

Longitudinal assessment of metabolic abnormalities in adolescents and young adults with HIV-infection acquired perinatally or in early childhood

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Abstract

Metabolic complications of HIV pose challenges for health maintenance among young adults who acquired HIV in early childhood. Between July 2004 and July 2009, we evaluated 47 HIV-infected subjects who acquired HIV in early life. Participants completed glucose tolerance testing; insulin, lipid, urine albumin, and creatinine determinations; and dual-energy x-ray absorptiometry scans. Longitudinal data were available for 39 subjects; duration of follow-up was 26.4 ± 16.8 months. At baseline, participants were 17.1 ± 3.9 years old; and duration of antiretroviral therapy was 12.7 ± 3.4 years. CD4 count was 658 ± 374 cells per cubic millimeter, and 55% had undetectable viral load. Impaired glucose tolerance was present in 15%; 33% had insulin resistance (homeostasis model assessment of insulin resistance >4.0). Furthermore, 52% had triglycerides of at least 150 mg/dL, 36% had high-density lipoprotein cholesterol less than 40 mg/dL, 18% had low-density lipoprotein cholesterol of at least 130 mg/dL, and 25% had total cholesterol of at least 200 mg/dL. Microalbuminuria was present in 15% of participants and was inversely correlated with CD4% ($P = .001$). During follow-up, more than one third remained insulin resistant; lipid parameters tended to improve. There were significant increases in body mass index ($P = .0002$), percentage leg fat ($P = .008$), and percentage trunk fat ($P = .002$). Impaired glucose tolerance, insulin resistance, dyslipidemia, and microalbuminuria are common among young adults with HIV. Long-term exposure to therapy may translate into substantial persistent metabolic risk.

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1. Introduction

Morbidity and mortality associated with HIV/AIDS decreased dramatically with the advent of potent antiretroviral therapies (ARTs). However, ART has also been

associated with metabolic complications, alterations in body fat distribution, and chronic kidney disease [1–3]. Relatively fewer data exist to characterize these associations in adolescents and young adults infected with HIV in early childhood.

In adults, the use of ART is associated with insulin resistance, diabetes, and cardiovascular disease (CVD) [4–8]. Previous investigation demonstrated that increased exposure to the nucleoside reverse transcriptase inhibitor (NRTI) stavudine (d4T)—and, to a lesser extent, didanosine (ddI) and zidovudine (AZT)—was associated with an increased risk of developing diabetes in adults [5]. Although long-term effects of insulin resistance are unknown, it may be an important CVD risk factor among HIV-infected adults [9].

There is currently a paucity of data pertaining to metabolic disturbances associated with long-term ART among adolescents and young adults who acquired HIV

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perinatally or in early childhood. In HIV-infected children, protease inhibitors (PIs) have been shown to contribute to lipid abnormalities and the presence of lipodystrophy [10–14]. HIV-infected children with lipodystrophy have higher fasting insulin compared with children without lipodystrophy [15]. Exposure to ART and inflammation in children with HIV were identified in association with increased carotid intima media thickness, a marker for CVD risk [16,17]. Insight into the metabolic complications associated with long-term ART will allow development of preventive strategies to reduce CVD risk. Here we characterize metabolic disturbances both cross-sectionally and over time in a group of HIV-infected adolescents and young adults.

2. Methods

2.1. Subjects and data collection

We performed a cross-sectional analysis, followed by a longitudinal analysis, of a cohort of subjects who acquired HIV perinatally or in early childhood. Subjects received medical care independent of the study and were evaluated at the National Institutes of Health from 2004 to 2009. The research was approved by the National Institute for Allergy and Infectious Diseases' Institutional Review Board; and informed consent was obtained from all subjects and parents or legal guardians, as appropriate.

Thirty-nine of 47 subjects were included in the longitudinal analysis (Fig. 1). Six subjects included in the cross-sectional analysis were lost to follow-up, and 2 had not yet completed a follow-up oral glucose tolerance test (OGTT). Mean duration of follow-up was 26.4 ± 16.8 months, and data were analyzed based on the baseline visit and last follow-up.

