# Obesity and Dyslipidemia in Behaviorally HIV-Infected Young Women: Adolescent Trials Network Study 021

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***Background.*** The goal of this study was to determine the nature and prevalence of abnormalities in lipids, glucose metabolism, and body composition in behaviorally human immunodeficiency virus (HIV)–infected young women and the relationship of these abnormalities to different classes of antiretroviral therapy regimens.

***Methods.*** We conducted a cross-sectional, multicenter study involving 173 behaviorally HIV-infected women aged 14–24 years and 61 HIV-seronegative control subjects. HIV-infected women were categorized as follows: antiretroviral therapy naive ($n = 85$), receiving a regimen containing a nonnucleoside reverse-transcriptase inhibitor (NNRTI; $n = 33$), receiving a regimen containing a protease inhibitor (PI; $n = 36$), or receiving a regimen not containing an NNRTI or a PI ($n = 19$). Measurements included fasting lipid levels, glucose and insulin levels before and 2 hours after an oral glucose challenge, high-sensitivity C-reactive protein (hsCRP) levels, anthropometry, fat distribution (measured by dual energy X-ray absorptiometry), and antiretroviral therapy and medical histories. Race-adjusted results were compared across groups and within HIV-infected groups.

***Results.*** The median age of participants was 20 years. Of HIV-infected subjects, 77% were African American, 35% smoked cigarettes, and 32% reported exercising regularly. More than 40% had a body mass index $\geqslant$25. Triglycerides; total, high-density lipoprotein (HDL), and non-HDL cholesterol; and hsCRP levels differed significantly among groups, with higher levels being most common among those receiving antiretroviral therapy. Indices of glucose metabolism did not differ among groups. In general, cholesterol levels, hsCRP levels, and indices of glucose metabolism worsened as body mass index increased.

***Conclusions.*** Obesity, dyslipidemia, and inflammation were prominent among HIV-infected adolescent women and, coupled with other risk factors, may accelerate the lifetime risk of cardiovascular disease and other adverse events. These results underscore the need for a multifaceted approach to addressing risk reduction in this population.

The human immunodeficiency virus (HIV) epidemic in the United States among adolescents and young adults remains unabated, with an estimated 20,000 new infections annually [1]. Indeed, 34% of incident infections in the United States in 2006 are estimated to have occurred among 13–29-year-old persons [1]. These new behaviorally acquired infections occur disproportionately among ethnic and racial minority populations, and in the younger age groups, infections in females now outnumber those in males [2].

The prevalence of obesity is also increasing among adolescents in the United States [3], particularly among young women and among racial and ethnic minority populations [4]. Obesity contributes to diabetes, dyslipidemia, hypertension, inflammation, kidney disease, and other comorbidities that cumulatively are associated with increased risk of cardiovascular disease and other disorders [5–7]. Moreover, minority youth may have a genetic predisposition to insulin resistance, which, in the presence of environmental modulators,

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could exacerbate their risk of diabetes and result in disease expression during physiologic (puberty) or pathologic (obesity) states of insulin resistance [8]. Thus, there is an intersection between the HIV epidemic in young women and the emerging problems associated with obesity in this age group [9, 10].

Both HIV infection and its therapies are known to contribute to metabolic and morphologic alterations that may increase risk of cardiovascular disease, including dyslipidemia, altered glucose metabolism, central fat accumulation, and inflammation (as reviewed by Grunfeld et al [11]). All 3 major classes of antiretroviral therapy (ART) drugs, including protease inhibitors (PIs), nucleoside reverse-transcriptase inhibitors (NRTIs), and nonnucleoside reverse-transcriptase inhibitors (NNRTIs), have been implicated in these complications, with the nature and magnitude of effects differing among drugs in a given class [11]. The extent to which metabolic abnormalities in adolescents are related to HIV infection, specific antiretroviral regimens, obesity, puberty, or background risks associated with race, ethnicity, and lifestyle is unknown. This study was designed to determine the nature and prevalence of abnormalities in glucose metabolism, lipids, and body composition among HIV-infected and HIV-uninfected female adolescents and young adults and to examine the relationship of these abnormalities to different classes of ART regimens.

## METHODS

A total of 173 HIV-infected young women, aged 14–24 years, were recruited consecutively for this cross-sectional study from December 2003 through August 2005 at 17 clinical sites, on behalf of the Adolescent Medicine Trials Network for HIV/AIDS Interventions. Participants were grouped as follows: ART naive ($n = 85$); receiving an ART regimen for ⩾3 months that contained an NNRTI but no PI ($n = 33$); receiving an ART regimen for ⩾3 months that included a PI but no NNRTI ($n = 36$); and receiving a regimen for ⩾3 months that did not contain a PI or an NNRTI (non-NNRTI/non-PI group; $n = 19$). An HIV-seronegative control group ($n = 61$) was recruited at the same clinical sites. Recruitment of HIV-seronegative subjects was initiated after the first 65 HIV-infected subjects had been enrolled, to ensure comparability in age between the 2 groups. Sites were encouraged to recruit subjects from the same racial and demographic backgrounds as the HIV-infected subjects.

