Cardio-Ankle Vascular Index Among Perinatally HIV-infected Thai Adolescents

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Background

- Cardiovascular disease (CVD) is a growing concern in the management of people living with HIV, including adolescents.
  - Several studies showed that cardiovascular death becomes the most common cause of death in this population.
  - Atherosclerosis is the most important pathophysiology.
- Factors contributing to CVD in HIV-infected individuals include HIV itself and antiretroviral therapy (ART)-related metabolic derangement.
  - Protease inhibitors are associated with dyslipidemia, insulin resistance, hyperglycemia, and central adiposity.
- Diagnostic measurements for atherosclerosis include many modalities.
  - The ideal tests should be simple, safe, not invasive, not expensive, and reproducible.
- Cardio-ankle vascular index (CAVI) is a very good and simple measurement for evaluating arterial stiffness, independent of blood pressure.
  - A previous study in HIV-infected Thai adults (mean age 42 years) showed that the prevalence of arterial stiffness (CAVI ≥9 m/s) was 38%.
- Yet, the data regarding CAVI in HIV-infected adolescents is scarce, particularly among those living in resource-limited countries.

Objective

- This study aimed to assess CAVI in perinatally HIV-infected Thai adolescents.

Methods

- **Study design:** A multicenter, cross-sectional study.
- **Study site:** 2 pediatric HIV centers in Thailand.
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Methods (Cont'd)

- **Study population:** 2 groups of participants were enrolled in the ratio of 3:1.
  - Group 1: Perinatally HIV-infected adolescents aged 10-25 years who received ART for ≥12 months.
  - Group 2: Healthy, HIV-uninfected adolescents who had age group and sex matched with HIV-infected participants.
- **Outcome measurements:**

Cardio-ankle vascular index (CAVI):





  - A measurement of pulse wave propagation time from heart to ankle.
  - Adding the pulse wave propagation from aortic valve single heart sound to the notch of brachial pulse wave to the propagation time from brachial to ankle.
  - Measured by the VaSera System™ (VS-1500, Fukuda Denshi, Japan) on both arms and legs.
  - An average value of the two sides represents CAVI for each adolescent.
  - CAVI ≥9 m/s defines arterial stiffness.

Metabolic profiles:

- Lipid profiles: cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG) levels.
- Fasting plasma glucose level.
- Fasting insulin level.
- **Definition:**
  - Risk for metabolic disorder was defined as having either (1) body mass index (BMI) ≥30 kg/m^2; (2) TG ≥ 150 mg/dL; (3) LDL-C ≥130 mg/dL; (4) HDL-C <40 mg/dL; (5) homeostasis model assessment of insulin resistance (HOMA-IR) >3.16.
- **Statistical analysis:**
  - Linear regression analysis was performed to identify factors associated with CAVI among HIV-infected adolescents.
  - Covariates with a P <0.1 in a univariable model were included in the multivariable analysis.

Results

- Between January and March 2017: 200 participants were enrolled, consisting of 150 HIV-infected and 50 healthy adolescents.
- Overall characteristics, HIV-related characteristics, and metabolic profiles of study participants are summarized in Table 1, Table 2, and Table 3, respectively.

Table 1. Overall characteristics of study participants (n = 200).

Characteristics[1]	HIV-infected adolescents (n = 150)	Healthy adolescents (n = 50)	P[2]
Demographic characteristics			
Age, years	17.8 (14.5-20.1)	18.0 (15.2-21.6)	0.23
Age ≥18 years	74 (49.3)	25 (50.0)	0.94
Male sex	75 (50.0)	25 (50.0)	0.99
Anthropometric measurements			
BMI, kg/m^2	19.3 (17.5-22.4)	21.2 (18.6-22.9)	0.02
BMI category			0.33
Underweight	32 (21.3)	6 (12.0)	
Normal weight	98 (64.0)	35 (70.0)	
Overweight/Obese	22 (14.7)	9 (18.0)	
Waist circumference, cm	69 (64.0-77.5)	72.3 (67.0-78.0)	0.05
Obesity[3]	18 (12.0)	4 (8.0)	0.43
Waist-to-hip ratio	0.8 (0.8-0.9)	0.8 (0.8-0.9)	0.01
Central obesity[4]	34 (22.7)	4 (8.0)	0.02
Systolic BP, mmHg	110 (103-118)	111 (105-120)	0.28
Diastolic BP, mmHg	66 (62-72)	64 (61-71)	0.27
Systemic hypertension	8 (5.3)	6 (12.0)	0.11
Lifestyle characteristics			
Smoking			0.01
Non-smoker	138 (92.0)	39 (78.0)	
Former smoker	0 (0)	2 (4.0)	
Current smoker	12 (8.0)	9 (18.0)	
Alcohol drinking			0.16
Non-drinker	120 (80.0)	34 (68.0)	
Former drinker	1 (0.7)	0 (0)	
Current drinker	29 (19.3)	16 (32.0)	

