prolonged exposure to HIV and antiretroviral therapy.

Methods and Results—Coronary arteries and abdominal aorta PDAY scores were calculated for 165 perinatally HIV-infected adolescents, using a weighted combination of modifiable risk factors: dyslipidemia, cigarette smoking, hypertension, obesity, and hyperglycemia. Demographic and HIV-specific predictors of scores ≥1 were identified, and trends in scores over time were assessed. Forty-eight percent and 24% of the perinatally HIV-infected adolescents had coronary arteries and abdominal aorta scores ≥1, representing increased cardiovascular disease risk factor burden. Significant predictors of coronary arteries scores ≥1 included male sex, history of an AIDS-defining condition, longer duration of use of a ritonavir-boosted protease inhibitor, and no prior use of tenofovir. Significant predictors of abdominal aorta scores ≥1 included suppressed viral load, history of an AIDS-defining condition, and longer duration of boosted protease inhibitor use. No significant changes in coronary arteries and abdominal aorta risk scores were observed over the 4-year study period.

Conclusions—A substantial proportion of perinatally HIV-infected youth have high PDAY scores, reflecting increased aggregate atherosclerotic cardiovascular disease risk factor burden. High scores were predicted by HIV disease severity and boosted protease inhibitor use. PDAY scores may be useful in identifying high-risk youth who may benefit from early lifestyle or clinical interventions. **(*Circulation*. 2014;129:1204-1212.)**

Key Words: adolescence ■ atherosclerosis ■ HIV ■ risk factors

Advances in diagnosis and treatment of perinatal HIV infection in the United States have significantly improved life expectancy.[1,2] However, prolonged exposure to HIV and highly active antiretroviral therapy (HAART) has been associated with long-term complications. Atherosclerotic cardiovascular disease (CVD) risk factors, including hyperlipidemia, lipodystrophy, diabetes mellitus, and hypertension, have increased in prevalence and severity with the advent of HAART.[3–15] These CVD risk factors have been studied in adults,[3–6] with expanding research in children.[7–15] Potential contributors to CVD risk and

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clinical CVD events in adult HIV-infected populations include traditional risk factors such as male sex and lifestyle habits (eg, exercise, diet, and smoking), as well as HIV-specific risk factors, particularly exposure to HAART and specific antiretroviral drugs, including protease inhibitors such as indinavir and lopinavir/ritonavir and nucleoside reverse transcriptase inhibitors such as stavudine, didanosine, and abacavir.[3–6] In children, protease inhibitors have been primarily associated with CVD risk factors, although some studies note hypercholesterolemia and lipodystrophy with nucleoside reverse transcriptase inhibitors, particularly stavudine.[7–15]

The atherosclerotic disease process begins at an early age, with severity and progression into adulthood associated with established CVD risk factors.[16–19] Therefore, CVD risk should be tracked from childhood on. To identify and motivate high-risk children who may benefit from early interventions, it is clinically useful to obtain a measure of aggregate CVD risk by the use of a scoring system that sums the risks associated with each individual risk factor.[20] The Framingham Risk Calculator is among the most widely accepted instruments in predicting the 10-year overall risk of coronary heart disease based on a simple, validated algorithm that includes demographics, lifestyle behaviors, blood pressure, and lipid testing.[21] However, this risk score has not been validated for an adolescent population. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) scoring system may be useful for measuring long-term CVD risk in youth and young adults by identifying those with current advanced atherosclerosis.[18]

Developed with autopsy data from >1100 individuals 15 to 34 years of age who died of external causes, the PDAY scoring system estimates the risk of currently having an advanced atherosclerotic lesion in the coronary arteries (CA) or the abdominal aorta (AA) relative to an individual of the same age and sex without any CVD risk factors.[18] The CA risk score predicts coronary artery calcium and carotid artery intima-media thickness measures of atherosclerosis in a number of population-based cohorts.[22–24] The risk factors included in the CA and AA scores are also associated with noninvasive measures of atherosclerosis among HIV-infected children.[25,26] Thus, as a validated measure of the atherosclerotic disease process, we used PDAY scores to describe CVD risk in perinatally HIV-infected adolescents enrolled in the Pediatric HIV/AIDS Cohort Study (PHACS). We additionally identified demographic and HIV-specific predictors of high scores and evaluated trends in scores over the 4-year study follow-up period.

Methods

The Adolescent Master Protocol of the PHACS was designed to evaluate the impact of HIV infection and antiretroviral therapy on youth with perinatal HIV infection. Between March 2007 and December 2009, 451 infected and 227 uninfected youth from 15 study sites in the United States were enrolled if they were born to HIV-infected mothers, were 7 to 16 years of age, and had complete medical history of antiretroviral therapy use, plasma HIV RNA (viral load) concentrations, and lymphocyte subset measurements since birth. The Adolescent Master Protocol was approved by the institutional review boards at the Harvard School of Public Health and at each participating site. Written informed consent was obtained from each participant's parent or legal guardian. Assent was obtained from child participants according to local institutional review board guidelines. Of the 451 infected participants, 225 were in the validated age range for the PDAY score (≥15 years) as of April 1, 2012, and 165 had the clinical measures needed to calculate the PDAY score for at least 1 time point (Table I in the online-only Data Supplement).

For each participant, CA and AA risk scores were calculated at each annual visit with available clinical data after reaching 15 years of age by summing the scores associated with modifiable measures of atherosclerotic risk, including lipids, glucose, smoking, blood pressure, and obesity defined by body mass index.[18] In the PDAY study, CA and AA risk scores ≥1 were shown to indicate at least an 18% (95% confidence interval, 14–22) or 29% (95% confidence interval, 23–35) increased odds of currently having an advanced atherosclerotic lesion in the CAs or AA, respectively, relative to a score of 0.[18]

Fasting serum and plasma were drawn annually to measure levels of total and high-density lipoprotein (HDL) cholesterol and glucose, respectively. Hyperglycemia was defined as a fasting plasma glucose concentration ≥126 mg/dL, a diagnosis of diabetes mellitus, or reporting the use of medication to treat diabetes mellitus. The serum thiocyanate measure of smoking used in the development of the PDAY scores closely correlated with smoking an average of 1 pack per day (ie, heavy smoking).[27] Information on smoking an average of at least 1 pack per day in the past 3 months was collected with an Audio Computer-Assisted Self-Interview. Hypertension was defined as an average systolic or diastolic blood pressure ≥95th percentile for age, sex, and height at ≥3 clinic visits.[28]