All participants were required to be classified as Tanner 4 or 5, to have a negative pregnancy test result at the time of study (unless surgically sterilized), and to have an accessible medical history. Exclusion criteria included pregnancy in the past year, type 1 diabetes mellitus, or history of anorexia or bulimia. The institutional review board at each site approved the study, and appropriate written informed consent was obtained before enrollment.

***Assessments.*** Fasting (for ⩾8 h) blood samples were collected for determination of lipids, glucose, insulin, C-peptide, proinsulin, and high-sensitivity C-reactive protein (hsCRP) levels. Participants then consumed a 75-g oral glucose load, and samples were collected after 2 h for measurement of glucose, insulin, C-peptide, and proinsulin levels. Height, weight, and waist circumference were measured in accordance with standard protocols. Study personnel at each site underwent centralized training to standardize the anthropometric measurements. Body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) was categorized according to World Health Organization criteria [12]. Whole-body dual-energy X-ray absorptiometry (DXA) scanning was performed to measure total lean body mass and fat, as well as regional fat distribution. All scans underwent central analysis at Tufts University by a reader who was blinded to HIV status and ART regimen. A standard phantom was scanned on each DXA instrument used in the study. All scans at a given clinical site were performed on the same DXA instrument.

All participants underwent detailed medical histories. Participants also completed food frequency (Block Dietary Systems; NutritionQuest) and body image questionnaires that included questions about exercise, smoking, and alcohol use.

***Laboratory analyses.*** Samples were processed locally and then were stored at −70°C in a central repository. After completion of the study, samples were analyzed at Quest Diagnostics (Baltimore, MD) and Quest Diagnostics Nichols Institute (Chantilly, VA). Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides levels were measured by enzymatic techniques, and low-density lipoprotein (LDL) cholesterol was calculated for those with triglyceride levels <400 mg/dL [13]. Specimens for glucose were collected on sodium fluoride/potassium oxalate and were measured by the hexokinase technique. Serum insulin, C-peptide, and proinsulin levels were measured by immunoassay. The homeostasis model of insulin resistance (HOMA-IR) was calculated from fasting insulin and glucose levels [14]. hsCRP level was measured by a particle-enhanced immunonephelometric assay. HIV-1 RNA levels (Roche Amplicor v1.5 assay; detection limit, 400 copies/mL) and CD4 cell counts were measured locally at each site.

***Statistical analyses.*** Simple univariate statistics (frequency, percentage, median, and range) were used to describe characteristics of the study population according to HIV infection status and, for HIV-infected subjects, according to ART regimen. Statistical testing for differences in characteristics among groups was based on $\chi^2$ and Fisher's exact tests for categorical measures, and nonparametric testing (the Kruskal-Wallis test) was used for continuous measures. Model-based estimates of race-adjusted means and standard errors for the metabolic and morphologic outcomes are reported. The effects of HIV infection and the type of ART regimen on continuous-scaled outcomes were assessed using linear regression. When significant

differences among groups were observed overall, pairwise comparisons were performed (between each HIV treatment group and the HIV-seronegative group and/or between each HIV-infected group receiving ART compared with the HIV-infected, ART-naive group). Linear regression was also used to explore the relationship of BMI with the metabolic outcomes in the group as a whole, with adjustment for race and HIV status.

All analyses were performed using the SAS, version 8.0 (SAS Institute). An $\alpha < .05$ indicated statistical significance. There were few missing values, so no imputation was performed, nor were adjustments made for multiple comparisons.

## RESULTS

***Demographic characteristics.*** The median age was 20 years for both HIV-infected and HIV-seronegative groups (Table 1). The HIV-infected group included a higher proportion of African Americans. More than half of the HIV-infected women had had at least 1 pregnancy ($P = .04$, compared with HIV-seronegative subjects). More than 60% of participants reported alcohol use. A greater proportion of HIV-infected subjects reported drug use, predominantly marijuana. Cigarette smoking was reported by approximately one-third of women in both groups. Approximately one-third of HIV-infected women reported exercising regularly ($P = .005$, compared with HIV-seronegative subjects). Family histories of type 2 diabetes and cardiovascular disease were reported by approximately 40% and 30% of participants, respectively; neither differed significantly between groups.

***HIV disease–related data.*** Among the HIV-infected groups, the median time since HIV diagnosis ranged from 0.9 years for the ART-naive group to 3.9 years for the group receiving a PI-containing regimen (Table 2). Current CD4 cell count did not differ among groups; among those receiving ART, the nadir CD4 cell count and current HIV RNA level were significantly lower, and their peak HIV RNA levels were significantly higher than those of their untreated counterparts.

