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Changes in Insulin Sensitivity over Time and Associated Factors in HIV-Infected Adolescents

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Abstract

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Authors' contributions: TLM and MS contributed to data collection; KP analyzed the data; MEG, DLJ, JW, TLM, RH, MG, TS, MS, JJ, JKT, RBVD, and LAD interpreted the data; and MEG and KP drafted the manuscript. All authors revised the manuscript and approved the final version of manuscript. KP takes responsibility for the integrity of the data analysis.

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Objective—To compare prevalence of IR between perinatally HIV-infected (PHIV+) and perinatally HIV-exposed, but uninfected adolescents (PHEU), determine incidence of and contributory factors to new and resolved cases of IR in PHIV+, and evaluate glucose metabolism.

Design—Cross-sectional design for comparison of prevalence among PHIV+ and PHEU. Longitudinal design for incidence and resolution of IR among PHIV+ at risk for these outcomes.

Methods—The source population was adolescents from pediatric HIV clinics in the US and Puerto Rico participating in PHACS AMP, an ongoing prospective cohort study designed to evaluate impact of HIV infection and its treatment on multiple domains in pre-adolescents and adolescents. IR was assessed by HOMA-IR. Those with incident IR underwent 2-hr OGTT and HbA1c. Baseline demographic, metabolic, and HIV-specific variables were evaluated for association with incident or resolved IR.

Results—Unadjusted prevalence of IR in PHIV+ was 27.3% vs 34.1% in PHEU. After adjustment for Tanner stage, age, sex, and race/ethnicity, there was no significant difference between groups. Factors positively associated with developing IR included female sex, higher BMI z-score, and higher waist circumference; those associated with resolving IR included male sex and lower BMI z-score.

Conclusions—Prevalence of IR in PHIV+ and PHEU was substantially higher than that reported in HIV-uninfected non-overweight youth, but similar to that in HIV-uninfected obese youth. Factors associated with incident or resolved IR among PHIV+ were similar to those reported in HIV-negative obese youth. However, a contributory role of HIV infection and/or its treatment to the incident risk of IR cannot be excluded.

Keywords

Insulin resistance; HOMA-IR; OGTT; BMI; waist circumference

Introduction

Since the advent of combination antiretroviral therapy (cART), patients with human immunodeficiency virus (HIV) have longer life expectancies; however, chronic conditions, such as metabolic and cardiovascular disease (CVD), are becoming more prevalent in this population [1]. In addition to lifestyle factors, cART and HIV itself may be associated with metabolic syndrome in youth and adults that places them at risk for CVD [2]. Increased rates of insulin resistance (IR) have been reported in some studies of HIV-infected youth as has the presence of other risks factors for clinical CVD [3–9].

In our initial study, we measured IR by the homeostatic model assessment (HOMA) of IR (HOMA-IR) [10] among 402 perinatally HIV-infected (PHIV+) youth (mean age 12.3 yr, of whom 47% were male and ~25% were pre-pubertal) enrolled in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS). We found that 61 (15.2%) had IR and that IR was significantly associated with elevated alanine aminotransferase (ALT), Tanner stage 5 puberty, higher body mass index (BMI), higher nadir CD4%, and ever having received amprenavir [11]. In that study, 45 youth had an oral glucose tolerance test (OGTT) of whom three had impaired fasting glucose (IFG) only, three

(6.7%) had impaired glucose tolerance (IGT) only, and one other (2.2%) had both IFG and IGT. In addition, three of 43 tested (7.0%) had a HbA1c > 42 mmol/mol, but none was > 48 mmol/mol, one of the criteria for diagnosing diabetes as set forth by the American Diabetes Association (ADA) [12]. In the current follow-up study, we proposed to: (1) compare the prevalence of IR between PHIV+ adolescents and perinatally HIV-exposed, but uninfected (PHEU) subjects, (2) determine incidence rates of and contributory factors to both new and resolved cases of IR in PHIV+ adolescents, and (3) evaluate abnormal glucose metabolism (by OGTT and HbA1c) in incident IR cases. We hypothesized that: (1) PHIV+ adolescents would have an increased prevalence of IR compared to PHEUs; (2) incident cases of IR over time among HIV+ adolescents would be associated with increasing age, worsening body composition [*e.g.,* increased adiposity assessed via body mass index (BMI) and waist circumference], less exercise, and specific ART use; and (3) resolution of IR over time among HIV+ adolescents would be associated with young age, improving body composition (*e.g.,* decreased truncal adiposity), more exercise, and ARVs with better metabolic profiles.