Participants completed a clinical evaluation, including a complete history of all ART exposure. Data collected included Tanner stage, fasting lipid profile, fasting and

2-hour glucose, and insulin following 75-g OGTT. *Impaired glucose tolerance* (IGT) was defined as a 2-hour glucose of at least 140 mg/dL but less than 200 mg/dL. Laboratories included CD4 T-lymphocyte counts, CD4%, and HIV-1 RNA by reverse transcriptase polymerase chain reaction. Abnormal fasting lipid levels were defined based on the National Cholesterol Education Program criteria [18]. *Hypertriglyceridemia* was defined as triglyceride greater than 150 mg/dL, *hypercholesterolemia* as total cholesterol greater than 200 mg/dL, *abnormal low-density lipoprotein cholesterol* (LDL-c) as greater than or equal to 130 mg/dL, and *abnormal high-density lipoprotein cholesterol* (HDL-c) as less than 40 mg/dL. *Microalbuminuria* was defined as the geometric mean urine albumin-to-creatinine (urine A/C) ratio of 17 to 250 mg/g (male) and 25 to 355 mg/g (female) using all available time points [19,20]. Thirty-five subjects provided 2 to 5 samples; 4 subjects provide 1 sample.

The homeostatic model of insulin resistance (HOMA-IR = fasting insulin [in microunits per milliliter] \times fasting glucose [in millimoles per liter]/22.5) was used to evaluate insulin resistance. Subjects with a HOMA-IR greater than 4.0 were classified as insulin resistant [21–23]. A HOMA-IR greater than 3.16 was also used as an alternative classification for insulin resistance [11,22], as both have been used in prior investigations. Duration of ART was calculated at the subjects' corresponding visit date for each individual antiretroviral agent and each class of agents. Ritonavir exposure was assessed by total years of exposure irrespective of the dose used.

2.2. Body measurements and dual-energy x-ray absorptiometry scan characteristics

Standardized anthropometric measurements included height, weight, hip and waist circumferences, and body mass index (BMI). Whole-body dual-energy X-ray absorptiometry (Hologic QDR4500A, Bedford, MA) was performed annually to measure regional and total fat and lean masses. All scans were analyzed by a single radiologist.

2.3. Statistical analyses

Clinical characteristics are summarized using mean \pm standard deviation; nonnormally distributed variables are presented as a median (interquartile range) or log transformed to approximate a normal distribution. Comparisons were made using Kruskal-Wallis tests and χ^2 statistics. Univariate regression analyses were performed to identify potential associations between metabolic parameters and clinical characteristics. Factors identified as significant on univariate analyses ($P < .05$) were entered into multivariate regression models to identify independent predictors. Paired t tests were used to compare longitudinal metabolic parameters between baseline and last follow-up. Statistical analyses were performed using SAS JMP Statistical Software (Version 7.0; SAS Institute, Cary, NC), using a 2-tailed α level of .05.

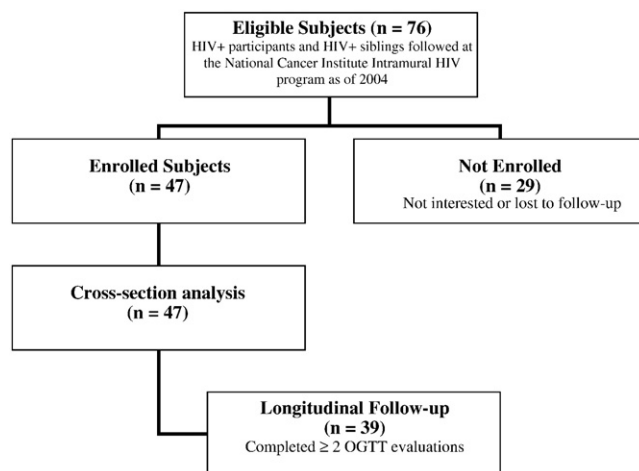


Fig. 1. Flow diagram of subject recruitment and participation.

