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Morphologic and Metabolic Abnormalities in Vertically HIV-infected Children and Youth

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Abstract

Objective—To compare the distribution of lipid and glucose abnormalities and altered fat distribution among vertically HIV-infected subjects and controls.

Design—Cross-sectional multicenter study in HIV-infected (HIVpos) subjects 7-24 years, stratified by Tanner stage and protease inhibitor (PI) use (PI; N=161 and non-PI; N=79) and seronegative controls (HIVneg; N=146).

Methods—Measurements included fasting lipids, glucose, insulin, 2-h oral glucose tolerance test, dual-energy X-ray absorptiometry, anthropometry, and ART and medical histories. Multiple linear regression models were used to compare distributions between HIVpos and HIVneg.

Results—Both HIVpos groups had long exposures to ART. PI and non-PI had similar current CD4 count and HIV RNA, but PI had lower nadir CD4, higher peak HIV RNA, and more advanced CDC disease stage. In adjusted analyses, both HIVpos groups had significantly lower mean z-scores for height, weight, BMI, and total and limb fat, compared with HIVneg. Mean triglycerides were significantly higher and HDL cholesterol lower in both HIVpos groups relative to HIVneg. PI also had significantly higher mean total, LDL, and non-HDL cholesterol. Mean fasting insulin was higher in both HIVpos groups, and 2-h glucose and insulin were higher in the PI group. Ritonavir was associated with increasing dyslipidemia and altered glucose metabolism.

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Preliminary results of this study were presented at the 9th International Workshop on Lipodystrophy and Adverse Drug Reactions in Sydney, Australia, July 2007.

Conclusions—In a large group of vertically-infected children/youth with extensive ART exposure, height, weight, and total and limb fat were lower than in controls. There was a high prevalence of lipid abnormalities among those on PI and evidence of developing insulin resistance, factors that may accelerate lifetime risk for cardiovascular disease.

Background

The use of combination antiretroviral therapy (ART) drastically reduces the mortality and morbidity associated with HIV infection[1-5] but is often associated with metabolic alterations involving glucose and dyslipidemia, and abnormalities in body fat distribution, including subcutaneous fat loss and/or central fat accumulation [6]. These alterations are likely a result of complex interactions between HIV infection, specific antiretroviral agents, race, gender and age, as well as host genetic and lifestyle factors[7]. The resemblance of these alterations to metabolic syndrome further complicates the analysis, as rates of childhood obesity and type 2 diabetes mellitus increase[8-11].

For children facing the prospects of life-long treatment with ART, the development of these complications is of particular concern. There are limited pediatric data on the prevalence of these abnormalities. Estimates range from 1 to 68% in studies with small numbers of subjects or lacking appropriate comparison groups[12-28]. The inclusion of appropriate controls is important since many HIV- infected children belong to racial/ethnic groups with high background rates of obesity, cardiovascular disease (CVD) and diabetes. Body composition varies with age, gender and race, and pubertal development unmasks lipid and glucose abnormalities in both HIV negative and positive children[29-31]. HIV is associated with delayed puberty, and children are often smaller and shorter than their peers, further complicating direct comparison. The objective of this study was to compare the distribution of morphologic and metabolic outcomes in two groups of vertically HIV-infected (HIVpos) children and youth on ART (protease inhibitor [PI] users and non-PI users), with those in a group of HIV-uninfected (HIVneg) controls of similar gender, race, and Tanner stage.

Methods

Study design and selection of participants

This cross-sectional study used a stratified sampling design to select a representative sample of HIVpos children/youth aged 7–24 years across six strata defined by PI use (PI: currently on the same PI at least 12 months; non-PI: currently on ART but less than two weeks lifetime exposure to PIs) and Tanner stage (Tanner 1, 2-3, and 4-5). Participants were selected at 37 Pediatric AIDS Clinical Trials Group (PACTG) sites. Probabilities to determine if a child would be invited to enroll in the study were generated for each stratum based on the estimated number of eligible children/youth, a sample size of 50, and an expected 25% refusal/ineligibility rate.

The comparison population comprised 50 HIVneg children/youth enrolled into each of the three Tanner strata with gender and race/ethnicity distributions similar to those of the first 100 HIVpos subjects enrolled. This was a form of group-matching, rather than individual matching. The institutional review board at each clinical site approved the study and appropriate informed consent was obtained before enrollment.