Abbreviations: BMI, body mass index; BP, blood pressure.
[1]Data presented as n (%) for categorical data and median (interquartile range) for continuous data.
[2]The comparisons were performed using Pearson Chi-square or Fisher's exact tests for categorical data, and Wilcoxon rank sum tests for continuous data.
[3]Obesity was defined as waist circumference Z-score >2 for adolescents aged <15 years, and waist circumference ≥80 cm and ≥90 cm for females and males aged ≥15 years, respectively.
[4]Central obesity was defined as waist-to-hip ratio Z-score >2 for adolescents aged <15 years, and waist-to-hip ratio >0.85 and >0.90 for females and males aged ≥15 years, respectively.

Table 2. HIV-related characteristics of perinatally HIV-infected participants (n = 150).

Characteristics[a]	HIV-infected adolescents (n = 150)
WHO clinical stage prior to ART initiation (n = 145)	
Stage 1-2	83 (57.2)
Stage 3-4	62 (42.8)
Nadir CD4 T-cell percentage, % (n = 116)	10 (2-16)
Zenith viral load, $\log_{10}$ copies/ml (n = 92)	5.3 (5.0-5.8)
Current WHO clinical stage	
Stage 1	148 (98.7)
Stage 2	2 (1.3)
Current ART regimens	
NNRTI-based	80 (53.4)
PI-based	65 (43.3)
Integrase inhibitor-based	5 (3.3)
Duration of ART, years	12.6 (9.2-14.2)
Current CD4 T-cell count, cells/mm^3	673 (521-907)
Current viral load, copies/ml	20 (20-40)

Abbreviations: ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; WHO, World Health Organization.
[a]Data presented as n (%) for categorical data and median (interquartile range) for continuous data.

Table 3. Metabolic profiles of study participants (n = 200).

Metabolic profiles[1]	HIV-infected adolescents (n = 150)	Healthy adolescents (n = 50)	P[2]
Cholesterol, mg/dl	175 (153-200)	174 (163-215)	0.35
Cholesterol ≥200 mg/dl	38 (25.3)	14 (28.0)	0.71
Triglyceride, mg/dl	106 (72-152)	62 (42-87)	<0.001
Triglyceride ≥150 mg/dl	39 (26.0)	4 (8.0)	0.01
HDL-cholesterol, mg/dl	45 (39-57)	55 (44-64)	<0.001
HDL-cholesterol <40 mg/dl	38 (25.3)	3 (6.0)	0.003
LDL-cholesterol, mg/dl	106 (87-130)	106 (96-126)	0.34
LDL-cholesterol ≥130 mg/dl	38 (25.3)	11 (22.0)	0.64
FPG ≥100 mg/dl	83 (78-88)	81 (76-85)	0.02
FPG ≥100 mg/dl	2 (1.3)	1 (2.0)	0.74
HOMA-IR	2.3 (1.5-3.3)	1.4 (1.0-1.7)	<0.001
HOMA-IR >3.16	45 (30.0)	4 (8.0)	0.002

Abbreviations: FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR: the homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.
[1]Data presented as n (%) for categorical data and median (interquartile range) for continuous data.
[2]The comparisons were performed using Pearson Chi-square or Fisher's exact tests for categorical data, and Wilcoxon rank sum tests for continuous data.