3. Results

3.1. Subject characteristics

Forty-two subjects acquired HIV perinatally, and 5 acquired HIV from transfusions in early childhood. Sixty-seven percent (31/46) of participants were Tanner stage 4 or greater at baseline (Table 1). At baseline, 55% of subjects had an undetectable viral load; the median CD4 T-cell count was 650 cells per cubic millimeter (interquartile range, 402–897). All subjects but one were ART experienced with a duration of 12.7 ± 3.4 years. All ART-experienced subjects also had a history of exposure to a PI, and 94% were currently receiving ART. Thirty-four percent of subjects were currently on a non-NRTI (NNRTI), whereas 85% were currently on a PI. One subject was on an integrase inhibitor, and 4 were on a fusion inhibitor. At entry, 2 subjects were on a fibrate; no one was receiving a statin or antihypertensive agent. One participant had a diagnosis of polycystic ovary syndrome and was on metformin at the time of evaluation.

Table 1
Demographics and clinical characteristics

	Cross-sectional study	Longitudinal study	
	Total cohort (N = 47)	Baseline (n = 39)	Last visit (n = 39)
Age, y	17.1 ± 3.9	17.5 ± 3.7	19.7 ± 3.7
Duration of follow-up, mo	—	—	26.4 ± 16.8
Range of follow-up, mo	—	—	8.4–56.4
Sex, n (%)	—	—	—
Male	26 (55%)	20 (51%)	20 (51%)
Female	21 (45%)	19 (49%)	19 (49%)
Tanner stage, n (%)	—	—	—
<4	15 (33%)	10 (26%)	1 (3%)
>4	31 (67%)	28 (74%)	35 (97%)
Race, n (%)	—	—	—
White	23 (49%)	20 (51%)	20 (51%)
Black	18 (38%)	14 (36%)	14 (36%)
Mixed race	3 (6.5%)	3 (8%)	3 (8%)
Hispanic ethnicity	1 (2%)	0 (0%)	0 (0%)
Native American	2 (4.5%)	2 (5%)	2 (5%)
HIV characteristics	—	—	—
HIV viral load <50 copies/mL, n (%)	26 (55%)	22 (56%)	24 (62%)
CD4 T-cell count, cells/mm ³	658 ± 374	626 ± 370	725 ± 475
CD4 T-cell %	29.5 ± 10.2	28.9 ± 10.5	30.3 ± 10.3
Current ART use, n (%)	44 (94%)	37 (95%)	37 (95%)
Current PI use, n (%)	40 (85%)	33 (85%)	30 (76.9%)
Current or past PI use, n (%)	46 (98%)	39 (100%)	39 (100%)
Current d4T use, n (%)	21 (45%)	17 (44%)	7 (17.9%)
Current or past d4T use, n (%)	41 (87%)	35 (90%)	35 (90%)
Current ABC use, n (%)	4 (9%)	4 (10%)	8 (21%)
Current or past ABC use, n (%)	13 (28%)	10 (26%)	18 (46%)
Current TDF use, n (%)	9 (19%)	7 (18%)	13 (33%)
Current or past TDF use, n (%)	15 (32%)	12 (31%)	20 (51%)

Data are mean \pm standard deviation, except as indicated. ABC indicates abacavir.