Demographic characteristics considered as potential predictors of CA and AA scores included age, sex, and race/ethnicity. HIV-specific clinical characteristics included measures of disease severity: CD4 count, HIV viral load, and Centers for Disease Control and Prevention clinical classification for HIV disease (N/A=not/mildly symptomatic, B=moderately symptomatic, C=severely symptomatic/meets the case definition for AIDS),[29] and antiretroviral therapy previously associated with CVD risk: HAART, any ritonavir-boosted protease inhibitor, lopinavir/ritonavir, indinavir, didanosine, abacavir, stavudine, zidovudine, lamivudine, and tenofovir disoproxil fumarate.[3–15] All characteristics were collected through either self-report (eg, race/ethnicity) or medical chart abstraction (eg, immunologic, virological, and antiretroviral characteristics). Current measures were those closest to the most recent visit at which a PDAY score could be calculated within 90 days before to 7 days after the visit. Nadir CD4 count and peak viral load were defined as the lowest CD4 count and the highest viral load documented before or at the most recent visit with a PDAY score. HAART was defined as concomitant use of at least 3 drugs from at least 2 classes of antiretrovirals. Antiretroviral use was classified as use at the most recent visit (ie, current use), prior or ever use, and cumulative duration of use up to and including the most recent visit with a PDAY score.

Statistical analyses were conducted separately for CA and AA scores. Demographic and HIV-specific characteristics were compared among children with low scores (≤0) and high scores (≥1) at their most recent visit by use of the Wilcoxon rank-sum test or the Fisher exact test as appropriate. The cutoff for low versus high scores was based on the distribution of scores in the study population and was consistent with definitions of low risk used in previous studies.[22–24] To identify significant predictors of a high-risk score, univariable predictors of a high score at the $P<0.10$ level were included in a multivariable logistic regression model. Among highly correlated univariable predictors, the predictor with the highest univariable c statistic was included in the final multivariable model. Sensitivity analyses were conducted with the study population restricted to virologically suppressed (HIV viral load ≤400 copies/mL) participants. Mixed-effects models with time as the independent variable and an assumed compound symmetry correlation structure were used to describe changes in CA and AA scores over the study follow-up period, starting with the baseline visit and including all study visits at which a PDAY score could be calculated. All analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

Results

The 165 perinatally HIV-infected adolescents in the study population were 15 to 19 years old (median age, 16.7 years) at their

Table 1. Demographic and Clinical Characteristics of the 165 Perinatally HIV-Infected Children in the Study Population

Characteristic	Total (n=165)
Current* age, median (q1, q3), y	16.7 (15.9, 17.8)
Female, n (%)	84 (51)
Race/ethnicity, n (%)	
White/other	12 (7)
Black	113 (68)
Hispanic	39 (24)
Missing	1 (1)
Current* CD4 count, n (%)	
<200 cells/mm^3	19 (12)
200–500 cells/mm^3	46 (28)
>500 cells/mm^3	94 (57)
Missing	6 (4)
Nadir CD4 count, n (%)	
<200 cells/mm^3	68 (41)
200–500 cells/mm^3	81 (49)
>500 cells/mm^3	16 (10)
Current* HIV viral load, n (%)	
≤400 copies/mL	98 (59)
401–5000 copies/mL	25 (15)
>5000 copies/mL	35 (21)
Missing	7 (4)
Peak HIV viral load, copies/mL, n (%)	
<10 000 copies/mL	7 (4)
10 000–100 000 copies/mL	45 (27)
>100 000 copies/mL	113 (68)
Current* CDC category, n (%)	
N/A	59 (36)
B	55 (33)
C	51 (31)
HAART	
Current* use, n (%)	143 (87)
Ever use, n (%)	160 (97)
Cumulative duration of use, median (q1, q3), y	11.0 (7.7, 12.5)
Boosted protease inhibitor	
Current* use, n (%)	95 (58)
Ever use, n (%)	122 (74)
Cumulative duration of use, median (q1, q3), y	4.0 (0.0, 7.4)
Lopinavir/ritonavir	
Current* use, n (%)	48 (29)
Ever use, n (%)	95 (58)
Cumulative duration of use, median (q1, q3), y	1.4 (0.0, 4.8)
Indinavir	
Current* use, n (%)	0 (0)
Ever use, n (%)	18 (11)
Cumulative duration of use, median (q1, q3), y	0.0 (0.0, 0.0)
Didanosine	
Current* use, n (%)	17 (10)
Ever use, n (%)	138 (84)
Cumulative duration of use, median (q1, q3), y	3.3 (1.0, 7.1)
Abacavir	
Current* use, n (%)	46 (28)
Ever use, n (%)	79 (48)
Cumulative duration of use, median (q1, q3), y	0.0 (0.0, 3.3)
Stavudine	
Current* use, n (%)	11 (7)
Ever use, n (%)	136 (82)
Cumulative duration of use, median (q1, q3), y	6.1 (1.8, 8.5)
Zidovudine	
Current* use, n (%)	18 (11)
Ever use, n (%)	145 (88)
Cumulative duration of use, median (q1, q3), y	3.7 (1.6, 7.4)
Lamivudine	
Current* use, n (%)	53 (32)
Ever use, n (%)	149 (90)
Cumulative duration of use, median (q1, q3), y	5.7 (2.8, 9.4)
Tenofovir disoproxil fumarate	
Current* use, n (%)	80 (48)
Ever use, n (%)	100 (61)
Cumulative duration of use, median (q1, q3), y	0.9 (0.0, 3.2)

CDC indicates Centers for Disease Control and Prevention (N/A, not/mildly symptomatic; B, moderately symptomatic; C, severely symptomatic/AIDS definition); HAART, highly active antiretroviral therapy; q1, quartile 1; and q3, quartile 3.

*Current is defined as the measurement at the most recent visit.

most recent visit with a PDAY score (Table 1). Forty-nine percent were male. Sixty-eight percent were self-identified as black and 24% as Hispanic. At their most recent visit with a PDAY score, the majority (57%) of the adolescents had CD4 counts >500 cells/mm^3, but a large proportion (41%) had a history of immunosuppression as evidenced by a low nadir CD4 count (<200 cells/mm^3). A similar pattern of disease severity over time was observed with HIV viral load in which 59% of the study population was virologically suppressed (≤400 copies/mL) at their most recent visit, but 68% had a history of viral load >100 000 copies/mL. Almost all of the adolescents had prior HAART exposure (97%). Seventy-four percent had been exposed to a boosted protease inhibitor regimen, with 58% currently on a boosted protease inhibitor as of their most recent visit.