Methods

Study Population

The source population for this study was 451 PHIV+ and 227 PHEU youth enrolled in the PHACS AMP, an ongoing prospective cohort study designed to evaluate the impact of HIV infection and cART on multiple domains in pre-adolescents and adolescents with perinatally acquired HIV infection. Between March, 2007 and December, 2009, youth from 15 study sites in the U.S. and Puerto Rico were eligible for enrollment into AMP if they were born to HIV-infected mothers, were between 7–16 yr of age, and had available medical record history since birth on ARV exposure, opportunistic infection prophylaxis, HIV viral load and CD4 count, and major medical events. The AMP protocol was approved by the institutional review board (IRB) at each participating site and by that of the Harvard T.H. Chan School of Public Health. Written informed consent was obtained from each youth's parent or legal guardian, and assent was obtained from youth participants according to local IRB guidelines.

To be eligible for the current study, youth had to have had at least one simultaneously-obtained set of centrally-assessed fasting measurements of both plasma glucose and serum insulin and Tanner stage information. Exclusions included an alanine aminotransferase (ALT) greater than three times the upper limit of normal or a diagnosis of hepatitis C, a diagnosis of diabetes or use of medication affecting blood glucose, and diagnoses of chronic renal disease, Cushing disease, or mitochondrial disease.

Outcome definition

Glucose and insulin levels (obtained after a fast of ≥ 8 hr) were measured centrally at the Diabetes Research Institute Clinical Chemistry Laboratory at the University of Miami Miller School of Medicine in the laboratory of Armando Mendez, PhD. From these glucose and insulin measurements, HOMA-IR was calculated according to the formula: [Glucose (mmol/L) x Insulin (μU/mL)]/22.5. Insulin resistance was defined for pre-pubertal subjects (less than Tanner stage 2) as HOMA-IR > 2.5 and for pubertal subjects as > 4.0 [13].

Pubertal assessments by Tanner staging for genitalia and pubic hair were done by physical examination by trained examiners and the maximum Tanner stage based on genitalia or pubic hair was assigned to the participant. Of the total HOMA-IR measurements among the study participants, 14% were missing a Tanner stage assessment on the visit that specimens were obtained for glucose and insulin. However, the majority of these missing Tanner stages (88%) had a previous Tanner stage 5 measurement and the remainder was imputed based on available longitudinal assessments of Tanner stage and expert opinion of the study pediatric endocrinologist (MEG).

Prevalence of IR was assessed from the first centrally measured HOMA-IR measurement (*i.e.,* baseline). Among PHIV+ participants, incidence of IR was assessed by following those without defined IR at baseline and resolution of IR was assessed by following PHIV+ participants with IR at baseline (*i.e.,* prevalent cases of IR). Those children with incident IR were further characterized based on results of a 2-hr OGTT and simultaneous HbA1c measurement. Abnormal glucose tolerance was defined according to the ADA criteria: IFG = fasting glucose > 5.5 mmol/L, but < 6.9 mmol/L; IGT = 2-hr glucose (post-glucose load) between 7.7–11.0 mmol/L; and diabetes mellitus = fasting plasma glucose ≥ 6.9 mmol/L, 2-hr glucose (post-glucose load) ≥11.0 mmol/L, or HbA1c ≥ 48 mmol/mol [12].

Covariates

Baseline variables evaluated for their association with incident IR or resolution of IR included demographic (sex, race/ethnicity, and age), metabolic (BMI, waist circumference, fasting lipids, physical activity, and diet), and HIV-specific (CD4 cell count, HIV viral load, and ARV history) characteristics. The specific ART assessed for their association with IR included those reported to be associated with hyperglycemia (http://www.globalrph.com/glycemia.htm): abacavir, didanosine, stavudine, amprenavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir. Current use of an ART was defined as use at baseline. An indicator of use of other medications known to be associated with hyperglycemia (http://www.globalrph.com/glycemia.htm) was also a covariate of interest. All characteristics were collected either through self-report (*e.g.,* race/ethnicity), clinical evaluation (*e.g.,* BMI and waist circumference), or medical chart abstraction (*e.g.,* immunological, virological, and ART characteristics). BMI was expressed as a z-score for age and sex [14]. Dietary intakes and physical activity were assessed by child and adolescent-specific food frequency questionnaires and physical activity screeners developed by Block Dietary Data Systems (Nutriquest, Berkeley, CA) (http://nutritionquest.com/assessment/).