Table 2

Glucose homeostasis, lipid, anthropometric assessment

	Cross-sectional study	Longitudinal study		
	Total cohort (N = 47)	Baseline (n = 39)	Last visit (n = 39)	P value
Glucose	—	—	—	—
Fasting glucose, mg/dL	86.3 ± 10.0	85.9 ± 10.2	90.9 ± 12.5	.06
2-h OGTT glucose, mg/dL	108.1 ± 31.4	109.7 ± 31.5	104.3 ± 29.2	.3
Fasting insulin, μ U/mL	19.7 ± 18.5	21.2 ± 19.9	20.3 ± 22.7	.8
2-h OGTT insulin, μ U/mL	94.5 ± 119.7	99.6 ± 128.1	78.1 ± 70.6	.1
HOMA-IR	4.4 ± 4.5	4.8 ± 4.9	5.1 ± 7.8	.8
Lipids	—	—	—	—
TC, mg/dL	177 ± 42	174 ± 43	165 ± 45	.2
HDL-c, mg/dL	44 ± 10	45 ± 10	43 ± 12	.3
LDL-c, mg/dL	106 ± 30	103 ± 27	95 ± 38	.2
TC/HDL ratio	4.1 ± 1.1	3.9 ± 0.9	4.0 ± 1.5	.7
Triglycerides, mg/dL	248 ± 266	226 ± 216	177 ± 151	.07
Anthropometrics	—	—	—	—
Height, cm	161.2 ± 11.9	162.2 ± 10.0	164.7 ± 8.9	.003
Weight, kg	56.5 ± 12.7	57.8 ± 11.8	63.7 ± 12.4	.0001
BMI, kg/m ²	21.6 ± 3.4	21.9 ± 3.4	23.5 ± 4.4	.0002
Waist-hip ratio	0.92 ± 0.07	0.92 ± 0.08	0.90 ± 0.15	.3
Percentage body fat (%)	19.4 ± 8.0	19.9 ± 8.1	22.5 ± 9.8	.0006
Percentage trunk fat (%)	18.2 ± 8.7	19.0 ± 8.9	22.1 ± 11.1	.002
Percentage leg fat (%)	20.8 ± 9.7	20.8 ± 9.6	23.2 ± 11.2	.008

Data are presented as mean \pm standard deviation, except as indicated. TC indicates total cholesterol.

Mean BMI was 21.6 ± 3.4 kg/m²; 15% were overweight (BMI >25 kg/m²), and one subject had a BMI greater than 30 kg/m². Waist-hip ratio was 0.92 ± 0.07 , and 17% had a waist-hip ratio of at least 1.0. Percentage body fat was $19.4\% \pm 8.0\%$, percentage trunk fat was $18.2\% \pm 8.7\%$, and percentage leg fat was $20.8\% \pm 9.7\%$.

3.2. Baseline evaluations of metabolic parameters

At baseline, IGT was present in 15% of subjects; but no subject had type 2 diabetes mellitus. Thirty-three percent of subjects had a HOMA-IR greater than 4.0, which is considered insulin resistance in adolescents [21,23]. Using a less stringent cutoff of HOMA-IR greater than 3.16 to define insulin resistance [11,22], 46% were insulin resistant. Dyslipidemia was common: 52% of subjects had hypertriglyceridemia, 36% had low HDL-c, and 25% had elevated total cholesterol. The mean total to HDL cholesterol ratio was 4.1 ± 1.1 (Table 2), and 18% of participants had suboptimal LDL-c. In univariate regression analyses, duration of AZT exposure ($r = -0.31$, $P = .03$) was inversely correlated with HOMA-IR. Years of ddI and d4T did not correlate with HOMA-IR; however, subjects with exposure

to ddi ($P = .0008$) or d4T ($P = .0005$) had significantly higher HOMA-IR compared with ddi/d4T-naïve subjects. Subjects with a HOMA-IR greater than 4 were more likely to have received ddi ($\chi^2 = 7.1$, $P = .008$) or d4T ($\chi^2 = 5.2$, $P = .02$). Subjects with a HOMA-IR greater than 4 had higher triglycerides ($P = .01$), waist circumference ($P = .02$), and waist-hip ratio ($P = .009$). There were no significant differences in HOMA-IR based on sex, Tanner stage, and PI or NNRTI use. In a multivariate logistic regression model including significant factors identified in univariate analysis, only waist-hip ratio ($P < .05$) remained an independent predictor of HOMA-IR greater than 4.