Figure 1 shows the distribution of the most recent CA and AA scores in the study population. Forty-eight percent had CA scores ≥1, with 24%, 16%, and 12% having CA scores ≥2, ≥3, and ≥4, respectively. High CA scores were attributed primarily to increased levels of non-HDL cholesterol, with additional risk from low levels of HDL cholesterol and high body mass index (Table 2 and Table II in the online-only Data Supplement). Few adolescents were defined as hypertensive (1%) or hyperglycemic (1%), and none were defined as heavy smokers. Two adolescents with CA scores ≥10 had elevated levels of non-HDL cholesterol in the range of 160 to 189 mg/dL and were obese (body mass index >30 kg/m^2). Twenty-four percent of the study population had AA scores ≥1. Ten percent,

3%, and 1% had AA scores ≥2, ≥3, and ≥4, respectively. High AA scores were also attributable primarily to dyslipidemia.

Univariable predictors of CA scores ≥1 versus ≤0 at the $P<0.10$ level included male sex, Centers for Disease Control and Prevention category C disease (AIDS-defining conditions), current use of a boosted protease inhibitor, prior use of a boosted protease inhibitor, longer cumulative duration of boosted protease inhibitor use, current use of lopinavir/ritonavir, prior use of lopinavir/ritonavir, and no prior use of tenofovir (Table 3 and Table III in the online-only Data Supplement). Current use, ever use, and duration of use of a boosted protease inhibitor and current and ever use of lopinavir/ritonavir are highly correlated. Thus, the one with the highest c statistic was entered into the final multivariable model. Male sex, Centers for Disease Control and Prevention category C disease (relative to category B), longer cumulative duration of boosted protease inhibitor use, and no prior use of tenofovir were all significant predictors of CA scores ≥1 at $P<0.05$ with a final model c statistic of 0.74 (Table 4). Results were consistent among the virologically suppressed subset of the population (Table IV in the online-only Data Supplement).

Univariable predictors of AA scores ≥1 versus 0 at the $P<0.10$ level included current HIV viral load ≤400 copies/mL, Centers for Disease Control and Prevention category C disease, current HAART use, current and prior use of a boosted protease inhibitor, a longer cumulative duration of boosted protease inhibitor use, current and prior use of lopinavir/ritonavir, a longer cumulative duration of lopinavir/ritonavir use, current abacavir use, current lamivudine use, and no prior tenofovir use (Table 3). In the final model, current HIV virological suppression (≤400 versus 401–5000 copies/mL), Centers for Disease Control and Prevention clinical category C disease (relative to category B), and longer cumulative duration of boosted protease inhibitor use significantly predicted AA scores ≥1 at $P<0.05$ with a total model c statistic of 0.84 (Table 5). Results of sensitivity analyses were consistent with those observed in the overall population (Table V in the online-only Data Supplement).

Figure 2 shows the mean PDAY scores during the 4-year study follow-up period (mean follow-up of study population, 2.5 years). The slope of the CA scores was 0.10 per year and did not change significantly over time (95% confidence interval, −0.05 to 0.24; $P=0.19$). AA scores were also stable over time, with a slope of 0.03 per year (95% confidence interval, −0.03 to 0.08; $P=0.34$).

Discussion

Previous studies of perinatally HIV-infected children raised concern about increased CVD risk resulting from distributions of individual risk factors in this population.[7–15] Our study uniquely sought to measure and describe aggregate CVD risk resulting from the combination of risk factors in perinatally HIV-infected youth by using the validated PDAY scoring system, which integrates individual risk factors into a single score for the CA and AA. Forty-eight percent of perinatally HIV-infected youth had high scores, with 12% having scores associated with combinations of dyslipidemia plus high individual score risk factors such as obesity, high blood pressure, and hyperglycemia.

Twenty-two percent of our study population had non-HDL cholesterol levels ≥130 mg/dL, and 29% had HDL cholesterol <40 mg/dL. These findings are consistent with the high prevalence of dyslipidemia observed in perinatally HIV-infected cohorts compared with national youth estimates.[7–10,13,30] The prevalence of obesity in our study population was 13%, which is lower than the 18% prevalence of obesity recently reported among adolescents in the United States.[31] This is consistent with previous studies.[9,10] However, a recent study showed that HIV-infected children have trends in obesity similar to those of the general population.[32] The combination of dyslipidemia and obesity in the perinatally HIV-infected population would further the concern for premature atherosclerotic CVD.

Male participants in our study population were more likely to have high CA scores compared with female participants. Among studies of CVD risk factors that evaluated sex differences among perinatally HIV-infected adolescents, 1 study found significantly higher cholesterol levels in male relative to

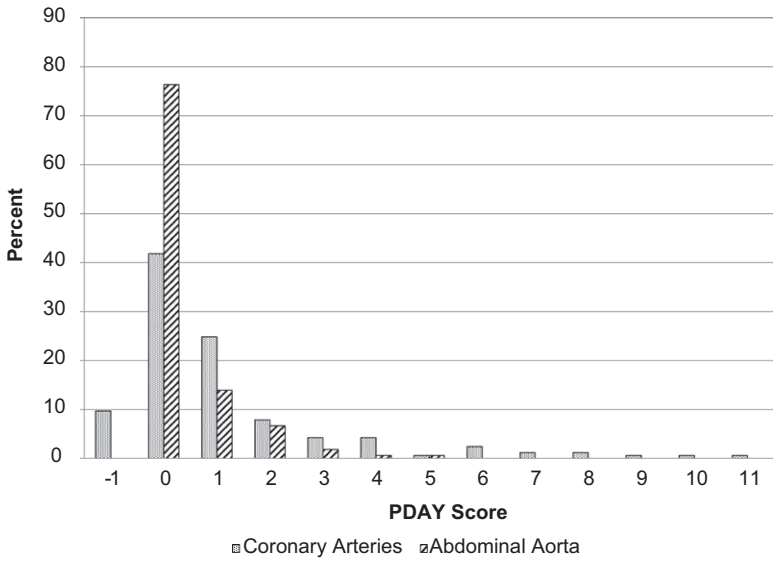

Figure 1. Distribution of Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk scores in the study population.

