

# Left Ventricular Function, Epicardial Adipose Tissue, and Carotid Intima-Media Thickness in Children and Adolescents With Vertical HIV Infection

Fabio Marsico, MD,<sup>a,b</sup> Andrea Lo Vecchio, MD, PhD,<sup>c</sup> Stefania Paolillo, MD, PhD,<sup>a</sup> Claudia D'Andrea, MD, PhD,<sup>a</sup> Vittoria De Lucia, MD,<sup>a</sup> Eugenia Bruzzese, MD, PhD,<sup>c</sup> Gianfranco Vallone, MD,<sup>d</sup> Santo Dellegrottaglie, MD, PhD,<sup>e</sup> Caterina Marciano, MD,<sup>f</sup> Bruno Trimarco, MD,<sup>a</sup> Alfredo Guarino, MD,<sup>c</sup> and Pasquale Perrone Filardi, MD, PhD<sup>a</sup>

**Background:** Life expectancy of HIV patients has increased considerably as a result of antiretroviral therapy (ART), and cardiovascular (CV) disease has emerged as an important late concern. People with HIV infection could have an impaired systolic function; however data on diastolic function and markers of CV risk, such as epicardial adipose tissue (EAT) and intima-media thickness (IMT), are lacking. Aim of this study is to evaluate left ventricular function, EAT, and IMT in children and adolescents with vertically acquired HIV infection.

**Methods:** We enrolled 29 subjects on ART (13, 45% men; median age of 13.0, and interquartile range 9–18), and 29 age-matched controls. All patients and controls underwent echocardiographic evaluation, with study of the systolic and diastolic function and measurement of the EAT, and a carotid ultrasound study for IMT measurement.

**Results:** Comparing HIV-infected patients to healthy controls, we found a statistically significant increase of EAT and IMT (mean  $\pm$  SD) (EAT:  $3.16 \pm 1.05$  vs  $1.24 \pm 0.61$  mm;  $P < 0.0001$ . IMT:  $0.77$

$\pm 0.15$  vs  $0.51 \pm 0.11$  mm;  $P < 0.0001$ ), and a significant reduction of ejection fraction, evaluated with the biplane Simpson method (mean  $\pm$  SD) ( $58.5\% \pm 6.66\%$  vs  $66\% \pm 4.24\%$ ;  $P = 0.029$ ). These results are not related with age, gender, degree of lipodystrophy, dyslipidemia, hyperinsulinism, and ART duration or the use of single antiretroviral classes.

**Conclusions:** Vertically infected HIV children and adolescents show an increased thickness of EAT and IMT, expression of potentially increased CV risk. They also show an impaired systolic function.

**Key Words:** Human immunodeficiency virus, antiretroviral therapy, left ventricular ejection fraction, diastolic dysfunction, intima-media thickness, epicardial adipose tissue

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## INTRODUCTION

HIV infection is a major cause of morbidity and mortality worldwide. In developed countries, where life expectancy has increased considerably as a result of antiretroviral therapy (ART), cardiovascular (CV) diseases have emerged as an important late comorbidity in HIV patients.<sup>1,2</sup>

Results from the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P2C2 HIV) study have shown that subclinical cardiac abnormalities develop early in HIV1-infected children, and that cardiac alterations are frequent, persistent, and often progressive.<sup>3–6</sup>

Echocardiographic abnormalities can be found in up to 44% of patients infected with HIV.<sup>7</sup> These findings include pericardial effusion, left ventricular (LV) dysfunction, dilated cardiomyopathy, infective endocarditis, pulmonary arterial hypertension, and cardiac masses such as lymphoma and Kaposi sarcoma of the heart. In addition, ART has been associated with the development of ischemic heart disease and LV diastolic abnormalities.<sup>8</sup>

Although most data come from adult populations, evidence is also available for an association between HIV infection and systolic and diastolic dysfunction in children,<sup>9,10</sup> and it has been demonstrated that children undergoing ART show decreased incidence of CV diseases.<sup>11,12</sup>

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From the <sup>a</sup>Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; <sup>b</sup>Center for Congenital Heart Disease, University Hospital Inselspital, Bern, Switzerland; <sup>c</sup>Department of Translational Medical Sciences, Section of Pediatrics, University of Naples Federico II, Naples, Italy; <sup>d</sup>Department of Advanced Biomedical Sciences, Section of Radiology, University of Naples Federico II, Naples, Italy; <sup>e</sup>Villa dei Fiori, Naples, Italy; and <sup>f</sup>Istituto Diagnostico Varelli, Naples, Italy.