Statistical methods

A log-binomial model was fit to calculate an unadjusted prevalence ratio for IR comparing PHIV+ and PHEU participants, and prevalence ratios adjusted for Tanner stage, age, sex, and race/ethnicity. Inverse probability weights were used to adjust for Tanner stage and age. Cox proportional hazards models were used to identify factors associated with incident IR and resolution of IR. Covariates significantly associated with incident IR or resolution of IR at $p<0.10$ or with univariable hazard ratios showing at least a 50% increase or decrease in the hazard of IR or resolution of IR were included in respective multivariable models. Due to

the collinearity between BMI z-score and waist circumference, separate multivariable models were fit, including each one individually with the other covariates. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary NC).

Results

Three hundred and sixty-two PHIV+ and 185 PHEU participants had at least one set of simultaneous glucose and insulin levels measured. After excluding three PHIV+ participants with Type 2 diabetes mellitus, two on metformin, four with hepatitis C, one with chronic renal disease, and seven with high ALT values prior to or at baseline, 345 PHIV+ and 185 PHEU participants were available for analyses. PHIV+ were older than PHEU (mean age 15 vs. 11.1 yr) at baseline. A larger proportion of PHIV+ participants had also achieved sexual maturation (Tanner stage 5) at baseline compared to PHEU participants (52% vs. 12%). The unadjusted prevalence of IR in the PHIV+ was 27.3% (95% CI 22.6–32.3%) vs 34.1% (95% CI 27.3–41.4%) in the PHEU group. After adjustment for Tanner stage, age, sex, and race/ethnicity, however, there was no significant difference in the prevalence of IR between the two groups [prevalence ratio (95% CI): 1.02 (0.70, 1.48)].

After excluding the 94 PHIV+ participants with IR at baseline, the incidence of IR over follow-up among the remaining 251 PHIV+ participants was 14.6/100 person-years (95% CI: 11.2–18.8/100 person-years, N=62 cases, 423.2 person-years at risk). At the start of follow-up, mean (SD) age was 15.1 (2.9) yr, 51% were female, mean (SD) BMI z-score was 0.0 (1.1), and mean (SD) waist circumference was 73.5 ± 11.4 cm (Table 1). Factors positively associated with the development of IR assessed by univariable analysis included female sex, higher BMI z-score, and higher waist circumference. Race/ethnicity and fasting lipids were not associated with IR. Viral load, CD4 count, history of AIDS-defining event, and specific ARV use were not significantly associated with incident cases of IR (Table 1). Additionally, physical activity (minutes/day), TV exposure, and carbohydrate/fat intake were not significantly associated with incident cases of IR (data not shown). In multivariable analyses, only higher BMI z-score and waist circumference at baseline were significantly associated with development of IR, although females had a marginally significantly increased hazard of IR compared to males (Tables 2a and 2b). Of the 62 incident cases of IR, 47 (76%) had OGTT results available. Two (4%) had IFG only, 2 (4%) IGT only, and 1 (2%) had both IFG and IGT. None had a HbA1c > 48 mmol/mol.

Among the 94 participants with IR at baseline, 43 had resolution of their IR over a follow-up of 155.4 person-years, yielding a resolution rate of 27.7/100 person-years (95% CI 20.0, 37.3). At baseline, mean (SD) age was 14.8 (2.5) yr, 59% were female, mean (SD) BMI z-score was 1.1 (1.0), and mean (SD) waist circumference was 86.7 (16.2) cm (data not shown). Factors positively associated with resolution of IR assessed by univariable analysis included male sex and lower BMI z-score. None of the other metabolic or HIV-specific factors, such as physical activity, diet, CD4, viral load, or specific ART use, were significantly associated with resolution of IR in univariable analyses. In multivariable analyses, only male sex and lower BMI z-score were consistently associated with resolution of IR, although, in the model including waist circumference, lower waist circumference was marginally associated with resolution of IR and those who used lopinavir/ritonavir at

baseline were twice as likely to show resolution of IR. (Table 3a and 3b). Of the 27 participants who used lopinavir/ritonavir at baseline, seven (26%) had switched from lopinavir/ritonavir at the time of resolution or the last visit.