**Table 1. Demographic Characteristics of Study Participants**

| Characteristic | HIV-seronegative subjects ($n = 61$) | HIV-infected subjects ($n = 173$) | $P$[a] |
|---|---|---|---|
| Age, median years (range) | 20 (15–24) | 20 (14–24) | .15 |
| Race | | | |
| Black/African American | 34 (55.7) | 133 (76.9) | .005 |
| White | 11 (18.0) | 13 (7.5) | |
| Other/mixed/Asian/Pacific Islander | 16 (26.2) | 27 (15.6) | |
| Hispanic ethnicity | 17 (27.9) | 30 (17.3) | .08 |
| Ever been pregnant | 22 (36.1) | 89 (51.4) | .04 |
| No. of pregnancies | | | |
| 0 | 39 (63.9) | 84 (48.6) | .09 |
| 1 | 15 (24.6) | 52 (30.1) | |
| 2–5 | 7 (11.5) | 37 (21.4) | |
| No. of full-term births | | | |
| 0 | 11 (50.0) | 33 (37.5) | .30 |
| 1 | 10 (45.5) | 36 (40.9) | |
| 2 | 1 (4.5) | 14 (15.9) | |
| 3 | 0 (0.0) | 5 (5.7) | |
| Drinks alcohol | 41 (67.2) | 106 (61.3) | .41 |
| Ever used or currently uses drugs | 22 (36.1) | 102 (59.0) | .002 |
| Ever used cocaine | 5 (8.2) | 16 (9.2) | .80 |
| Ever used marijuana/hash/THC | 22 (36.1) | 102 (59.0) | .002 |
| Currently smokes cigarettes | 21 (34.4) | 60 (34.7) | .97 |
| Exercises regularly | 32 (52.5) | 56 (32.4) | .005 |
| Family history of | | | |
| Type I diabetes | 14 (24.1) | 34 (21.1) | .63 |
| Type II diabetes | 24 (41.4) | 70 (44.3) | .70 |
| Lipid disorders | 15 (25.9) | 38 (26.6) | .92 |
| Coronary heart disease | 18 (32.1) | 58 (37.7) | .46 |

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated. THC, tetrahydrocannabinol.

[a] Except for age, $P$ values were obtained using $\chi^2$ analysis; for age, the $P$ value was obtained using Student's $t$ test.

**Table 2. Human Immunodeficiency Virus (HIV) Disease Characteristics**

| HIV disease characteristic | HIV-infected subjects, by treatment category | | | | $P$[a] |
|---|---|---|---|---|---|
| | ART naive ($n$ = 85) | Receiving regimen containing NNRTI ($n$ = 33) | Receiving regimen containing PI ($n$ = 36) | Receiving regimen not containing NNRTI or PI ($n$ = 19) | |
| Years since HIV diagnosis | 0.9 (0.1–10.6) | 2.6 (0.3–12.2) | 3.9 (0.4–10.2) | 2.8 (0.1–7.7) | <.001 |
| Current CD4 cell count, cells/$\mu$L | 499 (64–1374) | 485 (25–1424) | 469 (56–3011) | 487 (13–1730) | .99 |
| Nadir CD4 cell count, cells/$\mu$L | 450 (16–1012) | 247 (2–740) | 250 (0–1366) | 272 (0–858) | <.001 |
| Current CD4 cell percentage | 28.0 (5.7–50.0) | 29.6 (4.2–49.0) | 26.0 (6.0–59.0) | 31.0 (1.0–48.0) | .84 |
| Nadir CD4 cell percentage | 24.3 (1.0–45.1) | 17.9 (2.0–37.0) | 18.5 (0.0–50.0) | 21.0 (0.0–39.0) | <.001 |
| Current HIV RNA level, copies/mL | 6066 (<400–652,000) | <400 (<400–57,386) | <400 (<400–404,926) | <400 (<400–95,095) | <.001 |
| Current HIV RNA level, copies/mL | | | | | <.001 |
| ⩽400 | 13 (15.3) | 26 (78.8) | 24 (66.7) | 11 (63.2) | |
| 401–2000 | 18 (21.2) | 2 (6.1) | 0 (0.0) | 1 (5.3) | |
| 2001–10,000 | 19 (22.4) | 1 (3.0) | 6 (13.7) | 1 (5.3) | |
| 10,000–40,000 | 22 (25.9) | 3 (9.1) | 2 (5.6) | 2 (10.5) | |
| >40,000 | 13 (15.3) | 1 (3.0) | 3 (8.3) | 2 (10.5) | |
| Peak HIV RNA level, copies/mL | 13,399 (25–750,000) | 44,600 (25–567,000) | 72,754 (75–2,947,581) | 35,343 (25–476,330) | .007 |
| CDC stage | | | | | |
| A/none | 62 (72.9) | 17 (51.5) | 17 (47.2) | 8 (42.1) | <.001 |
| B | 16 (18.8) | 3 (9.1) | 5 (13.9) | 2 (10.5) | |
| C | 7 (8.2) | 13 (39.4) | 14 (38.9) | 9 (47.4) | |
| Currently receiving any NRTI | NA | 33 (100.0) | 36 (100.0) | 19 (100.0) | |
| Zidovudine | NA | 24 (72.7) | 26 (72.2) | 19 (100.0) | |
| Lamivudine | NA | 31 (93.9) | 33 (91.7) | 18 (94.7) | |
| Stavudine | NA | 2 (6.1) | 3 (8.3) | 0 (0.0) | |
| Didanosine | NA | 5 (15.2) | 3 (8.3) | 0 (0.0) | |
| Abacavir | NA | 1 (3.0) | 2 (5.6) | 18 (94.7) | |
| Tenofovir | NA | 4 (12.1) | 6 (16.7) | 2 (10.5) | |
| Currently receiving any NNRTI | NA | 33 (100.0) | NA | NA | |
| Efavirenz | NA | 16 (48.5) | NA | NA | |
| Nevirapine | NA | 17 (51.5) | NA | NA | |
| Currently receiving any PI | NA | NA | 36 (100.0) | NA | |
| Nelfinavir | NA | NA | 21 (58.3) | NA | |
| Lopinavir/ritonavir | NA | NA | 9 (25.0) | NA | |
| Other ritonavir[b] | NA | NA | 6 (16.7) | NA | |
| Atazanavir[c] | NA | NA | 7 (19.4) | NA | |