Measurements

Anthropometry—Height, weight, and waist and hip circumferences were measured using standard techniques[32]. Study coordinators underwent standardized training and were required to show proficiency before performing measurements.

Dual energy X-ray Absorptiometry (DXA)—Whole body scans were performed to assess total lean body mass (LBM) and fat, and limb (arm+leg) and trunk fat. All scans were analyzed at Tufts University without knowledge of HIV status or PI use. A standard phantom was scanned on all DXA instruments used in the study.

Laboratory—Subjects fasted ≥ 8 hours before collection of samples for measurement of triglycerides, total, LDL, HDL, and non-HDL cholesterol (LDL-C, HDL-C, non-HDL-C) high sensitivity C-reactive protein (hsCRP), and lactate. A 2-hour oral glucose tolerance test (OGTT) was administered according to WHO guidelines-[33]. Glucose, insulin, proinsulin, and C-peptide were measured at baseline and 2 hours. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using fasting glucose and insulin [34].

All specimens were stored at -70°C , batched, and analyzed centrally (Quest Diagnostics, Baltimore, MD or Quest Diagnostics Nichols Institute, Chantilly, VA) at the end of the study. Plasma HIV-1 RNA levels (Monitor UltraSensitive Assay, Roche Molecular Diagnostics, Branchburg, NJ) and CD4 T cell counts were measured locally.

Disease history and other clinical data—Disease and ART history were collected by chart abstraction and interview. Dietary intake was evaluated using the Block Food Frequency Questionnaire (NutritionQuest, Berkeley, CA). Exercise data were collected by questionnaire in which subjects were asked if they exercised regularly, with ‘regularly’ defined as more than once a week.

Statistical methods

Standardization of measures—To account for the effects of age and gender, measurements were standardized using the HIVneg group as the reference population. For each body composition measure, local regression (LOESS) lines[35] were fit across age for HIVneg with a smoothing parameter of 90%. Lines were fit separately by gender up to 18 years of age only, because few subjects over 18. Using the predicted mean outcome at a given age, a Z-score could then be calculated. A Z-score of “0” on this scale corresponds to the mean of the P1045 HIVneg participants for a given age and gender. To check if results were sensitive to the analytic scale, model-fitting was repeated using Z-scores calculated from available NHANES IV outcomes[36]. Conclusions were similar so results are presented using the LOESS-generated Z-scores based on our HIVneg. Laboratory outcomes were $\log_{10}$ transformed when used in multivariate analyses.

Unadjusted analyses—Unadjusted pairwise comparisons were done across strata using Fisher’s exact test for categorical outcomes and Wilcoxon rank sum tests for continuous outcomes. Median age at initiation of puberty (moving from Tanner stage 1 to 2), was estimated using Turnbull’s algorithm[37] and compared using an exponential survival model.

Adjusted analyses—Multiple linear regression models were used to test for differences in each HIVpos group compared to HIVneg adjusted for potential confounders including race/ethnicity, Tanner stage, CDC disease category (HIVneg set to N/A), gender and CDC BMI z-scores[38] (for laboratory outcomes) and height Z-scores (for circumferences and body fat), excluding Z-scores < -3 or > 3 and laboratory outcomes $< 2^{\text{nd}}$ or $> 98^{\text{th}}$ percentile. Predicted mean Z-scores were calculated for each HIV/PI group at selected levels of each determinant in the model.

Association of ART with outcomes in HIVpos—We used multivariate linear regression models to evaluate the effect of time on specific nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs on each outcome

in the HIV-pos subjects, adjusted for the confounders listed above. Medication exposure was modeled as years on each of the following medications in the participant's current regimen: ZDV, ddI, d4T, 3TC, nevirapine, lopinavir, ritonavir, nelfinavir, saquinavir. There were too few participants on other ARVs, so these were grouped into an 'other' category by class. Within each class, the medication with the longest duration of use defined the exposure time. Backwards selection was used to find the most parsimonious set of ART predictors for each outcome. As each individual drug was dropped from the model, the 'other' category was updated to the maximum time of that drug or any other drug in that class. If no individual ARVs were significant predictors, the simplest possible model would include a covariate for longest time on each drug class.

We report Wald p-values for the regression models using $p < 0.05$ to highlight specific comparisons, but it should be recognized that with the large number of outcomes and comparisons, some statistically significant results would be expected by chance. All analyses were conducted using Statistical Analysis Software (SAS Institute, Version 9.0, Cary, NC).