4. Discussion

Insulin resistance is a contributor to the metabolic syndrome, a cluster of risk factors (in childhood including abdominal obesity, hypertriglyceridemia, low HDL cholesterol, hypertension, and elevated fasting plasma glucose) [15] that predisposes to CVD and type 2 diabetes. This was first described in HIV-infected adults 35 years ago [16]. The exact etiology of IR in the HIV setting remains unknown, but is likely multifactorial, with contributions from traditional risk factors (*e.g.,* obesity, family history, and racial/ethnic background), co-morbid conditions (*e.g.,* hepatitis C virus infection), ARV-related factors (*e.g.,* direct effects of protease inhibitors, cumulative exposure to nucleoside reverse transcriptase inhibitors, hepatic steatosis, and fat redistribution), and HIV itself (*e.g.,* chronic inflammation) [17]. Mechanistically, IR may result from an abnormal hormonal secretory profile by adipose tissue; non-competitive, reversible direct inhibition of the insulin-responsive facilitative glucose transporter isoform 4 (GLUT4) in muscle and fat; and/or mitochondrial abnormalities including reduction in mitochondrial DNA (mtDNA) copies/cell and decreased oxygen consumption [18–22].

We demonstrate in this study that the prevalence of IR in the PHIV+ children in PHACS/AMP was 27.3% and 34.1% in the PHEU group. After adjustments for Tanner stage, age, sex, and race/ethnicity, however, there was no significant difference in the prevalence of IR between the two groups. In this report, IR in the PHIV+ cohort was almost twice as prevalent as in our prior study [11]; however, only 5/62 subjects who developed IR over time had an abnormality of glucose tolerance (vs 10/45 with IR in our previous study) and none met criteria for diabetes in either study. This contrasts with two cases of diabetes at baseline, with no incident cases, and no cases of IFG at baseline and two incident cases in the National Institute of Child Health and Human Development International Site Development Initiative (NISDI) Pediatric Latin American Countries Epidemiologic Study (PLACES) cohort [23]. This increase in prevalence of IR in the current study (compared to our prior report) is likely related to the older age and greater degree of pubertal maturation in the current PHIV cohort. Use of a central laboratory for assessment of insulin and glucose compared to local laboratories, as was done in the previous analysis, may also account for some of the difference in prevalence of IR among PHIV in both studies. The prevalence of IR in HIV+ youth in other recent smaller studies ranged from 5.3–6.8% in Latin America [8,23], 10.0% in South Africa [3], 11.2–40.7% in Spain [4,7,24,25], and 42.9% in Thailand [5]. A possible explanation for these disparate results includes the fact that different definitions of IR by HOMA are used in different series, reflecting a failure to adjust for the normally lower insulin sensitivity that occurs during puberty compared to pre-puberty. Historically, the reported prevalence of IR is 25–33% in HIV-infected adults [26]. Of note, our current prevalence in HIV+ youth approximates the 34.9% prevalence of IR by HOMA-IR recently reported in 219 HIV-infected Peruvian adults with HIV on highly active ART [27].

In a previous study of this cohort, PHEU children had higher BMI z-scores than did PHIV+, and were more likely to be obese [28]. Our finding of an approximately 30% prevalence of IR in both groups in the current analysis is substantially higher than the prevalence reported in over 2000 Korean non-overweight, non-obese healthy adolescents (4.9%) [29], but mirrors the high prevalence of IR found in otherwise healthy obese youth. In a study of 1356 obese youth (2–19 years), 53.8% of 9–11-year-olds and 79.3% of those > 12 years old manifested IR by HOMA-IR, although the cut-off used of 2.5 did not take into account the naturally decreased insulin sensitivity of puberty [30]. In a study of 100 obese Spanish youth (11.6 ± 2.7 yr), the prevalence of IR was 29% by HOMA-IR [31]. Of note, other methods of assessment of IR may yield different prevalences of IR. For example, in the aforementioned Spanish study of non-HIV-infected obese youth, when defining IR by serum insulin responses to an oral glucose load, the prevalence of IR increased to 50% [30], which may reflect greater sensitivity of detection of IR derived from 2-hr OGTT glucose and insulin data than by fasting values alone [32]. The gold standard for quantifying IR in adolescents is the euglycemic hyperinsulinemic clamp. The frequently sampled intravenous glucose tolerance test (FSIVGTT) and steady-state plasma glucose (SSPG) methods are also valid measurements. However, for large cohort studies, these methods are labor-intensive, require intravenous infusions and frequent blood sampling, are burdensome for participants, are expensive, and require a research setting for optimal performance [33].