Compared with those without IGT, participants with IGT had significantly higher total cholesterol (215 ± 46 vs 169 ± 38 mg/dL, $P = .04$), triglycerides (377 ± 212 vs 226 ± 274 mg/dL, $P = .005$), and total to HDL cholesterol ratio (5 ± 1 vs 4 ± 1 , $P = .03$). Participants with IGT had greater total percentage body fat ($P = .009$), had greater percentage leg fat ($P = .02$), and were more likely to be male ($\chi^2 = 9.6$, $P = .002$). There was no significant relationship between Tanner stage and IGT.

Higher viral load ($r = -0.41$, $P = .009$) and greater years of abacavir use ($r = -0.31$, $P < .05$) were associated with lower HDL-c, whereas NNRTI use ($r = 0.35$, $P = .02$) was related to higher HDL-c. In multivariate regression, only viral load remained a significant independent predictor of HDL-c ($P = .03$). In addition, total number of years of ritonavir was positively correlated with LDL-c ($r = 0.34$, $P = .03$). There were no significant relationships identified between total or LDL-c and other HIV parameters, waist-hip ratio, BMI, trunk fat, or limb fat.

3.3. Microalbuminuria

Microalbuminuria was present in 15% (6/39) of subjects (95% confidence interval, 7%–30%) during follow-up; median urine A/C ratio was 5.4 (range, 1.6–125.8 mg/g). Five of 6 subjects with microalbuminuria were male, and 4 were African American. African American subjects had elevated baseline A/C ratio compared with other subjects (A/C ratio 39 ± 49 vs 8 ± 13 mg/g, $P = .008$). No subject had macroalbuminuria. Baseline urine A/C ratio was inversely correlated with CD4% ($r = -0.53$, $P = .001$) and positively correlated with systolic blood pressure ($r = 0.35$, $P = .04$). Although no other ART medication correlated with urine A/C ratio, number of years of tenofovir (TDF) was highly positively correlated with baseline urine A/C ratio ($r = 0.53$, $P = .001$). In a multivariate model, number of years of TDF ($P = .003$) and African American race ($P = .008$) remained significant independent predictors of urine A/C ratio. Although not statistically significant, subjects with microalbuminuria tended to have higher viral load (368 vs 100 copies per milliliter) and lower median CD4 counts (389 vs 747 cells per cubic millimeter) compared with those without microalbuminuria. There was no significant difference in HOMA-IR or IGT in relation to microalbuminuria.

3.4. Longitudinal evaluation of metabolic parameters

For longitudinal analysis, the mean number of visits per subject was 2.9 ± 1 ($n = 39$). HIV viral load was less than the limit of detection in 56% at entry and 62% at last follow-up; median CD4 T-cell counts were unchanged over time. Two subjects were not on ART throughout the entire duration of follow-up. Eighty-five percent of subjects were on a PI at baseline vs 76.9% at follow-up, and 44% were on d4T at baseline vs 17.9% at last follow-up.

Of the subjects followed longitudinally, 13% met criteria for IGT at entry vs 10% at last follow-up. Mean HOMA-IR remained constant; 14 subjects had HOMA-IR greater than 4 at entry and last follow-up (Fig. 2). Increases in fasting glucose between entry and last follow-up approached statistical significance (85.9 ± 10.2 vs 90.9 ± 12.5 mg/dL, $P = .06$). In general, lipid values tended to improve over time, but not significantly (Table 2). Change in lipids did not differ between those who started or discontinued a PI.

Changes in body composition were characterized by an increase in total percentage body fat and BMI. There were significant increases in BMI (21.9 ± 3.4 vs 23.5 ± 4.4 kg/m², $P = .0002$) and in percentage body fat ($19.9\% \pm 8.1\%$ vs $22.5\% \pm 9.8\%$, $P = .0006$), leg fat ($20.8\% \pm 9.6\%$ vs $23.2\% \pm 11.2\%$, $P = .008$), and trunk fat ($19.0\% \pm 8.9\%$ vs $22.1\% \pm 11.1\%$, $P = .002$). There was a significant positive correlation between change in BMI and change in fasting glucose ($r = 0.37$, $P = .02$). Individuals who remained on a d4T, a medication associated with lipoatrophy, had smaller increases in BMI compared with those who stopped or who had not been on d4T (0.23 ± 0.96 vs 1.95 ± 2.64 , $P = .007$). In addition, subjects with BMI greater than 25 kg/m² increased from 15% to 26% ($P = .0001$). There were no significant changes in total lean mass or waist-hip ratio.