**NOTE.** Data are no. (%) of subjects or median (range), unless otherwise indicated. ART, antiretroviral treatment; CDC, Centers for Disease Control and Prevention; NA, not applicable; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] $P$ values for comparison of categorical measures among HIV-infected subjects were obtained using $\chi^2$ analysis, and $P$ values for continuous measures were obtained using nonparametric testing (the Kruskal-Wallis test). Distribution of antiretroviral use is included for descriptive purposes and did not undergo statistical analysis.

[b] Includes subjects receiving therapeutic or boosting doses of ritonavir who are not receiving lopinavir.

[c] Includes subjects receiving boosted and unboosted atazanavir-containing regimens.

With regard to Centers for Disease Control and Prevention disease stage, the ART-naive group had a greater proportion of participants classified as stage A/none and a smaller proportion classified as stage C. The predominant NRTIs used in each group receiving ART were zidovudine and lamivudine. The rate of current or prior use of stavudine and/or didanosine was low to minimal. Approximately half of participants in the NNRTI group were receiving nevirapine, and the other half were receiving efavirenz. Among participants in the group receiving a PI-containing regimen, 58% were receiving nelfinavir, 42% were receiving a ritonavir-containing regimen (either lopinavir/ritonavir or other ritonavir), and 19% were receiving atazanavir. All but one participant in the non-NNRTI/non-PI group was receiving abacavir.

***Anthropometry and body composition.*** Mean BMI, height, and weight did not differ among groups (Table 3). More than 40% in each group had a BMI that was classified as overweight or obese (⩾25). There were no significant differences in race-