Table 2. Distribution of Modifiable Atherosclerotic Risk Factors Included in the PDAY Scoring System Among the 165 Perinatally HIV-Infected Children in the Study Population at Their Most Recent Visit With a PDAY Score

Modifiable Risk Factor	Coronary Arteries Points*	Abdominal Aorta Points*	n (%)
Non-HDL cholesterol			
<130, mg/dL	0	0	128 (78)
130–159, mg/dL	2	1	24 (14)
160–189, mg/dL	4	2	12 (7)
190–219, mg/dL	6	3	1 (1)
≥220, mg/dL	8	4	0 (0)
HDL cholesterol			
<40, mg/dL	1	0	48 (29)
40–59, mg/dL	0	0	96 (58)
≥60, mg/dL	–1	0	21 (13)
Heavy smoking†			
No	0	0	165 (100)
Yes	1	4	0 (0)
Blood pressure‡			
Not hypertensive	0	0	163 (99)
Hypertensive	4	3	2 (1)
Body mass index (obesity)			
Male			
≤30, kg/m^2	0	0	74 (45)
>30, kg/m^2	6	0	7 (4)
Female			
≤30, kg/m^2	0	0	70 (42)
>30, kg/m^2	0	0	14 (9)
Glycemia§			
Not hyperglycemic	0	0	163 (99)
Hyperglycemic	5	3	2 (1)

BMI indicates body mass index; HDL, high-density lipoprotein; and PDAY, Pathobiological Determinants of Atherosclerosis in Youth.

*Adapted from McMahan et al 2005.[18] Copyright © 2005, American Medical Association. All rights reserved.

†Heavy smoking was defined as smoking an average of at least 1 pack per day in the past 3 months.

‡Hypertensive was defined as an average systolic or diastolic blood pressure ≥95th percentile for age, sex, and height at ≥3 visits.

§Hyperglycemic was defined as a fasting plasma glucose concentration ≥126 mg/dL, a diagnosis of diabetes mellitus, or the use of diabetes medication.

female participants.[7] Three studies found no sex differences in lipodystrophy or insulin resistance,[12–14] whereas 3 other studies found female participants to have a body fat distribution associated with increased CVD risk.[10,11] Independent of their CVD risk resulting from traditional risk factors, male participants had a higher risk of having a lesion in the CA compared with female participants in the PDAY study.[18]

A history of an AIDS-defining event also predicted higher PDAY scores in our study. Low levels of HDL cholesterol, often associated with inflammation and endothelial activation, are reported in HIV-infected adults with AIDS or untreated HIV infection.[33,34] In addition, independent of traditional CVD risk factors, HIV disease severity is correlated with higher levels of T-cell activation, which is further associated with the presence of subclinical carotid artery lesions.[35] In our study, suppressed HIV viral loads also predicted high PDAY scores for the AA relative to HIV viral loads in the range of 401 to 5000 copies/mL. These effects may reflect toxicities associated with exposure to antiretroviral medications because children currently on effective therapy are likely to have suppressed viral loads. Our observation is also consistent with studies among HIV-infected adults that show that the risk for vascular disease with ongoing inflammation is still increased in the presence of viral suppression.[35]

As expected from prior studies in HIV-infected youth,[7–15] boosted protease inhibitor use was a strong predictor of high CA and AA scores in our study population. Protease inhibitors promote hyperlipidemia by upregulating fatty acid and cholesterol biosynthesis and secretion and by increasing lipoprotein production in the liver.[36] Protease inhibitors can also suppress leptin expression and glucose transporter type 4 activity in adipocytes, thereby promoting lipodystrophy, insulin resistance, and diabetes mellitus.[36] Although 5 to 8 years of exposure to boosted protease inhibitors predicted high CA

Table 3. Univariable Predictors of PDAY Risk Scores Among the 165 Perinatally HIV-Infected Children in the Study Population at Their Most Recent Visit

	Coronary Arteries PDAY Score				Abdominal Aorta PDAY Score			
Characteristic	≤0 (n=85)	≥1 (n=80)	*P* Value*	c Statistic	0 (n=126)	≥1 (n=39)	*P* Value*	c Statistic
Female, n (%)	50 (59)	34 (43)	0.04	0.58			NS	
Current† HIV viral load, n (%)							0.01	0.64
≤400 copies/mL			NS		68 (54)	30 (77)		
401–5000 copies/mL					24 (19)	1 (3)		
>5000 copies/mL					29 (23)	6 (15)		
Missing					5 (4)	2 (5)		
Current† CDC category, n (%)			0.05	0.60			0.06	0.61
N/A	33 (39)	26 (33)			47 (37)	12 (31)		
B	33 (39)	22 (28)			46 (37)	9 (23)		
C	19 (22)	32 (40)			33 (26)	18 (46)		
HAART								
Current† use, n (%)			NS		105 (83)	38 (97)	0.03	0.57
Boosted protease inhibitor								
Current† use, n (%)	41 (48)	54 (68)	0.02	0.60	63 (50)	32 (82)	<0.01	0.66
Ever use, n (%)	56 (66)	66 (83)	0.02	0.58	88 (70)	34 (87)	0.04	0.59
Cumulative duration of use, median (q1, q3), y	2.8 (0.0, 7.5)	4.8 (1.3, 7.3)	0.09	0.63	3.2 (0.0, 7.3)	6.0 (4.5, 8.2)	<0.01	0.71
Lopinavir/ritonavir								
Current† use, n (%)	18 (21)	30 (38)	0.03	0.58	26 (21)	22 (56)	<0.01	0.68
Ever use, n (%)	42 (49)	53 (66)	0.04	0.58	66 (52)	29 (74)	0.02	0.61
Cumulative duration of use, median (q1, q3), y			NS		0.4 (0.0, 4.1)	4.5 (0.0, 6.8)	<0.01	0.66
Abacavir								
Current† use, n (%)			NS		29 (23)	17 (44)	0.02	0.60
Lamivudine								
Current† use, n (%)			NS		35 (28)	18 (46)	0.05	0.59
Tenofovir disoproxil fumarate								
Ever use, n (%)	58 (68)	42 (53)	0.06	0.58	81 (64)	19 (49)	0.09	0.58

CDC indicates Centers for Disease Control and Prevention (N/A, not/mildly symptomatic; B, moderately symptomatic; C, severely symptomatic/AIDS definition); HAART: highly active antiretroviral therapy; NS, not significant at $P<0.10$; and PDAY, Pathobiological Determinants of Atherosclerosis in Youth.

