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Antiretroviral Therapy Exposure and Insulin Resistance in the Women's Interagency HIV Study

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Abstract

Background—Evidence suggesting an increased risk of cardiovascular disease in HIV-infected individuals has heightened the need to understand the relation of HIV infection, antiretroviral therapy use, and non–HIV-related factors with insulin resistance (IR).

Methods—Prospective study of 1614 HIV-infected and 604 HIV-uninfected participants from the Women's Interagency HIV Study between October 2000 and March 2007. Homeostasis model assessment (HOMA)–estimated IR at 11,019 semiannual visits.

Results—HIV-infected women reporting highly active antiretroviral therapy (HAART) had higher median HOMA than HIV-uninfected women {1.20 [95% confidence interval (CI): 1.11 to 1.30] times higher for those reporting protease inhibitor–containing HAART; 1.10 (95% CI: 1.01 to 1.20) times higher for those reporting non–protease inhibitor–containing HAART}. Among HIV-infected, cumulative exposure to nucleoside reverse transcriptase inhibitors (NRTIs) of >3 years was associated with HOMA 1.13 (95% CI: 1.02 to 1.25) times higher than the HOMA without any cumulative NRTI exposure. Cumulative exposure to the NRTI stavudine of >1 year was associated with HOMA 1.15 (95% CI: 1.05 to 1.27) times higher than the HOMA without any cumulative stavudine use. Family history of diabetes, hepatitis C virus seropositivity, higher body mass index, or reporting menopause was associated with higher HOMA.

Conclusions—Longer cumulative exposure to NRTI; in particular, stavudine is associated with greater IR in HIV-infected women.

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Dr. P.C.T. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Keywords

antiretroviral therapy; HIV; HOMA; insulin resistance; nucleoside reverse transcriptase inhibitor; protease inhibitor

INTRODUCTION

Insulin resistance (IR) has been increasingly recognized in HIV-infected individuals since the introduction of effective antiretroviral therapy (ART). The protease inhibitor (PI) class of ART has most often been studied because early reports suggested an association between PIs and disorders of glucose metabolism.1–3 Some recent studies have shown an association between the nucleoside reverse transcriptase inhibitor (NRTI) class, which is considered the mainstay of effective ART and IR.4,5

Few studies have investigated the interplay of HIV infection, ART use, and non–HIV-related factors with IR. An understanding of the relationship of these factors with IR is imperative, given recent evidence suggesting an increased risk of premature cardiovascular disease in HIV-infected individuals. [6–9] IR is an important risk factor for cardiovascular disease. To our knowledge, only 1 published prospective study investigated factors associated with IR within the context of HIV infection and relative to HIV-uninfected individuals, but that study was primarily limited to white men.[4]

We examine the association of both the type and duration of ART exposure and non–HIV-related factors with IR using the homeostasis model assessment (HOMA) from October 2000 to March 2007 among participants from the Women's Interagency HIV Study (WIHS), a large ethnically diverse prospective cohort of HIV-infected and HIV-uninfected women.

METHODS

Setting and Participants

The WIHS is a multicenter prospective cohort study established in 1994 to investigate the progression of HIV in women with and at risk for HIV. A total of 3766 women (2791 HIV-infected and 975 HIV-uninfected) were enrolled in either 1994–1995 (n = 2623) or 2001–2002 (n = 1143) from 6 US cities (Bronx, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington, DC). Baseline sociodemographic characteristics and HIV risk factors were similar between HIV-infected and HIV-uninfected women.[10,11] An institutional review board approved study protocols and consent forms, and each study participant gave written informed consent.

Every 6 months, participants complete a comprehensive physical examination, provide biologic specimens for CD4 cell count and HIV RNA viral load determination, and complete an interviewer-administered questionnaire, which collects information on demographics, disease characteristics, and specific ART use.