**Table 3. Metabolic and Morphologic Data**

| Measurement | HIV-seronegative subjects ($n$ = 61) | HIV-infected subjects, by treatment category | | | | $P$[a] | |
|---|---|---|---|---|---|---|---|
| | | ART naive ($n$ = 85) | Receiving regimen containing NNRTI ($n$ = 33) | Receiving regimen containing PI ($n$ = 36) | Receiving regimen not containing NNRTI or PI ($n$ = 19) | Overall ($n$ = 234) | HIV-infected subjects ($n$ = 173) |
| Anthropometric measurements | | | | | | | |
| BMI distribution | | | | | | | |
| Underweight (BMI <18.5) | 5 (8.2) | 4 (4.7) | 1 (3.0) | 1 (2.8) | 1 (5.3) | .96 | .99 |
| Normal (BMI, 18.5–24.9) | 29 (47.5) | 40 (47.1) | 12 (36.4) | 15 (41.7) | 9 (47.4) | | |
| Overweight (BMI, 25.0–29.9) | 11 (18.0) | 16 (18.8) | 6 (18.2) | 7 (19.4) | 4 (21.1) | | |
| Obese (BMI ≥30) | 16 (26.2) | 25 (29.4) | 14 (42.4) | 13 (36.1) | 5 (26.3) | | |
| BMI | 26.5 ± 1.0 | 27.5 ± 0.8 | 29.0 ± 1.3 | 28.0 ± 1.3 | 27.0 ± 1.7 | .62 | .72 |
| Height, cm | 162.8 ± 1.0 | 162.1 ± 0.8 | 162.7 ± 1.3 | 162.9 ± 1.2 | 162.2 ± 1.7 | .97 | .94 |
| Weight, kg | 70.4 ± 2.8 | 72.5 ± 2.4 | 77.5 ± 3.8 | 74.4 ± 3.6 | 71.1 ± 5.0 | .64 | .66 |
| Waist circumference, cm | 83.9 ± 2.2 | 85.8 ± 1.8 | 91.1 ± 2.9 | 90.9 ± 2.8 | 87.7 ± 3.8 | .17 | .30 |
| Hip circumference, cm | 103.2 ± 2.1 | 102.6 ± 1.7 | 106.0 ± 2.8 | 105.2 ± 2.6 | 101.7 ± 3.6 | .79 | .63 |
| Waist-to-hip ratio | 0.81 ± 0.02 | 0.83 ± 0.01 | 0.86 ± 0.02 | 0.86 ± 0.02 | 0.92 ± 0.03[b] | .02 | .11 |
| DXA measurements | | | | | | | |
| Total body mass, kg/m | 42.8 ± 1.5 | 43.5 ± 1.3 | 45.7 ± 2.2 | 45.0 ± 2.1 | 43.3 ± 3.0 | .81 | .77 |
| Total lean body mass, kg/m | 25.2 ± 0.5 | 25.6 ± 0.4 | 27.0 ± 0.7 | 26.1 ± 0.7 | 26.5 ± 1.0 | .35 | .41 |
| Total body fat, kg/m | 16.1 ± 1.1 | 16.4 ± 1.0 | 17.2 ± 1.6 | 17.5 ± 1.5 | 15.3 ± 2.2 | .90 | .79 |
| Total body fat, % | 35.5 ± 1.3 | 35.0 ± 1.1 | 35.9 ± 1.9 | 37.0 ± 1.8 | 33.8 ± 2.5 | .86 | .69 |
| Trunk fat, kg/m | 7.3 ± 0.6 | 7.4 ± 0.5 | 7.9 ± 0.8 | 8.2 ± 0.8 | 7.3 ± 1.1 | .88 | .78 |
| Arm fat, kg/m | 1.6 ± 0.1 | 1.6 ± 0.1 | 1.7 ± 0.2 | 1.7 ± 0.2 | 1.6 ± 0.2 | .98 | .98 |
| Leg fat, kg/m | 6.7 ± 0.5 | 6.7 ± 0.4 | 6.9 ± 0.7 | 7.1 ± 0.6 | 5.8 ± 0.9 | .84 | .67 |
| Metabolic measurements[c] | | | | | | | |
| Triglycerides, mg/dL | 65.0 ± 6.9 | 84.2 ± 5.8[b] | 126.2 ± 9.2[b,d] | 106.7 ± 8.8[b] | 102.6 ± 12.2[b] | <.001 | .008 |
| Total cholesterol, mg/dL | 154.4 ± 4.0 | 152.3 ± 3.4 | 167.8 ± 5.4[b,d] | 173.3 ± 5.1[b,d] | 148.7 ± 7.1 | .002 | .003 |
| HDL cholesterol, mg/dL | 48.5 ± 1.6 | 40.5 ± 1.3[b] | 43.3 ± 2.1 | 46.1 ± 2.0 | 38.8 ± 2.8[b] | .001 | .10 |
| LDL cholesterol, mg/dL | 93.0 ± 3.6 | 95.1 ± 3.0 | 96.3 ± 4.9 | 105.9 ± 4.6 | 89.5 ± 6.3 | .16 | .14 |
| Non-HDL cholesterol, mg/dL | 106.0 ± 4.2 | 111.9 ± 3.5 | 124.5 ± 5.6[b] | 127.2 ± 5.3[b] | 109.9 ± 7.4 | .008 | .06 |
| Glucose, mg/dL | 88.4 ± 1.0 | 85.4 ± 0.8 | 87.9 ± 1.3 | 86.5 ± 1.2 | 87.4 ± 1.7 | .17 | .35 |
| 2-h Glucose, mg/dL | 92.2 ± 3.1 | 93.1 ± 2.6 | 93.8 ± 4.2 | 98.3 ± 4.0 | 105.6 ± 5.4 | .21 | .23 |
| Insulin,[e] $\log_{10}$ μIU/mL | 1.01 ± 0.04 | 1.02 ± 0.03 | 1.04 ± 0.05 | 0.98 ± 0.05 | 1.10 ± 0.07 | .74 | .54 |
| 2-h Insulin,[e] $\log_{10}$ μIU/mL | 1.68 ± 0.05 | 1.68 ± 0.04 | 1.60 ± 0.07 | 1.68 ± 0.06 | 1.70 ± 0.09 | .84 | .72 |
| Proinsulin, pmol/L | 12.9 ± 1.4 | 11.6 ± 1.2 | 14.3 ± 1.9 | 13.3 ± 1.8 | 18.8 ± 2.5 | .14 | .12 |
| 2-h Proinsulin, pmol/L | 51.5 ± 5.6 | 47.0 ± 4.7 | 50.5 ± 7.5 | 50.0 ± 7.1 | 52.9 ± 10.0 | .97 | .96 |
| C-peptide, ng/dL | 2.7 ± 0.2 | 2.7 ± 0.1 | 2.9 ± 0.2 | 2.8 ± 0.2 | 3.3 ± 0.3 | .53 | .41 |
| 2-h C-peptide, ng/dL | 7.2 ± 0.4 | 7.2 ± 0.4 | 7.6 ± 0.6 | 7.2 ± 0.6 | 7.2 ± 0.8 | .99 | .97 |
| HOMA-IR,[e] $\log_{10}$ | 0.35 ± 0.04 | 0.34 ± 0.04 | 0.37 ± 0.06 | 0.31 ± 0.06 | 0.44 ± 0.08 | .74 | .53 |
| hsCRP, mg/L | 2.2 ± 0.8 | 2.9 ± 0.7 | 5.7 ± 1.1[b,d] | 3.8 ± 1.1 | 7.5 ± 1.5[b,d] | .006 | .04 |

**NOTE.** Data are no. (%) of subjects or mean ± standard error, unless otherwise indicated. Descriptions of metabolic and morphologic characteristics of the study population are given according to human immunodeficiency virus (HIV) status and type of antiretroviral therapy (ART) regimen currently receiving, based on race-adjusted analyses. BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of insulin resistance [14]; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] $P$ values for categorical measures were obtained using Fisher's exact test, and $P$ values for continuous measures were obtained using linear regression modeling.