*Wilcoxon test *P* value for continuous variables and the Fisher exact test *P* value for categorical variables.

†Current is defined as the measurement at the most recent visit.

and AA scores, >8 years of exposure did not. This may be attributable to a lack of power to observe a significant effect resulting from few observed events among those with >8 years of exposure. Alternatively, our results may reflect the clinician practice of switching children with preliminary indications of hyperlipidemia from boosted protease inhibitors to more lipid-friendly regimens.

A recent study of HIV-infected adults found that tenofovir was significantly associated with the progression of subclinical atherosclerosis, mediated perhaps through the lack of reduction in plasma monocyte chemotactic protein 1 levels relative to therapy with abacavir and lamivudine.[6] Among our population of perinatally HIV-infected adolescents, however, tenofovir use predicted a lower likelihood of having high CA scores, consistent with other studies among HIV-infected adults showing improvement in dyslipidemia and arterial stiffness with nucleoside reverse transcriptase inhibitor switches to tenofovir.[37] With these contrasting results, the association between tenofovir and CVD requires further investigation.

Over our 4-year study follow-up, there were no significant changes in CA or AA scores. We may be observing the consistent tracking of CVD risk factors over time, or the duration of follow-up of our cohort may not have been sufficiently long to observe the acquisition of more adult lifestyle risk factors such as smoking and physical inactivity. Continued follow-up of adolescents in our study as they age into adulthood is necessary to better evaluate longitudinal trends in CVD risk and to identify associated factors.

Our study had some limitations. We were unable to validate the PDAY scoring system against noninvasive measures of atherosclerosis or CVD events. The Adolescent Master Protocol did not include these measures, and there is a low probability of observing CVD events in our relatively young study population. The CA and AA risk scores used in this study were developed from autopsy data, so the definitions

Table 4. Predictors of Coronary Arteries PDAY Risk Scores ≥1 Versus ≤0 Among the 165 Perinatally HIV-Infected Children in the Study Population at Their Most Recent Visit

Characteristic	Multivariable Odds Ratio (95% CI)	*P* Value
Sex		0.01
Male	2.47 (1.24–4.92)	
Female	Reference	
Current*,† CDC category		0.05
N/A	Reference	
B	0.67 (0.30–1.51)	
C	1.97 (0.84–4.60)	
Cumulative duration of boosted protease inhibitor use		0.04
0, y	Reference	
1–4, y	1.80 (0.70–4.64)	
5–8, y	3.97 (1.54–10.24)	
>8, y	1.75 (0.65–4.71)	
Ever tenofovir disoproxil fumarate use		0.02
Yes	0.43 (0.22–0.87)	
No	Reference	

CDC indicates Centers for Disease Control and Prevention (N/A, not/mildly symptomatic; B, moderately symptomatic; C, severely symptomatic/AIDS definition); CI, confidence interval; and PDAY, Pathobiological Determinants of Atherosclerosis in Youth.

*Current is defined as the measurement at the most recent visit.

†A significant association was seen for current CDC category C relative to category B (multivariable odds ratio, 2.94; 95% CI, 1.23–7.05).

Table 5. Predictors of Abdominal Aorta PDAY Risk Scores ≥1 Versus 0 Among the 165 Perinatally HIV-Infected Children in the Study Population at Their Most Recent Visit

Characteristic	Multivariable Odds Ratio (95% CI)	*P* Value
Current* HIV viral load		0.04
≤400, copies/mL	Reference	
401–5000, copies/mL	0.08 (0.01–0.67)	
>5000, copies/mL	0.45 (0.14–1.40)	
Current*† CDC category		0.04
N/A	Reference	
B	0.30 (0.09–1.02)	
C	1.37 (0.49–3.82)	
Cumulative duration of boosted protease inhibitor use		<0.01
0, y	Reference	
1–4, y	0.70 (0.15–3.28)	
5–8, y	5.85 (1.62–21.17)	
>8, y	3.82 (0.92–15.78)	
Current* abacavir use		0.30
Yes	1.77 (0.60–5.27)	
No	Reference	
Current* lamivudine use		0.21
Yes	2.19 (0.65–7.43)	
No	Reference	
Ever tenofovir disoproxil fumarate use		0.57
Yes	0.75 (0.28–2.03)	
No	Reference	

CDC indicates Centers for Disease Control and Prevention (N/A, not/mildly symptomatic; B, moderately symptomatic; C, severely symptomatic/AIDS definition); CI, confidence interval; and PDAY, Pathobiological Determinants of Atherosclerosis in Youth.

*Current is defined as the measurement at the most recent visit.

†A significant association was seen for current CDC category C relative to category B (multivariable odds ratio, 4.59; 95% CI, 1.42–14.78).

of some of the risk factors (eg, hypertension) were adapted using measures available in clinical practice. The difference in definitions, therefore, may not directly correlate with the odds ratio interpretations of the PDAY risk scores as stated by McMahan et al.[18] We used the PDAY score as an estimate of the aggregate atherosclerotic CVD risk in our population. The PDAY score, however, may underestimate the risk of atherosclerotic lesions in this population because of the independent effects of HIV and antiretroviral therapy on the development and progression of atherosclerosis.[35] Studies among HIV-infected adults suggest that risk scores incorporating both traditional and HIV-specific parameters may better predict CVD risk in HIV-infected populations.[38,39] Although our study has a relatively small sample size compared with other studies that have used PDAY scores,[22–24] it represents an understudied population of perinatally HIV-infected youth aging into young adulthood.