- The median CAVI (interquartile range; IQR) were 5.8 (5.6-6.2) m/s for HIV-infected adolescents, and 5.8 (5.4-6.3) m/s for healthy individuals (P = 0.48).
- Although there were no adolescents having arterial stiffness (CAVI ≥9 m/s) in this study, those with CAVI ranking ≥95th percentile of our cohort were predominately HIV-infected adolescents (n = 9), and had ≥1 risks for metabolic disorder (n = 8) (Table 4).

Table 4. Clinical profiles of study participants with cardio-ankle vascular index ranking at or above 95th percentile of the cohort.

No.	Age (yr)	Sex	HT	Risk for metabolic disorder	HIV-related characteristics				CAVI (m/s)
					ART regimen	ART duration (yr)	CD4 count (cells/mm^3)	Viral load (copies/mL)	
1	21	M	Yes	HDL-C <40	NNRTI	15	523	<20	8.6
2	20	M	Yes	LDL-C ≥130	NNRTI	13	1,374	40	7.4
3	25	M	No	BMI >30, TG ≥150, HDL-C <40, HOMA-IR >3.16	NNRTI	14	329	<20	7.4
4	25	M	No	TG ≥150, LDL-C ≥130	PI	13	510	18,784	7.2
5	20	M	No	TG ≥150, HDL-C <40	PI	15	459	<20	7.8
6	24	M	No	TG ≥150	PI	18	499	40	7.3
7	20	F	No	TG ≥150	II	15	680	40	7.6
8	20	F	No	LDL-C ≥130	PI	18	738	<20	7.2
9	19	F	No	No	NNRTI	14	645	<20	7.3
10*	15	F	No	No	NA	NA	NA	NA	7.4

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CAVI, cardio-ankle vascular index; F, female; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model assessment of insulin resistance; HT, systemic hypertension; II, integrase inhibitor; LDL-C, low-density lipoprotein cholesterol; M, male; NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TG, triglyceride.
*Healthy, HIV-uninfected adolescent.

- In the multivariable analysis, age ≥18 years, systemic hypertension, and ART duration were significantly associated with increased CAVI in our HIV-infected adolescents (Table 5).

Table 5. Factor associated with cardio-ankle vascular index among perinatally HIV-infected adolescents (n = 150).

Characteristics	Univariable analysis		Multivariable analysis	
	Mean difference	95% CI	Adjusted mean difference	95% CI
Age ≥18 years	**0.67**	**0.43 to 0.91**	**0.36**	**0.04 to 0.68**
Male sex	0.27	0.01 to 0.52	0.03	-0.23 to 0.29
BMI category				
Normal weight	Ref	Ref	Ref	Ref
Underweight	0.22	-0.10 to 0.53	0.30	-0.01 to 0.60
Overweight/Obese	-0.43	-0.80 to -0.06	-0.24	-0.65 to 0.17
Systemic hypertension	**1.01**	**0.45 to 1.56**	**0.71**	**0.17 to 1.26**
Smoking				
Non-smoker	Ref	Ref	Ref	Ref
Current smoker	0.51	0.04 to 0.99	0.19	-0.36 to 0.75
Alcohol drinking				
Non-drinker	Ref	Ref	Ref	Ref
Current drinker	0.57	0.26 to 0.88	0.02	-0.36 to 0.41
Duration of ART	**0.06**	**0.02 to 0.09**	**0.04**	**0.001 to 0.08**
Nadir CD4 T-cell <200 cells/mm^3	0.37	0.09 to 0.65	0.18	-0.09 to 0.45
HOMA-IR >3.16	-0.44	-0.72 to -0.17	-0.12	-0.45 to 0.21

Abbreviations, ART, antiretroviral therapy; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; 95% CI, 95% confidence interval.

Conclusions

- No adolescents in our cohort had arterial stiffness, evaluated by CAVI.
- Older age, systemic hypertension, and longer duration of ART appeared to be associated with increased CAVI among our HIV-infected adolescents.
- Despite low CAVI demonstrated in our study, HIV-infected adolescents with metabolic risk factors should be monitored for the progression towards significant arterial diseases.

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