[b] $P < .05$, compared with HIV-seronegative subjects.

[c] Fasting level, unless otherwise noted.

[d] $P < .05$, compared with HIV-infected, ART-naive subjects.

[e] Log-transformed results are reported for fasting and 2-h insulin and HOMA-IR because the distributions were skewed.

adjusted waist or hip circumferences. Waist-to-hip ratio differed significantly among groups and was significantly higher in the non-NNRTI/non-PI group, compared with both the HIV-seronegative group and the ART-naive group, reflecting the lower hip circumference in the non-NNRTI/non-PI group. There were no significant differences in total lean body mass or fat distribution. The mean total body fat was >30% in each group and did not differ significantly by HIV status or treatment category. There were no significant differences among groups in energy or macronutrient intake (data not shown).

***Metabolic outcomes.*** Fasting triglyceride and total cholesterol levels differed significantly among all groups and among

HIV-infected groups (Table 3). In pairwise comparisons, triglyceride levels were significantly higher in all HIV-infected groups, compared with the HIV-seronegative group, and were significantly higher in the group receiving an NNRTI regimen than in the ART-naive group. Total cholesterol was higher in the group receiving an NNRTI-containing regimen and the group receiving a PI-containing regimen, compared with both the HIV-seronegative and the ART-naive groups. HDL cholesterol levels differed significantly among groups overall. In pairwise comparisons, HDL cholesterol level was significantly lower in the ART-naive and non-NNRTI/non-PI groups than in the HIV-seronegative group. LDL cholesterol level did not differ significantly among groups. Non-HDL cholesterol level was significantly higher in the groups receiving an NNRTI- or PI-containing regimen, compared with the HIV-seronegative group.

There were no significant differences among groups in fasting or 2-h levels of glucose, insulin, proinsulin, C-peptide, or HOMA-IR (Table 3). hsCRP levels differed significantly among all groups and among HIV-infected groups, with significantly higher levels in the group receiving an NNRTI-containing regimen and the non-NNRTI/non-PI group, compared with the HIV-seronegative group and ART-naive group.

Using published classification criteria [15–17] and laboratory reference ranges, we examined the prevalence of abnormal values for lipids and hsCRP (Figure 1). Among ART-naive participants, 29% had low HDL cholesterol levels; abnormal lipid values were more frequently observed among the groups receiving NNRTI- and PI-containing regimens, whereas low HDL cholesterol level was the only major abnormality in the non-NNRTI/non-PI group. Approximately 40% of all 3 groups receiving ART had hsCRP levels that were above the upper limit of normal for the assay used (>3 mg/L). In contrast, glucose abnormalities (impaired fasting glucose, impaired glucose tolerance, or diabetes) were relatively infrequent (data not shown).

***Association of metabolic outcomes with BMI.*** In contrast to the comparisons among treatment groups, fasting and 2-h levels of glucose, insulin, proinsulin, and C-peptide, as well as HOMA-IR, differed significantly among BMI categories, generally increasing with increasing BMI (Table 4). All values for cholesterol and hsCRP levels also differed significantly among BMI categories. In general, participants classified as overweight or obese had levels that were higher than those of normal or underweight participants. Levels of HDL cholesterol decreased with increasing BMI category. Levels of triglycerides did not differ among BMI categories.

## DISCUSSION

In this survey of behaviorally HIV-infected young women, overweight or obesity, dyslipidemia, and inflammation were prominent. More than one-third of the HIV-infected participants reported a family history of heart disease or type 2 diabetes,

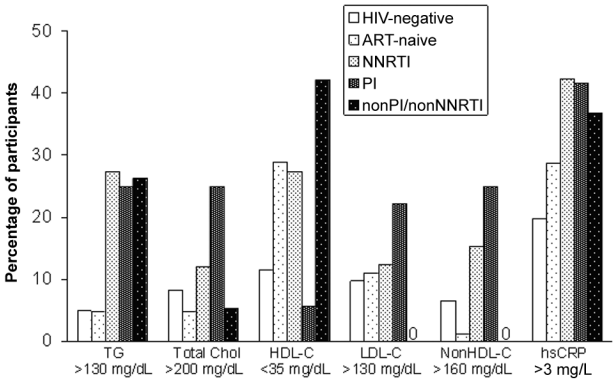


**Figure 1.** Proportion of study participants in each group with abnormal values for lipids and high-sensitivity C-reactive protein (hsCRP), on the basis of published classification criteria [15–17] and laboratory reference ranges. ART, antiretroviral therapy; Chol, cholesterol; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; TG, triglycerides.

more than one-third smoked cigarettes, and fewer than one-third exercised regularly. Given the known associations of each of these metabolic, genetic, and lifestyle factors with cardiovascular disease [6]; recent evidence linking hsCRP level to increased risk of death in patients with HIV infection [18]; and the likelihood of life-long exposure to ART, this population of young women may be at particularly high risk of cardiovascular disease and other adverse events.