Conclusions

A substantial proportion of perinatally HIV-infected adolescents have PDAY scores reflecting increased aggregate atherosclerotic risk factor burden. PDAY scores may be useful

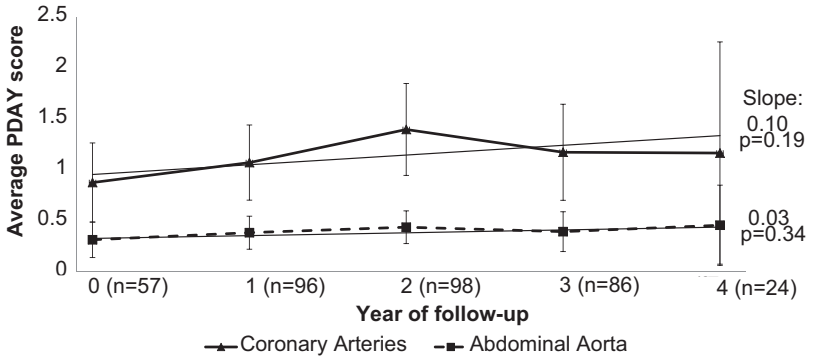

Figure 2. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk scores over the study follow-up.

in identifying and tracking such high-risk adolescents. Our findings suggest that lifestyle modifications (eg, diet and exercise) and switching to new antiretroviral regimens less likely to cause metabolic abnormalities should be considered.[40] Finally, our study contributes to growing literature showing increased global risk for premature CVD disease morbidity and mortality in the perinatally HIV-infected population, including risk of cardiomyopathy and cardiometabolic disease.[7–15,41,42] A comprehensive assessment and treatment plan based on validated screening and interventions may be useful for those at highest risk in the perinatally HIV-infected population.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Previous studies of perinatally HIV-infected children and adolescents raised concern about increased or accelerated risk of cardiovascular disease resulting from adverse distributions of individual atherosclerotic risk factors such as hyperlipidemia, insulin resistance, and body fat. For the first time, composite cardiovascular risk scores have been calculated for these HIV-infected youth using the previously validated Pathobiological Determinants of Atherosclerosis in Youth (PDAY) scoring system. These aggregate scores integrate a number of modifiable cardiovascular disease risk factors such as dyslipidemia, smoking, hypertension, obesity, and hyperglycemia. Forty-eight percent and 24% of our youth had high coronary arteries and abdominal aorta PDAY scores, respectively, identifying high-risk youth who may benefit from early lifestyle or clinical interventions. We additionally found HIV disease severity and ritonavir-boosted protease inhibitor use to significantly predict high scores, suggesting that switching to new antiretroviral regimens less likely to cause metabolic abnormalities should be considered for youth with increased atherosclerotic risk factor burden. Finally, our study contributes to growing literature showing increased global risk for premature cardiovascular disease morbidity and mortality in the perinatally HIV-infected population, including risk of cardiomyopathy, leading to heart failure, and risk of cardiometabolic disease, leading to atherosclerotic disease. A comprehensive assessment and treatment plan based on validated screening and interventions may be useful for those at highest cardiovascular disease risk in the perinatally HIV-infected population.

Aggregate Risk of Cardiovascular Disease Among Adolescents Perinatally Infected With the Human Immunodeficiency Virus

Kunjal Patel, Jiajia Wang, Denise L. Jacobson, Steven E. Lipshultz, David C. Landy, Mitchell E. Geffner, Linda A. DiMeglio, George R. Seage III, Paige L. Williams, Russell B. Van Dyke, George K. Siberry, William T. Shearer, Luciana Young, Gwendolyn B. Scott, James D. Wilkinson, Stacy D. Fisher, Thomas J. Starc and Tracie L. Miller
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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Enrollment characteristics of youth ≥ 15 years of age at their most recent visit in AMP, by inclusion in final study population.

Characteristic	Included n=165	Excluded n=60
Age, years		
Mean (SD)	13.8 (1.1)	12.3 (1.4)
Race/ethnicity, n (%)		
White/Other	12 (7)	4 (7)
Black	113 (64)	38 (63)
Hispanic	39 (24)	18 (30)
Missing	1 (1)	0 (0)
Female, n (%)	84 (51)	32 (53)
CD4 count, cells/mm^3		
Mean (SD)	626 (317)	747 (366)
Missing	19	5
HIV RNA, copies/mL		
Median (Q1, Q3)	400 (50, 2710)	400 (75, 1320)
Missing	2	1

Of the 451 youth enrolled in the original AMP protocol, 225 were in the validated age range for the PDAY score. 165 of the 225 had the necessary data to calculate PDAY scores. Comparison of demographic and clinical characteristics at enrollment between the 165 youth in our study population and the 60 youth who were excluded due to missing outcome information is presented above. Those excluded from the study population were younger and had higher CD4 counts than those included in the study population. Please note that while a difference was observed in CD4 count between those included and excluded in the study population, the mean CD4 counts for both groups were within normal ranges.

Supplemental Table 2. Distribution of modifiable atherosclerotic risk factors by PDAY scores.

Risk Factor	Total n=165	CA Scores Low n=85	CA Scores High n=80	AA Scores Low n=126	AA Scores High n=39
Modifiable risk factors, n (%)					
Non-HDL cholesterol, mg/dL					
<130	128 (78)	85 (100)	43 (54)	126 (100)	2 (5)
130-159	24 (14)	0 (0)	24 (30)	0 (0)	24 (61)
160-189	12 (7)	0 (0)	12 (15)	0 (0)	12 (31)
190-219	1 (1)	0 (0)	1 (1)	0 (0)	1 (3)
≥220	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HDL cholesterol, mg/dL					
<40	48 (29)	0 (0)	48 (60)	40 (32)	8 (20)
40-59	96 (58)	69 (81)	27 (34)	70 (55)	26 (67)
≥60	21 (13)	16 (19)	5 (6)	16 (13)	5 (13)
Heavy smoking[†]					
No	165 (100)	85 (100)	80 (100)	126 (100)	39 (100)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Blood pressure[‡]					
Not hypertensive	163 (99)	85 (100)	78 (98)	126 (100)	37 (95)
Hypertensive	2 (1)	0 (0)	2 (2)	0 (0)	2 (5)
Obesity (BMI), kg/m^2					
Male					
≤30	74 (45)	35 (41)	39 (49)	56 (44)	18 (46)
>30	7 (4)	0 (0)	7 (9)	3 (2)	4 (10)
Female					
≤30	70 (42)	38 (45)	32 (40)	55 (44)	15 (39)
>30	14 (9)	12 (14)	2 (2)	12 (10)	2 (5)
Glycemia[§]					
Not hyperglycemic	163 (99)	85 (0)	78 (98)	126 (0)	37 (95)
Hyperglycemic	2 (1)	0 (0)	2 (2)	0 (0)	2 (5)

[*]Adapted from McMahan *et al*. 2005.[18]

[†]A heavy smoker was defined as smoking an average of at least one pack/day in the past 3 months.

[‡]Hypertensive was defined as an average systolic and/or diastolic blood pressure ≥95th percentile for age, sex, and height at three or more visits.

[§]Hyperglycemic was defined as a fasting plasma glucose concentration ≥126 mg/dL, a diagnosis of diabetes, or using diabetes medication.