Results

Subject Characteristics

396 children/youth enrolled from January 2004 to July 2005. Only 55% of the targeted enrollment was achieved in the non-PI group. Five individuals were ineligible and five either withdrew consent or did not complete any study requirements, leaving 386 evaluable participants (161 PI, 79 non-PI, 146 HIVneg).

Distributions for most demographic, lifestyle and nutritional characteristics were similar across groups (Table 1). Median age of non-PI was greater than HIVneg ($p = 0.033$). Both HIVpos groups tended to have an older estimated median age at initiation of puberty, but the differences were significant only for males on PI ($p = 0.047$). Groups were similar in the proportion of participants exercising regularly, hours spent watching television and with family histories diabetes, coronary heart disease and lipid disorders. Median levels of energy or macronutrient intake were also similar.

CD4 count and HIV-1 RNA levels were similar in PI and non-PI (Table 2). However, there was evidence of differences in past disease severity, with the PI group having lower median nadir CD4 counts ($p < 0.001$), higher median peak HIV-1 RNA ($p < 0.001$) and a higher proportion of participants in CDC disease category C than non-PI ($p < 0.001$).

Both HIVpos groups had long histories of exposure to ART, with a median time since starting any ARVs of 9.9 and 9.0 years in PI and non-PI, respectively ($p = 0.050$, data not shown). Participants in PI had a longer median exposure to NNRTIs in their current regimen ($p = 0.004$), but exposure to NRTIs did not differ between the groups ($p = 0.973$, Table 2). In PI, 109 (68%) participants were on NRTI/PI combinations, and 48 (30%) were on NRTI/NNRTI/PI combinations. Use of ritonavir in the current regimen, either as part of Kaletra® or in other regimens, was reported by 58% of subjects in PI. Forty-six percent of non-PI were on NRTI/NNRTI combination therapy and the rest were only on NRTIs.

Growth and body composition—Both HIVpos groups had lower mean Z-scores for height, weight and BMI, relative to HIVneg after adjusting for race/ethnicity, Tanner stage and CDC disease category (Fig. 1). Total and limb fat were lower in both HIVpos groups vs. HIVneg in adjusted models. Trunk fat tended to be lower, especially in non-PI, but the differences vs. HIVneg did not achieve statistical significance. The ratios of trunk-to-limb fat and waist-to-hip circumference were significantly greater in PI vs. HIVneg. LBM did not differ between groups.

Serum lipids

PI differed significantly from HIVneg in models adjusted for race/ethnicity, Tanner stage, CDC disease category, gender and BMI z-scores, with higher mean levels of triglycerides, total, LDL, and non-HDL, and total to HDL-C ratio, and lower HDL-C (Table 3). In non-PI, mean triglycerides were higher and HDL-C lower, relative to HIVneg. When laboratory values were classified as normal/abnormal, using levels previously published in studies of children [39-41], the PI group had a higher prevalence of abnormal lipid values than HIVneg (total cholesterol >200 mg/dL: 29% vs. 10%, LDL-C >130 mg/dL: 19% vs. 6%, HDL-C <35 mg/dL: 10% vs. 4%, non HDL-C >160 mg/dL: 24% vs. 3% and triglycerides >130 mg/dL: 52% vs. 13%). Except for HDL-C, similar rates of abnormal lipid values were seen in nonPI and HIVneg.

Glucose metabolism

Although median levels of fasting glucose did not differ, in adjusted analyses (Table 3), mean fasting glucose was marginally higher in non-PI relative to HIVneg. Fasting insulin and HOMA-IR had significantly higher adjusted means in both PI and non-PI compared to the HIVneg. Two-hour glucose and insulin levels were higher in PI, but not non-PI, compared to HIVneg. Values for other measures were similar across groups, although both fasting and 2-h C-peptide and lactate levels were marginally higher in the PI group relative to HIVneg. Rates of impaired fasting (100-125 mg/dL; 5% and 7%) and 2-hour glucose levels (140-199 mg/dL; 4% and 4%) in PI and non-PI were low and similar to HIVneg (7% and 1%). In the PI group, only 0.7% of fasting glucose values and 1.4% of 2-h glucose values met criteria[33] for diabetes. Rates of elevated lactate levels were low in all groups (HIVneg: 1%; non-PI: 3%; PI: 1%). Although there were no differences in median hsCRP levels, twice as many subjects in PI had elevated hsCRP (>3 mg/L), compared with controls (HIVneg: 11%; non-PI: 14%; PI: 20%).