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Correspondence to: Pasquale Perrone Filardi, MD, PhD, Department of Advanced Biomedical Sciences, University of Naples Federico II, Via Pansini, 5, I-80131 Naples, Italy (e-mail: fpperron@unina.it).

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In recent years, new markers of increased CV risk have emerged. Epicardial adipose tissue (EAT), that has the same embryogenic origin of visceral fat,<sup>13</sup> has been reported to be associated with CV risk and metabolic syndrome.<sup>14,15</sup> Increased EAT thickness in HIV-infected adults compared with healthy controls has been reported,<sup>16,17</sup> with an association between EAT and lipodystrophy.<sup>18</sup> However, data on children and adolescents with vertically acquired HIV infection are lacking.

Similarly, the increase in intima-media thickness (IMT) is associated with higher CV risk, and a higher IMT has been reported in HIV-infected children, compared with noninfected patients.<sup>19</sup> The IMT thickness appears higher in naive children than in HIV-patients undergoing ART therapy.<sup>20</sup>

The aim of this study was to assess EAT, IMT, and left ventricle function in young patients with vertically acquired HIV infection, to correlate these parameters to metabolic profile and antiretroviral treatment.

## METHODS

This population study was carried out between January 1, and November 30 2017 at the Regional Reference Center for Pediatric HIV/AIDS of the University of Naples Federico II. The Referral Center covers a territory of about 5 million inhabitants in the most populous region of southern Italy, and manages about 30 HIV-infected children and adolescents with 1–2 new diagnosis/year of HIV infection in the last years.

All patients in follow-up at the Regional Reference Center were enrolled in the study, and a group of age-matched subjects was enrolled as controls. The study was conducted according to the principles of the Helsinki declaration and the study protocol was approved by the Ethical Committee of the University Federico II of Naples (protocol number 153/16). All patients and caregivers, according to age, signed an informed consent after receiving specific information from the study coordinators.

## Clinical Evaluation

All patients underwent clinical and lifestyle evaluation (physical activity, smoking, drinking, drug addiction, eating habits), and viroimmunological assessment with measurement of HIV viral load and CD4<sup>+</sup> count. In addition, current ART, history of ART regimens, and duration of single antiretroviral classes were reviewed.

## Evaluation of the Metabolic and CV Risk

All patients underwent clinostatic and orthostatic blood pressure measurement, followed by the evaluation on blood sample of lipid profile [total cholesterol, high density lipoprotein, low density lipoprotein (LDL), and triglycerides] and glucose profile [fasting glucose, basal insulin, and homeostatic model assessment (HOMA) index]. We also evaluated the presence of metabolic syndrome, considering the International Diabetes Federation diagnostic

criteria and the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria.<sup>21,22</sup> Lipodystrophy was classified as absent, mild (mild lipodystrophy of face and arms), and severe (severe lipodystrophy of face and arms, with involvement of abdomen and legs).

## Echocardiography and Carotid Assessment

For all echocardiographic measurements, the final values were obtained after averaging over 2 cardiac cycles. The evaluation of LV ejection fraction was made with Simpson biplane mode, tracing telediastolic and telesystolic volume both in a 4- and 2-chamber apical view (n.v. 52%–70%).<sup>23</sup>

The evaluation of LV diastolic function was made evaluating the E/A waves ratio and the E/E' waves ratio. The E/A ratio was evaluated in a 4-chamber apical view, using pulsed Doppler, applied on the coaptation point of the mitral leaflets. The E wave is the early component of the left ventricle diastolic filling, whereas the A wave corresponds to the atrial systole. The E/A ratio was considered normal for a value higher than 1.<sup>23</sup> The E' wave was obtained applying a tissue Doppler on the mitral annulus (medial and lateral). A E' mean value lower than 8 indicates a diastolic dysfunction, but, considering the E/E' ratio, the normal value is lower than 8.<sup>23</sup> A value between 8 and 13 can be considered as class 1 or 2 of diastolic dysfunction, whereas a value higher than 13 can be considered as class 3 or 4 of diastolic dysfunction.