Beginning in October 2000, fasting glucose (FG) and insulin levels were measured after participants had fasted for ≥8 hours (except for intake of prescribed ART). Of the 2870 women with a visit between October 2000 and March 2007, 2583 had at least 1 FG and insulin measurement at the same visit; the first visit with both FG and insulin data available will be referred to as the index visit. Of the 2583 women with an index visit, 68 were excluded due to either a positive (n = 60) or missing (n = 8) report of pregnancy at the index visit. Of the remaining 2515 women, 284 were excluded due to prevalent diabetes mellitus (DM) (defined as a FG ≥ 126 mg/dL or self-reported DM or self-reported anti diabetic medication use, all at

or before the index visit). Thirteen women who were HIV-uninfected at WIHS study entry and seroconverted during follow-up were also excluded. Our final study population consisted of 2218 women (1614 HIV-infected and 604 HIV-uninfected) who contributed a total of 11,019 visits with FG and insulin data. The median number of visits with FG and insulin data available for both HIV-infected and HIV-uninfected women was 5 (interquartile range: 3 –7). One hundred thirty-six HIV-infected women (8% of 1614 HIV-infected women) and 51 HIV-uninfected women (8% of 604 HIV-uninfected women) with incident DM after the index visit were censored at the visit of DM diagnosis and only contributed data to analyses from the index visit through the visit immediately before incident DM. Incident DM was considered to have occurred at the first follow-up visit after the index visit at which: FG ≥ 126 mg/dL, anti-diabetic medication use was reported, or DM was reported with subsequent confirmation by either an FG ≥ 126 mg/dL or report of anti-diabetic medication use.[12]

Assessment of IR Outcome

IR was quantified using the HOMA, defined as (insulin × glucose)/405 with insulin measured in μIU/mL and glucose measured in mg/dL.[13] Fasting specimens for glucose determination were collected in tubes with glycolytic inhibitors. Serum for insulin determination was obtained at the same time, and all specimens were stored at −70°C until the day of assay. Plasma glucose was measured using the hexokinase method, and insulin was measured using the IMMULITE 2000 assay at a central laboratory.

Assessment of ART Use

At each semiannual visit, HIV-infected participants were shown photo-medication cards and were asked the names of specific ART medications used since the previous visit. The WIHS uses a standard definition of highly active antiretroviral therapy (HAART)14 adapted from the Department of Health and Human Services/Kaiser Panel guidelines.15 All non-HAART combination therapy regimens were classified as combination therapy; reports of a single NRTI, PI, or nonnucleoside reverse transcriptase inhibitor (NNRTI) were classified as monotherapy.

At each visit from index through the end of follow-up, participants were categorized into 1 of 5 groups based on HIV status and self-reported ART since the previous visit: (*a*) HIV-uninfected, (*b*) HIV-infected with no ART, (*c*) HIV-infected with monotherapy or combination therapy, (*d*) HIV-infected with PI-based HAART, or (*e*) HIV-infected with non–PI-based HAART. HIV-infected women reporting no ART use at a particular visit may have been exposed to ART at earlier visits or be completely ART-naive.

At each visit from index through the end of follow-up, we also determined drug-years of exposure to NRTI, PI, and NNRTI as the product of the time (in years) between the current and previous visit and the number of drugs that were reported within a given class of ART (ie, NRTI, PI, and NNRTI) since the previous visit. For each class of ART, drug-years of exposure from the current visit were added to the total drug-years from all previous visits from the index visit forward to measure the duration of cumulative exposure. Drugs within each class were considered exchangeable and additive. Finally, we determined the cumulative drug-years of exposure to the 5 most commonly used NRTIs (ie, lamivudine, zidovudine, stavudine, abacavir, and tenofovir) in our cohort from index visit to the end of follow-up in the same way that we defined the duration of cumulative exposure for NRTI, PI, and NNRTI.

For analyses, we categorized the cumulative exposure to each class of ART and the 5 NRTIs at all person-visits as:(*a*) unexposed (reference category); (*b*) exposed and less than or equal to the median; or (*c*) exposed and greater than the median. In separate analyses, we treated cumulative exposure to each class of ART and the 5 NRTIs as continuous exposures to assess

the change in IR per drug-year. In multivariable analyses, we also adjusted for the cumulative duration of exposure to each ART class that was reported from WIHS study entry through the visit immediately before the index visit.

Statistical Analyses

Comparisons of continuous and categorical characteristics among HIV-infected and HIV-uninfected women at the visit immediately before the index visit were made by Wilcoxon rank sum tests and Pearson χ^2 tests, respectively. Linear regression models with generalized estimating equations were used to quantify the association of HIV infection and ART exposures with IR while accounting for the statistical dependence incurred by repeated HOMA over time on the same individual.16 The logarithm of HOMA was modeled as the outcome variable in regression models because the log-transformed HOMAs were more normally distributed than the raw HOMA. Relative median HOMA levels between 2 groups with different exposures were obtained by exponentiation of select model coefficients and used as the measure of association.[17] Ninety-five percent confidence intervals (CIs) were used as a measure of precision.