Longitudinal data regarding the natural history of IR in HIV+ children are relatively sparse [18]. In a Latin-American cohort, 3.8% developed IR during follow-up (in addition to 5.5% of children who had IR at baseline) [23]. In multivariable analyses, only higher BMI z-score and waist circumference were significantly associated with development of new IR in our study, although females had a marginally significantly increased risk of IR compared to males. Conversely, only male sex and lower BMI z-score were associated with resolution of IR, although, in the model including waist circumference, use of lopinavir/ritonavir at baseline was significantly associated with an over twofold rate of resolution compared to no use at baseline. A lower waist circumference was also marginally associated with resolution of IR. The associations of female gender and increased BMI/waist circumference are not unexpected as these are well known to predict risk of IR in healthy populations [30]. Thus, it stands to reason then that resolution of IR would be greater in males and with decreasing BMI/waist circumference even in an HIV+ population.

Other studies have suggested a relationship between the use of protease inhibitors and IR. The association of improvement in insulin sensitivity that we found with usage of lopinavir/ritonavir is somewhat unexpected and of unclear etiology. Lack of adherence to lopinavir/ritonavir is an unlikely explanation given that viral loads were higher during follow-up among those whose IR did not resolve. In normal males, short-term use of this combination leads to a deterioration in glucose tolerance at the 2-hour time point of an OGTT, without a significant change in insulin-mediated glucose disposal rate as determined by a euglycemic hyperinsulinemic clamp [34]. In a cross-sectional study in consecutive HIV-infected adults treated with regimens containing efavirenz, lopinavir/ritonavir or atazanavir, HOMA-IR was greatest in those subjects treated with lopinavir/ritonavir [35]. Furthermore, in adult males with HIV, the incidence of insulin resistance and metabolic syndrome was increased by use of lopinavir/ritonavir [36].

Factors known to be associated with increasing IR in healthy children also include puberty and race/ethnicity [30]. Puberty was not a factor in our comparison between PHIV and PHEU youth as we adjusted for Tanner stage in statistical analysis. As to race/ethnicity, there were no significant differences between groups recognizing that IR is ordinarily most common in African-Americans and Hispanics, which constituted the bulk of our cohort (~90% in both groups) perhaps making it difficult to detect differences between other races/ethnicities.

There are strengths and limitations to the study. This is a well-characterized longitudinal cohort in which glucose and insulin levels were assayed in a central laboratory to standardize measurements. We may have had limited power to detect differences in the incidence or resolution of IR by factors that are not common and we needed to impute Tanner staging in some participants who had not reached Tanner stage 5. Additionally, allocation to treatment with ARVs was not randomized so that these drugs may have been used differently in groups that also had different IR risks.

Although only a small percentage of those youth in our study with IR, even when persistent, had associated disturbances in glucose metabolism, the possibility of future abnormalities, including type 2 diabetes, as well as development of other components of the metabolic syndrome, *i.e.,* high blood pressure and unfavorable lipid profiles, remains a concern as HIV-infected youth face an increasing risk of obesity in adulthood and a lifetime exposure to both HIV disease and its treatment.

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Table 1

Baseline* characteristics of HIV-infected incident study population by incident insulin resistance during follow-up