The EAT was measured in a parasternal long-axis view, on the top of the right ventricle free wall, considering the maximum thickness, as end-systolic measurement (Fig. 1). In the evaluation of the CV profile, we also included a carotid ultrasonography, with a Doppler linear probe, for the evaluation of the IMT. Specifically, IMT was measured at common carotid level 1 cm before carotid bifurcation in both right and left carotid arteries, using on average all the 2 measurements. All measurements were performed by FM. Inter-observer variability for EAT, LV ejection fraction, and IMT were calculated in 10 randomly selected examinations. A second observer (C.D.A.), who was blinded to the initial analysis, repeated all measurements for quantification of interobserver variability.



**FIGURE 1.** Echocardiographic assessment of epicardial adipose tissue. The left side is an end-systolic image, where EAT is more represented. The right side is an end-diastolic image, with the minimum thickness of EAT.

**TABLE 1.** Patients Baseline Characteristics

General Characteristics	Patients (n = 29)	Controls (n = 29)	P
Male (N, %)	13 (45)	13 (45)	
Age in yrs at enrollment (median, IQR)	13.0 (9–18)	13.6 (9.9–19)	0.932
Age in yrs at diagnosis (median, IQR)	1 (0–6)	NA	
Smokers (N, %)	7 (24.1)	5 (17.2)	0.265
Regular alcohol consumer (N, %)	1 (3.4)	0 (0)	
Drug consumer (N, %)	0 (0)	0 (0)	
Viroimmunological characteristics			
Patients in class 1 (N, %)	5 (17.2)	NA	
Patients in class 2 (N, %)	3 (10.4)	NA	
Patients in class 3 (N, %)	21 (72.4)	NA	
Patients with undetectable HIV load (N, %)	21 (72.4)	NA	
HIV viral load (median, IQR)	40 (40–112)	NA	
CD4 <sup>+</sup> cell count (median, IQR)	876 (582–1228)	NA	
Percentage of CD4 <sup>+</sup> (mean ± SD)	33.9 ± 10.6	NA	
Duration of ART (mo) (median, IQR)	120 (30–188)	NA	
Duration of PI treatment (mo) (median, IQR)	96 (31–168)	NA	
Duration of NRTI treatment (mo) (median, IQR)	98 (31–164)	NA	
Duration of NNRTI treatment (mo) (median, IQR)	25 (15–44)	NA	
Duration of II treatment (median, IQR)	6 (1–28)	NA	
Metabolic and CV parameters			
BMI (mean ± SD)	20 ± 4	19 ± 6	0.153
BMI <5 percentile (n)	3	2	0.765
BMI 5–25 percentile (n)	11	12	0.823
BMI 26–75 percentile (n)	9	11	0.532
BMI 76–95 percentile (n)	3	2	0.765
BMI >95 percentile (n)	3	2	0.765
Total cholesterol in mg/dL (mean ± SD)	157 ± 36	156 ± 46	0.959
HDL cholesterol in mg/dL (mean ± SD)	42 ± 12	54 ± 21	0.063
LDL cholesterol in mg/dL (mean ± SD)	95 ± 26	101 ± 29	0.407
Triglycerides in mg/dL (median, IQR)	78 (57–123)	74 (45–115)	0.058
Metabolic syndrome (N, %)	1 (3)	1 (3)	
No lipodystrophy (N, %)	21 (72.4)	NA	
Mild lipodystrophy (N, %)	5 (17.2)	NA	
Severe lipodystrophy (N, %)	3 (10.4)	NA	
Fasting glucose in mg/dL (mean ± SD)	72 ± 15	82 ± 28	0.151
HOMA index (median, IQR)	4 (1–5)	3.8 (0.9–4.8)	0.236
Systolic blood pressure (mean ± SD)	115 ± 12	117 ± 16	0.639
Diastolic blood pressure (mean ± SD)	68 ± 8	65 ± 11	0.725

PI, protease inhibitor; NRTI, nucleoside reverse-transcriptase inhibitors; NNRTI, non-nucleoside reverse-transcriptase inhibitors; HDL, high density lipoprotein; HOMA, homeostatic model assessment.