Relationship between current time on ART and outcomes—Use of ritonavir (in either therapeutic or boosting doses) and nelfinavir were significantly associated with most lipid measures (Table 4). For each year of ritonavir use, there were predicted increases of 2.5% in total cholesterol, 2.4% in LDL-C, 3.7% in non-HDL-C, and 7.7% in triglycerides. For each year of nelfinavir use, there were predicted increases of 1.5, 2.5, 2.3, and 3.3% in total cholesterol, LDL-C, non-HDL-C, and triglycerides, respectively. Nevirapine and efavirenz were associated with annual increases of 1.7% and 1.9% in HDL-C.

Ritonavir was also associated with predicted annual increases in 2-h values for glucose, insulin, and C-peptide. In contrast, each year of nelfinavir use was associated with a slight decrease in fasting glucose.

Discussion

To evaluate morphologic and metabolic abnormalities among vertically HIV infected children/youth, we performed a cross-sectional study within the PACTG. To our knowledge, this is the largest survey in HIV-infected children/youth that uses objective measurements of both metabolic and morphologic outcomes and features a carefully selected control group.

We observed a high prevalence of dyslipidemia in those with HIV infection, particularly those on PI-containing regimens, consistent with other studies in HIV-infected children/youth[16, 20,23,42]. Using a cutpoint of 130 mg/dL, fasting levels of triglyceride were elevated in 52% and 20% of HIV infected children in the PI and non-PI groups, respectively. Abnormalities in total (29%), non-HDL (24%), LDL (19%) and HDL (10%) cholesterol were also frequently observed in the PI group. Differences between the HIVpos and HIVneg subjects remained

significant after adjusting for race/ethnicity, Tanner stage, gender, BMI z-score and CDC classification. In models that also included ART exposure history, longer exposure to PIs in the current regimen was associated with dyslipidemia (higher total, LDL, non-HDL cholesterol and triglycerides and lower HDL-C) as well as glucose abnormalities (2-hour insulin and glucose). When the effects of nelfinavir and ritonavir were included in these models, ritonavir exposure had greater effects on total, non-HDL and triglycerides than nelfinavir.

Dyslipidemia, particularly LDL-C >130 mg/dL, has been associated with an elevated risk of CVD in adults[43], and dyslipidemic children are more likely than their normolipidemic counterparts to be dyslipidemic as adults[39]. In addition, elevations in total and LDL-C and reduced levels of HDL-C are associated with the presence of early atherosclerotic lesions in adolescents and children[39]. Indeed, carotid intima media thickness was found to be higher in HIV-infected children, who also had higher levels of total and non-HDL-C and triglycerides, relative to seronegative controls matched for age, gender, race, and BMI[12]. The risk of CVD is further elevated in certain racial/ethnic groups and in those with a family history[44-46]. In the United States, HIV infection disproportionately affects African-American and Hispanic children/youth[47], who may bear increased risk for CVD. Over a third of our HIV-infected subjects had a family history of CVD, 26% had family members with hyperlipidemia, and 37% with type 2 diabetes. Although not significantly different from the controls, elevated hsCRP levels were observed almost twice as frequently in HIV-infected children/youth. In addition, almost half of our subjects reported exercising less than once a week and approximately one-third watched television for more than 3 hours daily. Inactivity and television viewing have been associated with increased risk of obesity in HIVneg children[48]. This combination of factors suggests that these children are at high risk of developing CVD and should be closely monitored. Until specific guidelines are developed for monitoring metabolic and morphologic changes in HIV infected children, published guidelines for adults can be followed[7,49]. Increased emphasis should be also placed on identifying effective ways to not just improve eating and exercise habits but also prevent children/youth from beginning to smoke cigarettes.

In contrast to the high prevalence of dyslipidemia, abnormal fasting or 2-h glucose values were relatively uncommon in all groups. Although impaired fasting glucose or glucose intolerance are observed frequently in obese children and adolescents[50], these abnormalities occur rarely, if at all, in nonobese children and adolescents[51,52], a group that would be more comparable to those in this study. It should be noted that although we saw no clinically relevant differences in fasting glucose, insulin levels were approximately 40% higher in both HIV-infected groups, consistent with other studies in which fasting insulin, but not glucose, was higher in HIV-pos children[14,53]. We also found that ritonavir use was significantly associated with increasing 2-hour (but not fasting) values for glucose, insulin, and C-peptide. Thus, this dynamic test revealed an association that was not evident in fasting measurements. Overall, our results and those of others provide evidence of developing insulin resistance and, potentially, increasing risk of diabetes, which could contribute to overall risk for CVD as exposure to ART lengthens.