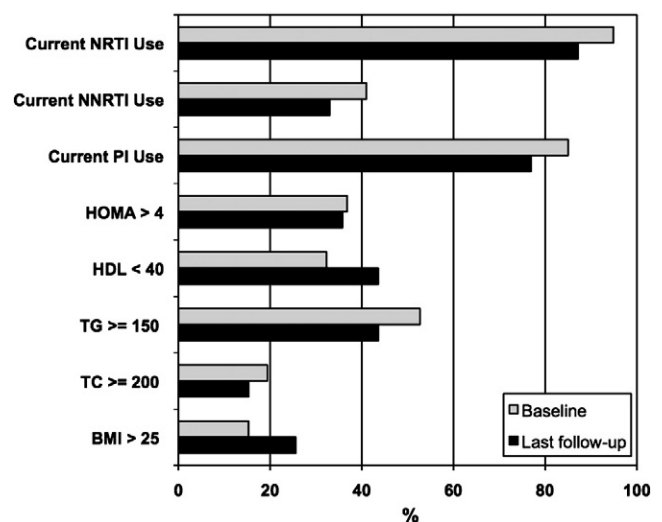


Fig. 2. Prevalence of metabolic abnormalities among HIV-infected participants in longitudinal follow-up at baseline and last visit ($n = 39$). TC indicates total cholesterol (in milligrams per deciliter); TG, triglycerides (in milligrams per deciliter).

4. Discussion

Few studies have described metabolic disturbances in relation to lifelong exposure to ART among HIV-infected adolescents and young adults. In this study, we identified insulin resistance, IGT, dyslipidemia, and microalbuminuria among a substantial proportion of HIV-infected adolescents and young adults with extensive ART exposure. Of interest, those individuals with IGT also had more dyslipidemia, which may translate into a considerable increase in the risk of CVD.

The PACTG 1045 study reported data from a large cohort of vertically infected children using OGTT and found fewer than 5% with abnormal results [24]. We identified a 15% prevalence of IGT that may be attributable to the older age of our cohort. Pediatric studies have also shown higher fasting insulin levels among HIV-infected children as a marker of insulin resistance [11,24–26]. Chantry et al [11] found that 48 weeks after initiating or changing ARTs, insulin resistance (HOMA-IR >3.16) increased from 1% to 8% among a cohort of HIV-infected children, whereas 46% of our participants had HOMA-IR greater than 3.16. Again, this may be due to the relatively older age, longer duration of therapy, and higher rates of PI use in the present study.

Several clinical factors were identified as associated with insulin resistance. Subjects with d4T and ddI exposure were more likely to have elevated HOMA-IR, whereas number of years of AZT exposure was associated with lower HOMA-IR. Waist-hip ratio was an important predictor of insulin resistance after adjusting for ART exposure. A study by Rosso et al [27] showed that BMI was a significant predictor of insulin resistance among HIV-infected youth, whereas Chantry et al [28] concluded that greater adiposity may not be linked to an increase in HOMA-IR in HIV-infected children. We found that distribution of adiposity as measured by waist-hip ratio was more closely related to insulin resistance than BMI per se.

Similar to the D:A:D findings on diabetes [5], we found that d4T and ddI were related to insulin resistance. However, d4T and ddI did not remain significant when waist-hip ratio was taken into account, suggesting that alterations in body fat distribution may underlie the observed drug effects on insulin resistance.