In the United States, the prevalence of overweight and obesity is increasing in all age groups, particularly among Hispanic and African American women [4]. Studies involving HIV-uninfected children and adolescents have demonstrated significant associations between obesity and dyslipidemia, alterations in glucose metabolism, and elevations in systolic blood pressure [8, 19, 20]. Although cardiovascular disease has not been studied extensively in children, children and adolescents in the United States have higher levels of cholesterol than do their counterparts in other countries; autopsy findings show evidence of atherosclerosis that correlate with dyslipidemia; and dyslipidemic children are likely to become dyslipidemic adults [16]. Moreover, the risk of cardiovascular disease is particular high among racial or ethnic minority populations [20]. Among HIV-infected adults, studies have demonstrated increased incidence of coronary artery disease and cardiovascular events [21, 22], with the risk increasing with increased duration of ART [23].

The prevalence of overweight or obesity in the current study is comparable to that reported previously in the Women's Interagency HIV Study [24, 25], which also includes a high proportion of participants representing racial and ethnic minority populations. However, in contrast to the Women's Interagency HIV Study, we found no differences in fat distribution mea-

**Table 4. Association of Metabolic Outcomes with Body Mass Index (BMI)**

| Metabolic outcome[a] | Underweight and normal weight (BMI <25.0) ($n$ = 117) | Overweight (BMI, 25.0–29.9) ($n$ = 44) | Obese (BMI ⩾30.0) ($n$ = 73) | $P$[b] |
|---|---|---|---|---|
| Glucose, mg/dL | 85.0 ± 0.7 | 87.8 ± 1.1 | 89.2 ± 0.9 | <.001 |
| 2-h Glucose, mg/dL | 90.3 ± 2.2 | 96.9 ± 3.6 | 100.7 ± 2.8 | .01 |
| Insulin,[c] $\log_{10}$ μIU/mL | 0.90 ± 0.03 | 1.10 ± 0.04 | 1.17 ± 0.03 | <.001 |
| 2-h Insulin,[c] $\log_{10}$ μIU/mL | 1.60 ± 0.03 | 1.69 ± 0.06 | 1.78 ± 0.04 | .007 |
| Proinsulin, pmol/L | 10.9 ± 1.0 | 13.2 ± 1.6 | 16.8 ± 1.3 | .002 |
| 2-h Proinsulin, pmol/L | 44.9 ± 4.0 | 41.7 ± 6.4 | 61.7 ± 4.9 | .01 |
| C-peptide, ng/dL | 2.4 ± 0.1 | 3.0 ± 0.2 | 3.3 ± 0.1 | <.001 |
| 2-h C-peptide, ng/dL | 6.7 ± 0.3 | 7.0 ± 0.5 | 8.3 ± 0.4 | .004 |
| HOMA-IR,[c] $\log_{10}$ | 0.22 ± 0.08 | 0.43 ± 0.05 | 0.52 ± 0.04 | <.001 |
| Total cholesterol, mg/dL | 152.0 ± 2.9 | 170.4 ± 4.7 | 160.0 ± 3.7 | .004 |
| HDL cholesterol, mg/dL | 46.0 ± 1.1 | 41.7 ± 1.8 | 41.2 ± 1.4 | .02 |
| LDL cholesterol, mg/dL | 89.5 ± 2.5 | 106.3 ± 4.1 | 100.1 ± 3.2 | .001 |
| Non-HDL cholesterol, mg/dL | 106.1 ± 2.9 | 128.7 ± 4.8 | 118.8 ± 3.7 | <.001 |
| Triglycerides | 83.0 ± 5.1 | 102.3 ± 8.2 | 94.7 ± 6.3 | .10 |
| hsCRP, mg/L | 2.6 ± 0.6 | 2.6 ± 0.9 | 5.8 ± 0.7 | .002 |

**NOTE.** Data are mean ± standard error, unless otherwise indicated. BMI was calculated as weight in kilograms divided by the square of height in meters. HDL, high-density lipoprotein; HOMA-IR, homeostasis model of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

[a] Fasting level, unless otherwise indicated.

[b] Least-squares estimated means, standard errors, and $P$ values were obtained from linear regression modeling, with adjustment for race and human immunodeficiency virus status.

[c] Log-transformed results are reported for fasting and 2-h insulin and HOMA-IR because the distributions were skewed.

sured by DXA, presumably reflecting the relatively lower duration of HIV infection and exposure to ART in our population. Overall, the major impact of body habitus on our findings appears to be consistent with conventional obesity, rather than altered fat distribution associated with HIV infection or ART.