Although ritonavir has long been recognized as a major factor in PI-associated dyslipidemia [54,55], our results and other recent studies point to an emerging role in insulin resistance as well. For example, in the Multicenter AIDS Cohort Study, ritonavir was the only PI associated with increased incidence of diabetes or hyperglycemia[48]. In addition, a study in healthy HIV-uninfected volunteers demonstrated that 4 weeks of exposure to ritonavir, in either a therapeutic or boosting dose combined with lopinavir, decreased insulin sensitivity[56,57]. The significant relationships of exposure to didanosine with fasting C-peptide and triglycerides are consistent with the recent observation that didanosine was associated with increased risk of diabetes in a large cohort study of HIV-infected adults[58].

Our DXA results demonstrated that both groups of HIV-infected subjects had significantly lower mean Z-scores for limb fat, which is consistent with observations from other cross-sectional studies that employed an objective measure of fat distribution[59] or clinical criteria to define lipoatrophy[20,23,42]. The extent to which this is due to impaired growth trajectories in vertically infected youth[31], or specific effects of ART on fat distribution cannot be discerned. The cross-sectional study design also prevents us from stating whether the difference is a result of specific fat loss or failure to accrue fat at the expected rates. Given the concerns about disfigurement and forced disclosure of HIV status among adults with lipoatrophy, low levels of extremity fat among HIV-infected children/youth may become an important factor in adherence to ART and may warrant interventions. Notably, a recent study demonstrated that substitution of tenofovir for d4T and an NNRTI for a PI in HIV-infected children with lipoatrophy normalized the rate of fat accrual in HIV-infected children[60].

Predicted mean Z-scores for trunk fat were, if anything, lower than those in HIVneg controls, which is consistent with studies that did not match for BMI[60-62]. A limitation is that DXA cannot distinguish between visceral and subcutaneous fat. Use of computed tomography in one study revealed no difference between PI-treated and PI-naïve HIV-pos children in either visceral or subcutaneous fat[17]. Other studies using magnetic resonance imaging have identified subgroups of HIV-infected children and adolescents with higher-than-normal volumes of visceral fat[59,63]. Given evidence of reduced levels of limb fat in the HIV-infected groups in this study, it is possible there may have been concomitant reduction in or impaired accrual of subcutaneous fat in the central region with relative sparing or even accumulation of visceral fat in these groups. The implications of conserved visceral fat on long-term cardiovascular risk are unknown.

We cannot account for the effects of delayed puberty or impeded growth trajectories in this analysis, but it is notable that Z-scores for LBM in both HIV-pos groups were not different from HIVneg. Thus, it appears that the lower weight and BMI in the HIV-infected groups was entirely attributable to differences in fat, primarily in the extremities. This pattern is strikingly different from that seen in vertically HIV-infected children studied before the HAART era, who were reported to have significantly lower levels of LBM with relative sparing of fat[64].

A strength of our study is that it featured a recruitment strategy that was designed to balance the groups with regard to gender, race, and Tanner stage. However, like all cross-sectional studies, our study has several important limitations. Although the two HIV-infected groups were similar with regard to current CD4 count or viral load, the PI group showed evidence of more extensive disease history and had longer exposure to NNRTIs. In addition, although our HIVneg and HIVpos subjects were chosen from similar backgrounds, we cannot exclude differences in important potential confounders. Our random selection procedures were designed to provide a representative sample of HIV-infected children/youth from sites and minimize selection bias, but about 40% of these candidates declined to participate. The reasons for refusal are unknown but if related to outcome measures, our sample may be biased. Although the LOESS Z-scores calculated relative to the study HIVneg yielded similar results to those from NHANES IV data when available, our Z-scores were based on a comparatively small number of subjects. As stated earlier, with the large number of outcomes reported, some statistically significant results may occur by chance. Finally, the fact that only 55% of the targeted enrollment was achieved in the non-PI group may have impaired our ability to detect associations between metabolic alterations among subjects on non-PI containing regimens and the potential role of individual NNRTIs in these alterations. The greater reliance on PI-based regimens in this population may reflect the challenges of managing the disease in this population with a long history of exposure to ART.