Dyslipidemia is frequently reported among HIV-infected patients [10,29,30]. We identified abnormal lipid values among a considerable proportion of our cohort, and the rates are similar to those reported in the PACTG 1045 cohort [24]. Both studies also identified abnormally low HDL-c levels in a large percentage of subjects who acquired HIV in infancy or early childhood and who had extensive ART experience. Protease inhibitor use is frequently implicated in hyperlipidemia in adults [30], and the extensive use of these agents in our cohort likely contributed to the observed dyslipidemia.

We identify higher viral load and cumulative exposure to abacavir as factors associated with lower HDL-c and increased exposure to NNRTIs in association with greater

HDL-c. These results suggest a potential protective effect of NNRTI exposure on lipids and are supported by recent studies of HIV-infected children in which NNRTI therapy was associated with increases in HDL-c [10]. In addition, NNRTIs are often used in ART regimens to replace a PI for their more favorable side effect profile with regard to lipids [1].

Microalbuminuria is a risk factor for CVD among otherwise healthy individuals [31,32]. In this HIV-infected adolescent population, microalbuminuria was present in 15% of subjects, a rate similar to what Szczech et al [33] described in HIV-infected adults (11%). Although the confidence interval of our result (7%–30%) encompasses the prevalence of 8.9% of microalbuminuria seen in healthy adolescents [34], our results are slightly higher than the estimated 10% observed in obese adolescents [35]. Our findings further highlight the importance of African American race in the risk of development of kidney injury in the context of HIV. Similar to previous findings in adults [33], we found that CD4% was inversely related to A/C ratio; and there was a trend for subjects with microalbuminuria to have a greater HIV viral burden. These data implicate HIV and immune function in the development of microalbuminuria and HIV-associated kidney disease.

The prevalence of insulin resistance was stable over time, whereas there were modest improvements in lipids. Although this may represent a lowering of underlying CVD risk, low HDL-c remained highly prevalent and significant increases in BMI were also noted. Increases in BMI are anticipated with growth, but disproportionate increases in body fat were seen without increases in lean mass. This could reflect restoration of fat stores previously depleted with lipoatrophy, but may also indicate unhealthy gains in adiposity. Leptin, an adipokine involved in glucose homeostasis, particularly in the context of lipoatrophy [36,37], was not measured; and its role in youth with HIV is less clear [38,39]. As previously suggested by Blass et al [40] and seen in the present study, emergent obesity in HIV cohorts may be driving the increase in fasting glucose levels, an indicator of prediabetes.

The strength of our study is the study cohort, which represents some of the most treatment-experienced HIV-infected adolescents and young adults. In addition, our study longitudinally evaluated insulin resistance and dyslipidemia combined with detailed body composition assessments as markers for CVD risk. Although we lack a control group for direct comparison, have a relatively small sample size, and did not directly measure adipokines, this is a well-characterized cohort with respect to ART exposure, metabolism, body composition, and pubertal development. Socioeconomic status, dietary factors, and lifestyle factors that contribute to metabolic disturbances may be enriched in this cohort relative to the general population. Another potential limitation is that the subjects were not characterized by clinical criteria of lipodystrophy; however, objective assessment methods, such as dual-energy x-ray

absorptiometry scans, were used. In addition, the very high prevalence of PI use and complex regimen modifications limit our ability to distinguish effects from individual drugs or classes of drugs.

In summary, our findings demonstrate that a substantial proportion of the study population have persistently altered glucose metabolism, dyslipidemia, and microalbuminuria. Although modest improvements in certain lipid parameters were noted over time, insulin resistance was stable and the prevalence of overweight was on the rise. This study has significant global implications, as HIV-infected children continue to survive into adulthood with expanded access to ART, and indicates the need for careful consideration of antiretroviral toxicities when treating children with HIV. Alterations in lipids and glucose metabolism may confer significant risk of future diabetes and CVD; and therefore, continued longitudinal follow-up evaluations are warranted to better understand the relationship between HIV infection, lifelong ART exposure, and CVD risk in this growing and unique population.

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