		Insulin Resistance	
	Total (N=251)	**Yes (N=62)**	**No (N=189)**
Female Sex, N (%)	128 (51)	38 (61)	90 (48)
Race/ethnicity, N (%)			
White/Multi/Other Non-Hispanic	28 (11)	8 (13)	20 (11)
Black Non-Hispanic	166 (66)	40 (65)	126 (67)
Hispanic	57 (23)	14 (23)	43 (23)
Age (years)			
Mean (SD)	15.1 (2.9)	14.1 (3.0)	15.4 (2.9)
Median (IQR)	15.5 (12.4, 17.2)	14.2 (11.4, 16.4)	15.8 (13.5, 17.3)
Tanner stage			
1	11 (4)	1 (2)	10 (5)
2	27 (11)	10 (16)	17 (9)
3	43 (17)	14 (23)	29 (15)
4	41 (16)	7 (11)	34 (18)
5	129 (51)	30 (48)	99 (52)
BMI Z-score			
Mean (SD)	0.0 (1.1)	0.4 (1.3)	−0.1 (1.0)
Median (IQR)	0.0 (−0.7, 0.7)	0.4 (−0.3, 1.5)	−0.2 (−0.8, 0.6)
Missing, N (%)	11 (4)	0 (0)	11 (6)
Waist circumference (cm)			
Mean (SD)	73.5 (11.4)	76.6 (13.3)	72.4 (10.5)
Median (IQR)	72.0 (64.8, 80.0)	76.6 (66.3, 85.2)	70.6 (64.8, 77.6)
Missing, N (%)	12 (5)	0 (0)	12 (6)
Total cholesterol > 5.2 mmol/L, N (%)	30 (12)	8 (13)	22 (12)
LDL cholesterol > 3.4 mmol/L, N (%)	16 (6)	5 (8)	11 (6)
Triglycerides > 1.2 mmol/L (age < 10 yr) or > 1.7 mmol/L (age ≥ 10 yr), N (%)	39 (16)	7 (11)	32 (17)
HDL cholesterol < 0.9 mmol/L, N (%)	32 (13)	8 (13)	24 (13)
Use of medications associated with hyperglycemia – N (%)	61 (24)	14 (23)	47 (25)
Log_{10} viral load (log_{10} copies/mL)†			
Mean (SD)	2.5 (1.2)	2.5 (1.2)	2.5 (1.2)
Median (IQR)	1.9 (1.7, 3.4)	1.7 (1.7, 3.4)	1.9 (1.7, 3.4)
Missing, N (%)	10 (4)	5 (8)	5 (3)
Viral load (copies/mL), N (%)†			
< 400	151 (60)	35 (56)	116 (61)
400–5000	41 (16)	10 (16)	31 (16)
> 5000	49 (20)	12 (19)	37 (20)
Missing	10 (4)	5 (8)	5 (3)
Percent of viral loads > 400 copies/mL during follow-up			

		Insulin Resistance	
	Total (N=251)	**Yes (N=62)**	**No (N=189)**
Mean (SD)	34.7 (39.4)	35.7 (41.9)	34.3 (38.7)
Median (IQR)	14.3 (0, 73.3)	10.6 (0, 85.7)	16.7 (0, 70.6)
Missing	8 (3)	0 (0)	8 (4)
Viral load (copies/mL) at end of follow-up (event/last HOMA-IR measurement), N (%)[†]			
< 400	154 (61)	40 (65)	114 (60)
400–5000	41 (16)	11 (18)	30 (16)
> 5000	49 (20)	10 (16)	39 (21)
Missing	7 (3)	1 (2)	6 (3)
CD4 count (cells/mm^3)[†]			
Mean (SD)	667 (336)	673 (326)	665 (340)
Median (IQR)	663 (461, 854)	625 (489, 847)	672 (449, 872)
Missing, N (%)	7 (3)	2 (3)	5 (3)
CD4 count (cells/mm^3), N (%)[†]			
< 200	21 (8)	3 (5)	18 (10)
200–350	22 (9)	5 (8)	17 (9)
351–500	31 (12)	8 (13)	23 (12)
> 500	170 (68)	44 (71)	126 (67)
Missing	7 (3)	2 (3)	5 (3)
History of an AIDS-defining event, N (%)	63 (25)	12 (19)	51 (27)
Abacavir, N (%)			
Ever up to baseline	110 (44)	26 (42)	84 (44)
Ever up to end of follow-up	118 (47)	28 (45)	90 (48)
Current	65 (26)	17 (27)	48 (25)
Didanosine, N (%)			
Ever up to baseline	171 (68)	46 (74)	125 (66)
Ever up to end of follow-up	171 (68)	46 (74)	125 (66)
Current	32 (13)	5 (8)	27 (14)
Stavudine, N (%)			
Ever up to baseline	190 (76)	49 (79)	141 (75)
Ever up to end of follow-up	190 (76)	49 (79)	141 (75)
Current	22 (9)	7 (11)	15 (8)
Amprenavir, N (%)			
Ever up to baseline	17 (7)	3 (5)	14 (7)
Ever up to end of follow-up	17 (7)	3 (5)	14 (7)
Current	1 (0)	0 (0)	1 (1)
Fosamprenavir, N (%)			
Ever up to baseline	9 (4)	2 (3)	7 (4)
Ever up to end of follow-up	9 (4)	2 (3)	7 (4)
Current	2 (1)	1 (2)	1 (1)
Indinavir, N (%)			