In summary, the current study included a randomized sampling design and comprehensive assessment of metabolic and morphologic alterations using objective techniques in a large group of vertically HIV-infected children and youth and seronegative controls. It revealed a high prevalence of dyslipidemia and evidence of reduced peripheral fat among the HIV—infected children. Ritonavir was associated with increased risk of dyslipidemia and altered glucose metabolism. These factors may combine to increase risk of CVD in children who are likely to be facing a lifetime of exposure to ART. Our data underscore the need for promoting lifestyles (diet, exercise, reduced television watching, smoking cessation) that decrease cardiovascular risk[65-70]. Further, they provide a rationale for continuing efforts to untangle the role of HIV infection and its treatment from genetic, developmental and lifestyle factors, which is essential to understanding basic pathophysiologic mechanisms and for the design of appropriate interventions to reverse or minimize progression of these complications.

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Figure 1.

Anthropometric outcomes: predicted mean z-scores and 95% confidence intervals for a Black, CDC disease category A, Tanner 2-3, height z-score of 0 child in PI, nonPI and HIVneg groups. Statistical significance (p) shown for comparisons of PI and nonPI groups relative to HIVneg.

Table 1
Demographic and selected nutrition and lifestyle characteristics by HIV status and PI use

Characteristic	Level	HIV-uninfected			HIV-infected			p-value ¹	
		HIVneg (n=146)	HIVpos (n=240)	PI (n=161)	Non PI (n=79)	HIVpos vs HIVneg	PI vs HIVneg	Non PI vs HIVneg	Non PI vs HIVneg
Gender (N, %) ²	Male	84 (57.5)	127 (52.9)	90 (55.9)	37 (46.8)	0.400	0.818	0.161	0.775
Race/ethnicity (N, %)	White non-Hisp.	17 (11.6)	27 (11.3)	16 (9.9)	11 (13.9)				
	Black non-Hisp.	80 (54.8)	131 (54.6)	87 (54.0)	44 (55.7)				
	Hispanic	46 (31.5)	78 (32.5)	56 (34.8)	22 (27.8)				
	Other	3 (2.1)	4 (1.7)	2 (1.2)	2 (2.5)				
Tanner stage (N, %)	1	47 (32.2)	70 (29.2)	52 (32.3)	18 (22.8)	0.734	0.928	0.293	
	2-3	50 (34.2)	91 (37.9)	58 (36.0)	33 (41.8)				
	4-5	49 (33.6)	79 (32.9)	51 (31.7)	28 (35.4)				
Age (median)		11.9	12.6	12.4	12.9	0.053	0.170	0.033	
Estimated median age (yrs) at initiation of puberty	Male	10.3	11.1	10.9	11.1	0.041	0.047	0.361	
	Female	9.5	9.8	10.1	9.7	0.721	0.639	0.925	
Exercise regularly ³ (N, %)	Yes	80 (57.6)	138 (58.0)	90 (56.3)	48 (61.5)	1.000	0.907	0.666	
Hours TV/wk (N, %)	1-6 hrs/wk	15 (10.5)	24 (10.3)	17 (10.9)	7 (9.0)	0.858	0.741	0.956	
	1-3 hrs/day	78 (54.6)	134 (57.3)	91 (58.3)	43 (55.1)				
	≥ 3 hrs/day	50 (35.0)	76 (32.5)	48 (30.8)	28 (35.9)				
Smoking (N, %)	Yes	2 (1.4)	7 (3.0)	5 (3.2)	2 (2.6)	0.492	0.450	0.614	
Calories (Kcal/kg) (median)		57.8	59.4	58.5	64.1	0.211	0.330	0.223	
Protein (g/kg) (median)		1.9	2.0	2.0	2.2	0.223	0.376	0.197	
Fat (g/kg) (median)		2.2	2.5	2.5	2.7	0.187	0.358	0.143	
Carbohydrate (g/kg) (median)		7.2	7.5	7.4	7.7	0.374	0.461	0.431	
Family history (%)	Type I diabetes	13.1	10.3	11.2	8.3	0.475	0.704	0.466	
	Type II diabetes	44.2	37.4	33.1	46.7	0.245	0.074	0.756	
	Coronary heart disease	39.2	36.3	32.8	43.3	0.636	0.297	0.635	
Lipid disorders		28.9	26.1	26.5	25.4	0.604	0.775	0.726	

¹ Fisher's exact test for categorical and Wilcoxon rank sum test for continuous comparisons. Wald test based on exponential model for time to initiation of puberty

² Percentages exclude subjects with missing data

³ Exercise regularly defined as more than once a week.