Inflammation, as evidenced by increases in hsCRP level, is an independent risk factor for cardiovascular disease in HIV-uninfected [26] and HIV-infected [27] populations. Studies involving HIV-uninfected adults [28] and youth [29, 30] have demonstrated relationships between C-reactive protein and features of the metabolic syndrome and markers of oxidative stress. A recent study found that non-obese, HIV-infected adults had hsCRP levels comparable to those seen in obese, seronegative participants [31]. In the current study, hsCRP level exceeded the upper limit of normal in ~40% of HIV-infected participants receiving ART, among whom more-advanced HIV disease was more common, and was higher among participants classified as obese. These results suggest that both HIV disease and obesity may have contributed to elevations in hsCRP.

There were no significant differences among groups in fasting or 2-h levels of glucose and insulin or HOMA-IR, consistent with results reported previously in the Women's Interagency HIV Study, which included a high prevalence of overweight or obese participants [32]. However, when we compared our results across BMI categories, we saw highly significant differences, with all indices of glucose metabolism worsening as BMI increased. Thus, it appears that, among overweight HIV-infected adolescent and adult women in the United States, obesity has a greater influence on glucose metabolism than does HIV infection or ART. In contrast, our data suggest that body habitus, HIV infection, and ART all play a role in dyslipidemia.

A unique feature of this study is the inclusion of an ART-naive, HIV-seropositive group, which provides the opportunity to explore the impact of both HIV infection and ART on metabolic and morphologic outcomes. Although the median duration of known HIV infection in this group was shorter than that in the groups receiving ART, triglyceride levels were significantly higher and HDL cholesterol levels were significantly lower in the ART-naive participants, compared with seronegative control subjects. Reductions in HDL cholesterol are a recognized effect of untreated HIV infection. However, studies performed before the era of highly active antiretroviral treatment suggested that triglycerides were increased only in patients with more-advanced HIV disease [33]. Thus, the finding that triglycerides were significantly higher in this group of relatively recently infected young women is novel.

Fewer than one-third of the HIV-infected participants exercised regularly, more than one-third already smoked cigarettes, and more than 40% were overweight or obese. Innovative approaches to motivating youth to modify current behaviors are clearly needed. Girls, older adolescents, minority populations, and individuals of lower socioeconomic status are least likely to

meet current guidelines for physical activity [34]. Sedentary behavior and television viewing are independently related to overweight and to biomarkers of cardiovascular risk [35, 36], and thus are potential targets for intervention. Although dietary interventions are particularly challenging in this population, which does not always have control over meal selection or preparation, information about nutrition and positive food choices should also be a component of behavioral interventions.

Other approaches to risk reduction must also be considered. Although cardiovascular risk increases with increasing duration of ART in adults, in the Strategies for Management of Antiretroviral Therapy study, the risk was found to be even greater for those who underwent treatment interruptions [37], and elevations in hsCRP were independently associated with increased risk of death [18]. It is not known whether this finding will apply to treatment interruptions in adolescents. It is notable that, among those receiving ART in the current study, 31% had detectable viremia, demonstrating the need for increased emphasis on adherence to ART in this population. Finally, in the absence of adolescent-specific guidelines for managing HIV-associated dyslipidemia, guidelines for HIV-infected adults [38, 39] or HIV-uninfected youth [40] can be used for reference.

To our knowledge, this is the first comprehensive survey of metabolic and morphologic alterations in behaviorally HIV-infected adolescent women. The study included objective measurements of body habitus and fat distribution, along with biochemical evaluations and extensive medical histories. However, we recognize that our ability to draw inferences from our results is limited by the cross-sectional study design. In addition, although our HIV-infected and HIV-seronegative participants had similar age distributions, the groups were not balanced with regard to race, parity, drug use, or exercise. Although our statistical analyses adjusted for race, it is possible that imbalances in these and other undocumented factors may have affected our results. Insulin resistance (HOMA-IR) and LDL cholesterol levels were calculated, rather than measured directly; thus, we may not have detected subtle differences among groups. Although we did not adjust for multiple comparisons, if we had required a more conservative $\alpha$ of 0.01 to establish statistical significance, there would still have been significant differences among study groups in levels of triglycerides; total, HDL, and non-HDL cholesterol; and hsCRP (Table 3) and, among BMI categories, in all metabolic outcomes except levels of HDL cholesterol and triglycerides (Table 4). Finally, the number of participants in our non-NNRTI/non-PI group was smaller than that in the other groups, which limits our ability to draw conclusions about this group or about the potential influence of abacavir on the results.

In summary, obesity, dyslipidemia, and inflammation were prominent findings in this group of behaviorally HIV-infected adolescent women. In addition to HIV infection and ART, our data illustrate the significant impact of overweight and obesity on dyslipidemia, insulin resistance, and elevated hsCRP levels in this population. Coupled with cigarette smoking, inactivity, and family history of type 2 diabetes and cardiovascular disease, these factors may accelerate the lifetime risk of cardiovascular disease and other adverse events in a group that is facing lifelong exposure to ART. These results underscore the need for a multifaceted approach to addressing risk reduction in this population.

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