		Insulin Resistance	
	Total (N=251)	**Yes (N=62)**	**No (N=189)**
Ever up to baseline	10 (4)	5 (8)	5 (3)
Ever up to end of follow-up	10 (4)	5 (8)	5 (3)
Current	0 (0)	0 (0)	0 (0)
Lopinavir/ritonavir, N (%)			
Ever up to baseline	149 (59)	40 (65)	109 (58)
Ever up to end of follow-up	151 (60)	41 (66)	110 (58)
Current	83 (33)	24 (39)	59 (31)
Nelfinavir, N (%)			
Ever up to baseline	147 (59)	35 (56)	112 (59)
Ever up to end of follow-up	147 (59)	35 (56)	112 (59)
Current	18 (7)	5 (8)	13 (7)
Ritonavir, N (%)			
Ever up to baseline	193 (77)	49 (79)	144 (76)
Ever up to end of follow-up	204 (81)	52 (84)	152 (80)
Current	144 (57)	39 (63)	105 (56)
Saquinavir, N (%)			
Ever up to baseline	25 (10)	5 (8)	20 (11)
Ever up to end of follow-up	25 (10)	5 (8)	20 (11)
Current	3 (1)	1 (2)	2 (1)

[*] Baseline defined as date of first HOMA measurement

[#] Closest measurement prior to or at baseline

[†] Closest measurement within 6 mo prior to baseline

Table 2a

Multivariable risk factors for incident insulin resistance among HIV-infected adolescents during follow-up (N=234) (including BMI Z-score)

	Univariable Hazard Ratio (95% CI)	P-value	Multivariable Hazard Ratio (95% CI)	P-value
Female Sex (reference = Male)	1.72 (1.03, 2.87)	0.04	1.62 (0.94, 2.80)	0.08
Tanner stage (reference = 1)		0.08		0.26
2	5.50 (0.70, 43.25)		5.19 (0.65, 41.16)	
3	4.12 (0.54, 31.48)		3.14 (0.40, 24.81)	
4	2.81 (0.34, 22.91)		1.92 (0.23, 16.30)	
5	6.01 (0.81, 44.49)		3.23 (0.41, 25.69)	
BMI Z-score (for every SD increase)	1.57 (1.22, 2.02)	<0.001	1.44 (1.10, 1.89)	0.01
Percent of viral loads > 400 copies/mL during follow-up (for every percent increase)	1.01 (1.00, 1.01)	0.05	1.00 (1.00, 1.01)	0.37
Didanosine: Ever up to end of follow-up (reference = never use)	1.55 (0.88, 2.74)	0.12	1.15 (0.58, 2.25)	0.69
Stavudine: Ever up to end of follow-up (reference = never use)	1.56 (0.84, 2.89)	0.15	1.29 (0.63, 2.66)	0.49
Ritonavir: Ever up to end of follow-up (reference = never use)	1.55 (0.79, 3.06)	0.18	1.09 (0.51, 2.33)	0.82

CI: confidence interval, SD: standard deviation

Table 2b

Multivariable risk factors for incident insulin resistance among HIV-infected adolescents during follow-up (N=232) (including waist circumference)