HIV disease status and current antiretroviral treatment exposure for HIVpos subjects

Table 2

Characteristic	Level	PI (n=161)	Non PI (n=79)	p-value ¹
Disease severity				
Current CD4 count (cells/mm ³) (N, %) ²	<200	5 (3.2)	1 (1.3)	
	200-<500	38 (24.1)	23 (29.9)	
	≥500	115 (72.8)	53 (68.8)	
Median (10 th , 90 th %ile)		668 (305, 1149)	640 (364, 1022)	0.325
Current HIV-1 RNA (copies/ml) (N, %)	≤400	89 (57.4)	39 (50.0)	
	>400	66 (42.6)	39 (50.0)	
Median (10 th , 90 th %ile)		<400 (<400, 14236)	410 (<400, 9650)	0.336
Lowest CD4 count (cells/mm ³)		290 (38, 640)	387 (147, 801)	<0.001
Median (10 th , 90 th %ile)				
Highest HIV-1 RNA (copies/ml)		156,000 (16836, >750000)	34,972 (2600, 252522)	<0.001
Median (10 th , 90 th %ile)				
CDC disease stage (N, %)	N/A	52 (32.3)	46 (58.2)	<0.001
	B	68 (42.2)	26 (32.9)	
	C	41 (25.5)	7 (8.9)	

Current Antiretroviral Medication:		%	Median (yrs)	%	Median (yrs)
Any NRTI	Stavudine (d4T)	97.5	8.0	100.0	8.1
	Didanosine (ddI)	54.0	5.8	36.7	5.9
	Lamivudine (3TC)	32.9	5.0	31.6	7.6
		43.5	5.1	68.4	6.0
Any NNRTI	Zidovudine (ZDV)	26.1	5.5	45.6	6.9
	Other NRTI ³	18.6	2.1	20.3	2.9
	Nevirapine (NVP)	32.3	5.0	45.6	3.1
	Efavirenz (EFZ)	16.8	5.7	10.1	5.2
Any PI		15.5	4.3	35.4	2.6
		100.0	5.9		
	Kaletra (KAL)	31.1	2.4		
	Nelfinavir (NFV)	39.8	5.8		
	Ritonavir (RTV)	27.3	5.8		

Current Antiretroviral Medication:	%	Median (yrs)	%	Median (yrs)
Saquinavir (SQV)	9.9	4.5		
Other PI ⁴	12.4	2.4		

¹ Wilcoxon rank sum test

² Percentages exclude subjects with missing data

³ Includes Abacavir (15), Zalcitabine (1), Tenofovir (12), and others (<5)

⁴ Includes Indinavir (5), Amprenavir (7) and others (<8)

Table 3
Laboratory outcomes: Medians and adjusted comparisons between PI, non PI and HIVneg groups

OUTCOME	HIVneg	Median ¹		Adjusted p-value ²	
		PI	Non PI	PI vs. HIVneg	Non PI vs. HIVneg
Lipids					
Cholesterol (mg/dL)	152.5	174.0	153.0	0.001	0.530
LDL cholesterol (mg/dL)	89.0	99.0	89.0	0.007	0.603
HDL cholesterol (mg/dL)	49.0	44.0	46.0	<0.001	0.010
non HDL cholesterol (mg/dL)	104.5	130.0	109.0	<0.001	0.756
Triglycerides (mg/dL)	66.5	134.0	82.0	<0.001	0.002
Cholesterol:HDL ratio	3.1	4.0	3.3	<0.001	0.122
Glucose metabolism					
Fasting glucose (mg/dL)	89.0	87.5	89.0	0.372	0.034
Fasting Insulin (uU/mL)	7.0	10.0	10.5	0.001	0.001
Fasting C-peptide (ng/mL)	2.0	2.3	2.2	0.067	0.110
Fasting Proinsulin (pm/L)	11.3	11.4	11.8	0.395	0.184
HOMA-IR	1.5	2.0	2.3	0.005	0.004
2-h glucose (mg/dL)	95.5	104.0	96.0	0.006	0.639
2-h Insulin (uU/mL)	39.0	40.0	34.5	0.020	0.884
2-h C-peptide (ng/mL)	5.7	5.9	5.5	0.067	0.591
2-h Proinsulin (pm/L)	39.7	43.8	38.2	0.604	0.848
Other					
hs CRP (mg/L)	0.5	0.6	0.6	0.354	0.490
Plasma lactate (mg/dL)	8.5	9.7	9.3	0.058	0.407

¹ Median of raw untransformed values

² p-values from linear regression on each laboratory value (log [0-transformed]) adjusted for gender, race/ethnicity, Tanner stratum, BMI z-score and CDC disease category. Values <2nd or >98th percentile excluded from models.