HDL: high-density lipoprotein, BMI: body mass index

Supplemental Table 3. Demographic and clinical characteristics of the 165 perinatally HIV-infected children in the study population stratified by PDAY risk score at their most recent visit.

Characteristic	Total (n=165)	Coronary Arteries PDAY Score ≤0 (n=85)	Coronary Arteries PDAY Score ≥1 (n=80)	P*	Abdominal Aorta PDAY Score 0 (n=126)	Abdominal Aorta PDAY Score ≥1 (n=39)	P*
Current† age, years, median (q1, q3)	16.7 (15.9, 17.8)	16.7 (15.7, 17.5)	16.8 (16.1, 17.9)	0.12	16.7 (15.8, 17.7)	17.1 (15.9, 18.1)	0.19
Female, n (%)	84 (51%)	50 (59%)	34 (43%)	0.04	67 (53%)	17 (44%)	0.36
Race/Ethnicity, n (%)				0.34			0.72
White/Other	12 (7%)	7 (8%)	5 (6%)		9 (7%)	3 (8%)	
Black	113 (68%)	61 (72%)	52 (65%)		88 (70%)	25 (64%)	
Hispanic	39 (24%)	16 (19%)	23 (29%)		28 (22%)	11 (28%)	
Missing	1 (1%)	1 (1%)	0 (0%)		1 (1%)	0 (0%)	
Current† CD4 count, cells/mm^3, n (%)				0.59			0.20
<200	19 (12%)	8 (9%)	11 (14%)		15 (12%)	4 (10%)	
200-500	46 (28%)	26 (31%)	20 (25%)		39 (31%)	7 (18%)	
>500	94 (57%)	49 (58%)	45 (56%)		67 (53%)	27 (69%)	
Missing	6 (4%)	2 (2%)	4 (5%)		5 (4%)	1 (3%)	
Nadir CD4 count, cells/mm^3, n (%)				0.95			0.93
<200	68 (41%)	34 (40%)	34 (43%)		51 (40%)	17 (44%)	
200-500	81 (49%)	43 (51%)	38 (48%)		62 (49%)	19 (49%)	
>500	16 (10%)	8 (9%)	8 (10%)		13 (10%)	3 (8%)	
Current† viral load, copies/mL, n (%)				0.65			0.01
≤400	98 (59%)	49 (58%)	49 (61%)		68 (54%)	30 (77%)	
401-5,000	25 (15%)	15 (18%)	10 (13%)		24 (19%)	1 (3%)	
>5,000	35 (21%)	17 (20%)	18 (23%)		29 (23%)	6 (15%)	
Missing	7 (4%)	4 (5%)	3 (4%)		5 (4%)	2 (5%)	
Peak viral load, copies/mL, n (%)				0.96			0.28
<10,000	7 (4%)	4 (5%)	3 (4%)		4 (3%)	3 (8%)	
10,000-100,000	45 (27%)	24 (28%)	21 (26%)		37 (29%)	8 (21%)	
>100,000	113 (68%)	57 (67%)	56 (70%)		85 (67%)	28 (72%)	
Current† CDC category, n (%)				0.05			0.06
N/A	59 (36%)	33 (39%)	26 (33%)		47 (37%)	12 (31%)	
B	55 (33%)	33 (39%)	22 (28%)		46 (37%)	9 (23%)	
C	51 (31%)	19 (22%)	32 (40%)		33 (26%)	18 (46%)	
HAART							
Current† use, n (%)	143 (87%)	72 (85%)	71 (89%)	0.50	105 (83%)	38 (97%)	0.03

Characteristic	Total (n=165)	Coronary Arteries PDAY Score ≤0 (n=85)	Coronary Arteries PDAY Score ≥1 (n=80)	P*	Abdominal Aorta PDAY Score 0 (n=126)	Abdominal Aorta PDAY Score ≥1 (n=39)	P*
Ever use, n (%)	160 (97%)	81 (95%)	79 (99%)	0.37	121 (96%)	39 (100%)	0.59
Cumulative duration of use, years, median (q1, q3)	11.0 (7.7, 12.5)	10.9 (7.6, 12.6)	11.3 (8.2, 12.5)	0.81	10.8 (7.6, 12.6)	11.3 (8.2, 12.4)	0.74
Boosted protease inhibitor							
Current† use, n (%)	95 (58%)	41 (48%)	54 (68%)	0.02	63 (50%)	32 (82%)	<.01
Ever use, n (%)	122 (74%)	56 (66%)	66 (83%)	0.02	88 (70%)	34 (87%)	0.04
Cumulative duration of use, years, median (q1, q3)	4.0 (0.0, 7.4)	2.8 (0.0, 7.5)	4.8 (1.3, 7.3)	0.09	3.2 (0.0, 7.3)	6.0 (4.5, 8.2)	<.01
Lopinavir/ritonavir							
Current† use, n (%)	48 (29%)	18 (21%)	30 (38%)	0.03	26 (21%)	22 (56%)	<.01
Ever use, n (%)	95 (58%)	42 (49%)	53 (66%)	0.04	66 (52%)	29 (74%)	0.02
Cumulative duration of use, years, median (q1, q3)	1.4 (0.0, 4.8)	0.0 (0.0, 4.6)	2.1 (0.0, 5.4)	0.11	0.4 (0.0, 4.1)	4.5 (0.0, 6.8)	<.01
Indinavir							
Current† use, n (%)	0 (0%)	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	1.00
Ever use, n (%)	18 (11%)	8 (9%)	10 (13%)	0.62	13 (10%)	5 (13%)	0.77
Cumulative duration of use, years, median (q1, q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.61	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.73
Didanosine							
Current† use, n (%)	17 (10%)	8 (9%)	9 (11%)	0.80	12 (10%)	5 (13%)	0.55
Ever use, n (%)	138 (84%)	74 (87%)	64 (80%)	0.29	105 (83%)	33 (85%)	1.00
Cumulative duration of use, years, median (q1, q3)	3.3 (1.0, 7.1)	2.7 (1.0, 7.5)	3.7 (1.1, 6.4)	0.89	2.9 (0.9, 7.2)	3.9 (2.0, 6.6)	0.26
Abacavir							
Current† use, n (%)	46 (28%)	23 (27%)	23 (29%)	0.86	29 (23%)	17 (44%)	0.02
Ever use, n (%)	79 (48%)	38 (45%)	41 (51%)	0.44	58 (46%)	21 (54%)	0.46
Cumulative duration of use, years, median (q1, q3)	0.0 (0.0, 3.3)	0.0 (0.0, 2.7)	0.1 (0.0, 4.3)	0.18	0.0 (0.0, 2.7)	0.4 (0.0, 5.6)	0.11
Stavudine							
Current† use, n (%)	11 (7%)	5 (6%)	6 (8%)	0.76	9 (7%)	2 (5%)	1.00
Ever use, n (%)	136 (82%)	69 (81%)	67 (84%)	0.69	104 (83%)	32 (82%)	1.00
Cumulative duration of use, years, median (q1, q3)	6.1 (1.8, 8.5)	6.5 (1.5, 8.5)	5.7 (2.8, 8.5)	0.85	6.1 (1.7, 8.5)	5.6 (3.0, 8.5)	0.99
Zidovudine							
Current† use, n (%)	18 (11%)	7 (8%)	11 (14%)	0.32	11 (9%)	7 (18%)	0.14