## Statistical Analysis

Data were collected in a Microsoft Excel database and statistical analysis were performed using IBM SPSS Statistics v25.0. Categorical variables were reported as percentages. Continuous variables were reported as mean ± SD, and variables with skewed distributions were presented as median and interquartile range (IQR). Normal distribution was assessed by the Kolmogorov–Smirnov test. Student *t* test for paired samples was used to compare mean for baseline characteristics and bio humoral parameters between patients and controls. Student *t* test for unpaired data was used to compare differences in LV systolic function, LV diastolic function, EAT, and IMT between HIV-infected patients and controls. Correlation between CV risk factors and type of therapy with EAT levels and IMT was assessed by Pearson (or Spearman) correlation and univariate regression. Multiple linear regression analysis was used to adjust for potential confounders. Interobserver variability was evaluated by calculating the interclass correlation coefficient, with a cut-off value >0.75 as indication of good agreement, as proposed by Burdock et al<sup>24</sup> Statistical significance has been accepted at  $P \leq 0.05$ .

## RESULTS

### Study Population

We enrolled 29 consecutive HIV-infected patients on ART [13 patients, 45% male; median age of 13.0 years, and IQR 9–18 (baseline characteristics reported in Table 1)], and 29 age-matched healthy volunteer controls, without differences for demographic, lifestyle, and metabolic characteristics with patients (Table 1). According to the Centers for Disease Control and Prevention classification of HIV-infected children,<sup>25</sup> most patients were in class 3 (21 patients, 72%), 3 patients in class 2 (10%), and 5 patients in class 1 (17%).

Most patients (72%) had undetectable viral load defined as HIV RNA <40 copies/mL and the median CD4<sup>+</sup> count value was 876 cells/μL at enrollment (Table 1). At the time of enrollment, all patients were on antiretroviral treatment with nucleoside reverse transcriptase inhibitors backbone in association with a protease inhibitor in 23 (79%) patients (15 patients on lopinavir/ritonavir, 8 patients on darunavir/ritonavir) or an integrase strand transfer inhibitor in 6 (21%) patients (5 dolutegravir and 1 raltegravir). The median duration of overall ART in the study population was 120 months (IQR 30–188); in more detail, patients were treated with at least one nucleoside reverse transcriptase inhibitor for 98 months (IQR 31–164), with protease inhibitors for 96 months (IQR 31–168), with nonnucleoside reverse transcriptase inhibitors for a median of 25 months (IQR 15–44) and with an integrase strand transfer inhibitor for a median of 6 months (IQR 1–28).

None of the patients in our cohort had hypertension (mean systolic blood pressure 115 ± 12, and mean diastolic blood pressure 68 ± 8 mm Hg) or diabetes (mean fasting glucose value 73 ± 15 mg/dL), but 6 patients (21%) showed an HOMA index >2.5, indicating an insulin-resistance state. Dyslipidemia was found only in 2 (7%) patients, with a mean

value of LDL cholesterol of  $95 \pm 26$  mg/dL. The mean body mass index (BMI) in our cohort was  $20 \pm 4$  kg/m<sup>2</sup>, with 3 patients reporting a BMI >95<sup>o</sup> percentile for age. One patient met International Classification of Diseases or NCEP-ATP III criteria for metabolic syndrome (Table 1).

A variable degree of lipodystrophy was reported in about a third of patients (Table 1).

### CV Evaluation

Compared with healthy controls, HIV-infected children showed a statistically significant increase in mean EAT ( $3.16 \pm 1.05$  vs  $1.24 \pm 0.61$  mm;  $P < 0.0001$ , Fig. 2A) and mean IMT ( $0.77 \pm 0.15$  vs  $0.51 \pm 0.11$  mm;  $P < 0.0001$ , Fig. 2B). Although absolute values of left ventricular ejection fraction were within the normal values in both populations, the mean left ventricular ejection fraction was significantly reduced in HIV-infected patients in comparison to healthy control subjects (mean  $58.5 \pm 6.66$  vs mean  $66 \pm 4.24\%$ ;  $P = 0.029$ ) (Fig. 2C). We did not find statistically significant differences between patients and controls regarding diastolic function. Both for mean E/A ratio ( $1.70 \pm 0.35$  vs  $1.90 \pm 0.46$ ;  $P = 0.068$ ) and for mean E/E' ratio ( $4.13 \pm 1.16$  vs  $4.46 \pm 1.02$ ;  $P = 0.259$ ).