	Univariable Hazard Ratio (95% CI)	P-value	Multivariable Hazard Ratio (95% CI)	P-value
Female Sex (reference = Male)	1.64 (0.98, 2.74)	0.06	1.62 (0.95, 2.78)	0.08
Tanner stage (reference = 1)		0.08		0.26
2	5.49 (0.70, 43.12)		4.61 (0.58, 36.83)	
3	4.21 (0.55, 32.13)		2.99 (0.38, 23.55)	
4	3.03 (0.37, 24.75)		1.69 (0.20, 14.26)	
5	6.28 (0.85, 46.51)		2.47 (0.30, 19.99)	
Waist circumference (for every cm increase)	1.04 (1.02, 1.07)	<0.001	1.04 (1.02, 1.06)	<0.001
Percent of viral loads > 400 copies/mL during follow-up (for every percent increase)	1.01 (1.00, 1.01)	0.08	1.00 (1.00, 1.01)	0.50
Didanosine: Ever up to end of follow-up (reference = never use)	1.58 (0.89, 2.79)	0.11	1.05 (0.54, 2.04)	0.90
Stavudine: Ever up to end of follow-up (reference = never use)	1.60 (0.86, 2.98)	0.12	1.42 (0.69, 2.93)	0.34
Ritonavir: Ever up to end of follow-up (reference = never use)	1.56 (0.79, 3.08)	0.18	1.20 (0.57, 2.50)	0.63

CI: confidence interval, SD: standard deviation

Table 3a

Multivariable risk factors for resolution of insulin resistance among HIV-infected adolescents during follow-up (N=92) (including BMI Z-score)

	Univariable Hazard Ratio (95% CI)	P-value	Multivariable Hazard Ratio (95% CI)	P-value
Female Sex (ref=Male)	0.46 (0.25, 0.86)	0.02	0.33 (0.17, 0.66)	0.002
Race/ethnicity (ref= White/Multi/Other Non-Hispanic)		0.38		0.76
Black Non-Hispanic	0.44 (0.15, 1.27)		0.66 (0.21, 2.04)	
Hispanic	0.51 (0.16, 1.68)		0.73 (0.20, 2.65)	
Tanner stage (reference = 1)		0.85		0.72
2	0.48 (0.13, 1.79)		0.84 (0.21, 3.34)	
3	0.65 (0.20, 2.15)		0.66 (0.17, 2.57)	
4	0.78 (0.23, 2.63)		0.98 (0.27, 3.62)	
5	0.76 (0.28, 2.08)		1.32 (0.42, 4.17)	
BMI Z-score (for every SD increase)	0.70 (0.50, 0.99)	0.04	0.63 (0.44, 0.92)	0.02
CD4 count (cells/mm^3, reference = > 500 cells/mm^3)		0.49		0.21
< 350	0.64 (0.15, 2.69)		0.72 (0.17, 3.08)	
351–500	1.63 (0.63, 4.20)		2.38 (0.84, 6.71)	
Lopinavir/ritonavir: Current (reference = no current use)	1.66 (0.88, 3.13)	0.13	1.92 (0.94, 3.94)	0.07

CI: confidence interval, SD: standard deviation

Table 3b

Multivariable risk factors for resolution of insulin resistance among HIV-infected adolescents during follow-up (N=87) (including waist circumference)

	Univariable Hazard Ratio (95% CI)	P-value	Multivariable Hazard Ratio (95% CI)	P-value
Female Sex (reference = Male)	0.45 (0.24, 0.85)	0.01	0.32 (0.16, 0.67)	0.002
Race/ethnicity (reference = White/Multi/Other Non-Hispanic)		0.40		0.73
Black Non-Hispanic	0.45 (0.16, 1.29)		0.64 (0.20, 2.04)	
Hispanic	0.45 (0.14, 1.52)		0.60 (0.16, 2.30)	
Tanner stage (reference = 1)		0.85		0.81
2	0.48 (0.13, 1.80)		0.68 (0.17, 2.82)	
3	0.65 (0.19, 2.27)		0.50 (0.10, 2.53)	
4	0.78 (0.23, 2.63)		0.78 (0.18, 3.28)	
5	0.77 (0.28, 2.11)		0.97 (0.19, 4.92)	
Waist circumference (for every cm increase)	0.98 (0.96, 1.00)	0.06	0.98 (0.95, 1.00)	0.09
CD4 count (cells/mm^3, reference = > 500 cells/mm^3)		0.58		0.37
< 350	0.82 (0.19, 3.43)		1.04 (0.24, 4.64)	
351–500	1.65 (0.64, 4.27)		2.16 (0.73, 6.33)	
Didanosine: Ever up to end of follow-up (reference = never use)	1.51 (0.74, 3.07)	0.25	1.64 (0.59, 4.51)	0.34
Lopinavir/ritonavir: Current (reference = no current use)	1.88 (0.98, 3.60)	0.06	2.42 (1.17, 4.99)	0.02

CI: confidence interval