Characteristic	Total (n=165)	Coronary Arteries PDAY Score ≤0 (n=85)	Coronary Arteries PDAY Score ≥1 (n=80)	P*	Abdominal Aorta PDAY Score 0 (n=126)	Abdominal Aorta PDAY Score ≥1 (n=39)	P*
Ever use, n (%)	145 (88%)	76 (89%)	69 (86%)	0.64	111 (88%)	34 (87%)	1.00
Cumulative duration of use, years, median (q1, q3)	3.7 (1.6, 7.4)	3.7 (1.7, 7.5)	3.8 (1.4, 7.4)	0.94	3.6 (1.5, 7.5)	3.9 (1.9, 7.4)	0.78
Lamivudine							
Current† use, n (%)	53 (32%)	25 (29%)	28 (35%)	0.51	35 (28%)	18 (46%)	0.05
Ever use, n (%)	149 (90%)	77 (91%)	72 (90%)	1.00	112 (89%)	37 (95%)	0.36
Cumulative duration of use, years, median (q1, q3)	5.7 (2.8, 9.4)	5.7 (3.9, 9.6)	6.1 (2.2, 9.2)	0.54	6.1 (2.8, 9.4)	4.9 (2.1, 10.7)	0.64
Tenofovir disoproxil fumarate							
Current† use, n (%)	80 (48%)	45 (53%)	35 (44%)	0.28	64 (51%)	16 (41%)	0.36
Ever use, n (%)	100 (61%)	58 (68%)	42 (53%)	0.06	81 (64%)	19 (49%)	0.09
Cumulative duration of use, years, median (q1, q3)	0.9 (0.0, 3.2)	1.0 (0.0, 3.0)	0.8 (0.0, 3.3)	0.44	1.0 (0.0, 3.3)	0.0 (0.0, 3.1)	0.23

*Wilcoxon Test p-value for continuous variables and Fisher's Exact Test p-value for categorical variables.

†Current defined as measurement at most recent visit.

CDC: Centers for Disease Control and Prevention (N/A: not/mildly symptomatic, B: moderately symptomatic, C: severely symptomatic (AIDS definition)), HAART: highly active antiretroviral therapy.

Sensitivity analyses restricting our population to treated and suppressed children are presented below. Our study population decreased to N=98 children who were virologically suppressed (VL ≤ 400 copies/mL). The prevalence of high CA and AA scores in this subset was 50% (N=49 with CA scores ≥1) and 31% (N=30 with AA scores ≥1), respectively. As expected given observed associations between PI exposure and CVD risk factors, the prevalence of high PDAY scores in the virologically suppressed subset was larger than the prevalence observed in the overall study population (48% with high CA scores and 24% with high AA scores in the overall study population, N=165).

Supplemental Table 4. Predictors of coronary arteries PDAY risk scores ≥1 versus ≤0 among the 98 virologically suppressed perinatally HIV-infected children in the study population at their most recent visit.

Characteristic	Multivariable Odds Ratio (95% CI)	P
Sex		0.02
Male	3.05 (1.24, 7.54)	
Female	Reference	
Current*,† CDC category		0.03
N/A	Reference	
B	0.53 (0.18, 1.52)	
C	2.37 (0.83, 6.79)	
Current lopinavir/ritonavir use*		0.05
Yes	2.54 (1.02, 6.34)	
No	Reference	

*Current defined as measurement at most recent visit.
†A significant association was seen for current CDC category C relative to category B - multivariable odds ratio (95% CI): 4.49 (1.45, 13.91).

CDC: Centers for Disease Control and Prevention (N/A: not/mildly symptomatic, B: moderately symptomatic, C: severely symptomatic (AIDS definition)).

- Consistent with the results observed in the overall study population, male sex and having an AIDS indicator condition (CDC C category), predicted high CA scores. Instead of duration of boosted PI use however, current use of lopinavir/ritonavir was a stronger predictor of high CA scores in the virologically suppressed subset. Tenofovir use also did not significantly predict high CA scores in the virologically suppressed sub-population, which is still in contrast to the recent study highlighted in the discussion section finding tenofovir to be significantly associated with progression of subclinical atherosclerosis among HIV-infected adults.

Supplemental Table 5. Predictors of abdominal aorta PDAY risk scores ≥1 versus 0 among the 98 virologically suppressed perinatally HIV-infected children in the study population at their most recent visit.

Characteristic	Multivariable Odds Ratio (95% CI)	P
Cumulative duration of boosted protease inhibitor use, years		0.03
0	Reference	
1-4	0.63 (0.13, 3.08)	
5-8	4.33 (1.23, 15.26)	
>8	2.35 (0.57, 9.76)	
Current* abacavir use		0.03
Yes	3.06 (1.13, 8.25)	
No	Reference	

*Current defined as measurement at most recent visit.

- Consistent with the results observed in the overall study population, a longer duration of boosted PI use significantly predicted high AA scores. However, in the virologically suppressed subset, CDC category did not significantly predict high AA scores, suggesting that the effect of past HIV severity may be mitigated by subsequent use of ART. In the subset analysis, current abacavir use significantly predicted high AA scores. This finding is consistent with some studies in HIV-infected adults reporting increased rates of myocardial infarctions with abacavir use. We note, however, that the literature on the association between abacavir use and CVD is conflicting and would like to stress that our study was not aimed at specifically assessing this association, but rather it focused on identifying predictors of aggregate CVD risk measured at one point in time.