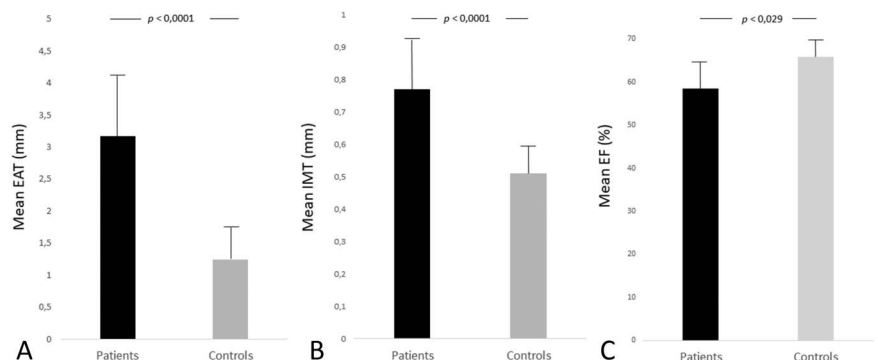
Patients' age and gender, HIV class and percentage or number of CD4<sup>+</sup>, the duration of ART (including each antiretroviral drug class), the use of first generation protease inhibitors, the use of specific antiretroviral drug class, the presence or degree of lipodystrophy, the presence of dyslipidemia, and the degree of insulin resistance were investigated as possible factors affecting the increase of EAT and/or IMT; however for none of them a significant correlation was demonstrated. Children with HOMA index >2.5 seemed to have a trend toward increase in EAT, showing higher value (mean  $3.25 \pm 0.87$ ) than children with HOMA <2.5 (mean  $2.92 \pm 0.85$ ), but this difference was not statistically significant ( $P = 0.34$ ). Similarly, children with HOMA >2.5 had slightly higher values of mean IMT ( $0.76 \pm 0.16$  vs  $0.64 \pm 0.31$ ), although this difference did not reach statistical significance ( $P = 0.27$ ).

The interclass correlation coefficient for interobserver variability for LV ejection fraction, EAT, and IMT were 0.796, 0.987, and 0.960 respectively.

### DISCUSSION

Cardiac dysfunction has been previously reported in adults and children with HIV infection, although it is not completely clear whether those alterations are directly related to HIV or to antiretroviral treatment. We confirmed a decrease of the absolute value of ejection fraction and increased values of IMT in a population of children and adolescents with vertically acquired HIV infection. Moreover, this is the first study documenting a significant increase of EAT in children and adolescents with HIV infection. Systolic function reduction is consistent with previous studies, that also documented a reduction in ejection fraction in subjects with HIV infection. Lipshultz et al,<sup>9</sup> showed in a cohort of 93 HIV children, a reduction of LV fractional shortening after 8 months of follow-up, compared with healthy control subjects. More recently, the same group<sup>10</sup> confirmed these data, showing a reduction in cardiac function in HIV children with higher current viral load. The CHAART-2 study<sup>26</sup> showed the effectiveness of ART in improving LV fractional shortening and LV contractility by comparing a cohort of 74 HIV children on ART with 140 HIV-infected controls unexposed to ART. In particular, they found a significant difference (expressed as Z-score of normal values) in LV fractional shortening ( $0.26$  vs  $-1.19$  respectively,  $P = 0.02$ ) and LV contractility ( $0.09$  vs  $-0.88$ ,  $P = 0.002$ ), between cases and controls respectively. According to our data, LV function appeared different from controls, but not significantly impaired; however, they also reported a relevant impact of ART on LV function, not confirmed in our study, because none of our patients was naive to ART when cardiological assessment was performed.