Table 4
Predicted Change in Laboratory Outcomes Per Year of Current ARV Use

OUTCOMES	PI		NRTI	NNRTI
Lipids				
Cholesterol				
Total	Ritonavir ³ 2.5 (1.3, 3.6) p<0.001	Nelfinavir 1.5 (0.4, 2.6) p=0.008	Other PI ² 0.5 (-1.5, 2.5) p=0.651	NRTI -0.3 (-1.3, 0.6) p=0.480
LDL	Ritonavir ³ 2.4 (0.8, 4.2) p=0.004	Nelfinavir 2.5 (0.9, 4.1) p=0.002	Other PI ² -0.2 (-3.0, 2.7) p=0.895	NRTI -0.3 (-1.6, 1.0) p=0.652
HDL	Nelfinavir -1.4 (-2.7, -0.0) p=0.046	PI -1.0 (-2.4, 0.4) p=0.159	ZDV -1.2 (-2.1, -0.2) p=0.016	Other NRTI ¹ 0.4 (-0.9, 1.7) p=0.525
Non-HDL	Ritonavir ³ 3.7 (2.1, 5.3) p<0.001	Nelfinavir 2.3 (0.8, 3.9) p=0.003	Other PI ² 1.8 (-0.8, 4.4) p=0.184	NRTI -0.3 (-1.5, 1.0) p=0.636
Triglycerides	Ritonavir ³ 7.7 (4.7, 10.7) p<0.001	Nelfinavir 3.3 (0.5, 6.1) p=0.021	Other PI ² 2.9 (-1.9, 8.0) p=0.242	ddl -2.8 (-4.9, -0.7) p=0.009
Glucose Metabolism				
Fasting glucose	Nelfinavir -0.4 (-0.8, -0.1) p=0.014	Other PI ² -0.2 (-0.6, 0.1) p=0.243	NRTI -0.1 (-0.4, 0.1) p=0.334	NRTI 0.3 (-0.0, 0.7) p=0.065
2-hour glucose	Ritonavir ³ 1.2 (0.2, 2.2) p=0.018	Other PI ² 0.5 (-0.4, 1.5) p=0.281	NRTI -0.3 (-1.2, 0.6) p=0.476	NRTI 0.1 (-0.9, 1.1) p=0.866
Fasting insulin	PI -0.3 (-3.2, 2.8) p=0.852		NRTI 0.1 (-2.6, 3.0) p=0.922	NRTI 1.6 (-1.8, 5.1) p=0.355
2-hour insulin	Ritonavir ³ 8.0 (3.3, 12.8) p<0.001	PI 2.4 (-1.8, 6.7) p=0.270	Other NRTI 2.8 (-1.0, 6.8) p=0.154	NRTI -0.3 (-4.7, 4.3) p=0.901
HOMA-IR	PI -0.3 (-3.3, 2.9) p=0.859		NRTI -0.5 (-3.4, 2.4) p=0.718	NRTI 2.1 (-1.4, 5.7) p=0.251
Fasting C-peptide	PI -0.5 (-2.4, 1.5) p=0.641		ddl -1.8 (-3.4, -0.1) p=0.044	Other NRTI ¹ 0.1 (-1.7, 1.8) p=0.940
2-hour C-peptide	Ritonavir ³ 4.2 (1.5, 6.9) p=0.002	Other PI ² 0.1 (-2.4, 2.6) p=0.951	NRTI 1.4 (-0.8, 3.7) p=0.208	NRTI -1.1 (-3.7, 1.6) p=0.437

OUTCOMES	PI		NRTI		NNRTI	
Lactate	PI 0.9 (-0.7, 2.5) p=0.276		NRTI -1.0 (-2.4, 0.5) p=0.194		NNRTI -0.5 (-2.2, 1.3) p=0.582	

¹ Includes all other NRTI that are not in model

² Includes all other PI that are not in the model

³ Includes ritonavir and ritonavir-boosted regimens

⁴ p-values from linear regression on each laboratory value (log10-transformed) adjusted for gender, race/ethnicity, Tanner stratum , BMI z-score, CDC disease category and years on each ARV drug shown in Table. Values <2nd or >98th percentile excluded