In addition, as previously reported in other cohort of HIV-infected children and young adults, we showed an increase of IMT in our population. Although other studies, even in large population, confirmed this finding in HIV-infected patient aged below 30 years,<sup>27</sup> the clinical relevance and the correlation of this finding with HIV state of infection and ART are still a matter of discussion. Charakida et al<sup>19</sup> reported a significant greater IMT in HIV infected children than in healthy control subjects, and demonstrated a potential role of ART, showing higher IMT in patients who received protease inhibitors. In contrast, Idris et al<sup>20</sup> found higher IMT values in naive children with vertically acquired HIV infection compared to those on ART and healthy children.



**FIGURE 2.** Difference of EAT, IMT, and left ventricular ejection fraction between patients and controls. A, Difference of EAT between patients and controls. B, Difference of IMT between patients and controls. C, Difference of left ventricular ejection fraction between patients and controls. EF, ejection fraction.

In the last 2 years, other studies confirmed an increase in the IMT in HIV-infected adults<sup>28</sup> and pediatric<sup>29</sup> patients. In contrast with our results, Augustemak de Lima et al<sup>29</sup> also reported alteration in CV profile and a possible role of ART on IMT in underage patients.

This is the first study investigating the EAT in HIV-affected children and adolescents. Several previous studies evaluated the potential CV role of EAT in patients with high CV risk, and in heart failure patients. In particular, Parisi et al,<sup>30</sup> described an increased EAT thickness in patients with heart failure, with a potential role of EAT in predicting impaired sympathetic cardiac innervation, widely involved in heart failure pathophysiology. The same group,<sup>31</sup> evaluated the potential role of EAT as an inflammatory marker for CV risk, defining a modulation role of statins directly on inflammatory status (well known) and indirectly also on EAT thickness, confirming the important role of EAT in CV disease, as equivalent of visceral adipose tissue.

However, currently, there are only few studies that evaluated EAT in HIV adult patients, showing an increase of epicardial fat in these patients. Zona et al,<sup>32</sup> in a cohort of 240 HIV adult patients, showed an increase of EAT, more evident in men than in women. Differently from our study, they found a correlation between the higher EAT and CD4<sup>+</sup> levels. Other studies correlated EAT to body-weight in HIV patients,<sup>16</sup> showing a correlation between EAT and metabolic syndrome. Guaraldi et al<sup>18</sup> found an increased EAT that correlated with metabolic syndrome in 876 adult patients and a correlation between EAT and lipodystrophy. More recently, another study of Brener et al,<sup>17</sup> studied 579 HIV-infected adult patients and 353 controls, showing a thicker EAT in HIV patients treated with ART. However, differently from our study, Brener et al<sup>17</sup> found a greater EAT in patients with greater BMI, in hypertensive patients, in diabetic patients, and in dyslipidemic patients, suggesting a potential contribution of CV risk factors on EAT. In our study, there was no correlation between CV risk factors and increased EAT or IMT. Moreover, we did not observe any correlation between EAT or IMT with HIV class and level of CD4<sup>+</sup>, duration of ART, use of old generation protease inhibitors or any different antiretroviral drug class, and presence and degree of lipodystrophy. These results suggest a potential role of the infection defining an increased CV risk in these patients. Finally, the study of Abd-Elmoniem et al,<sup>33</sup> performed on a population of 35 HIV young adults and 11 healthy controls, showed no difference for EAT evaluated by coronary computed tomography angiography, between patients and control. The latter is the only study reporting similar values of EAT in HIV-infected subjects and healthy controls. Differently from our study, the study by Abd-Elmoniem et al studied an older HIV-infected population, with no pairing between cases and controls and only 11 healthy controls assessed. In addition, they studied EAT by computed tomography angiography rather than by echocardiography.

### LIMITATIONS

The major limitation of this study is the small number of patients, that could have affected some results, such as the failed

correlation between echocardiographic findings with metabolic parameters, although the cohort of patients includes all subjects currently seen at the reference center and the matching with healthy controls may ensure a statistical reproducibility of results. Lack of follow-up makes the current findings hypothesis generating and warranting further evaluation.

### CONCLUSIONS

The findings of the present study demonstrated that in children and adolescents with vertically acquired HIV infection on ART, systolic function is reduced and IMT and EAT are increased compared with matched healthy controls. Taken together, these findings suggest early subclinical CV damage in HIV young patients despite the absence of conventional CV risk factors.

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