Regression models were used to adjust for the potentially confounding effects of variables measured at the visit immediately before the index visit (if data at the visit immediately before index were missing, then data concurrent with the index visit were used). Specifically, we adjusted for race; body mass index (BMI); smoking status (current versus noncurrent); hepatitis C virus (HCV) antibody status; self-reported family history of DM; menopause; an interaction between HIV infection and CD4 cell count (so that the association between CD4 and HOMA was only assessed in HIV-infected women in adjusted analyses that included both HIV-infected and HIV-uninfected women); history of ART use before the index visit (defined as the total number of drugs reported within each class of ART at all visits from WIHS baseline until the visit immediately before the index visit; in analyses, we defined exposure before index categorically as no exposure, exposed less than or equal to the median, or exposed greater than the median); and enrollment cohort (2001–2002 versus 1994–1995). To explore changes in body size as a possible pathway through which ART may affect IR, in separate analyses, we further adjusted for time-varying waist and hip size evaluated at the visit concurrent with HOMA assessment. The association of cumulative exposure to different ART exposure groups with HOMA was assessed for different ages in separate analyses by including age-by-ART exposure–interaction terms in indicated multivariable models. All analyses were conducted using SAS version 9 (SAS Institute, Cary, NC).

RESULTS

Characteristics of Study Population

At the visit immediately before the index visit, the 1614 HIV-infected women were older, more likely to be post-menopausal, and more likely to be HCV antibody positive than the 604 HIV-uninfected women (Table 1). The distribution of race/ethnicity and the proportion with a family history of DM were similar by HIV status. Both BMI and hip circumference were lower in HIV-infected women, but waist circumference was similar. Median FG levels were similar in HIV-infected and HIV-uninfected women (83 mg/dL; $P = 0.69$), but HIV-infected women had higher median insulin levels (11 versus 9 μIU/mL; $P < 0.001$) and therefore higher median HOMA (2.19 versus 1.83; $P < 0.001$) at index visit compared with HIV-uninfected women.

Thousand five hundred seventy-eight (71.1%) of the 2218 women completed follow-up. One hundred sixty-two of the 1578 women died (150 HIV-infected/12 HIV-uninfected), and the remaining 1416 either had an observed HOMA between April 2006 and March 2007 (876 HIV-infected/353 HIV-uninfected) or were censored at the visit immediately before incident DM

(136 HIV-infected/51 HIV-uninfected). The 640 (28.9%) participants who did not complete follow-up had their last HOMA before April 2006 (452 HIV-infected/188 HIV-uninfected).

Recent ART Exposure

The 2218 women contributed a total of 11,019 visits (7983 HIV-infected/3036 HIV-uninfected) with FG and insulin data (2 visits contributed by HIV-infected women did not have ART data available, yielding a total of 11,017 visits for analyses). Among women reporting recent ART use, ≥95% adherence to ART was reported at 76.5% of person-visits. Table 2 presents both the unadjusted and adjusted analyses of characteristics potentially associated with IR. HIV-infected women regardless of ART reported since the previous visit had higher HOMA compared with HIV-uninfected women even after adjustment for possible confounders. Relative to the median HOMA of 1.91 in HIV-uninfected women, HIV-infected women reporting a PI-containing HAART regimen demonstrated a median HOMA 1.20 times higher (95% CI: 1.11 to 1.30) and those reporting a non–PI-containing HAART regimen a 1.10 (95% CI: 1.01 to 1.20) times higher median HOMA. Those women reporting no therapy or either recent monotherapy or combination therapy had HOMA similar to HIV-uninfected women. The 1325 person-years included in the no therapy group in Table 2 were contributed by women who reported no therapy since their last visit but could have reported ART or HAART at prior visits (62% of 1325 person-years) or be completely ART-naive at all prior visits (38% of 1325 person-years).

Table 2 also shows the association of demographic and clinical characteristics with HOMA. Compared with the respective reference groups, being HCV antibody positive, having a family history of diabetes, having a higher BMI, or reporting menopause were associated with higher HOMA. Being Hispanic was associated with a 1.13-fold higher median HOMA compared with the median HOMA of African American women.

Cumulative ART Exposure

Table 3 presents the unadjusted and adjusted associations between IR and the cumulative number of NRTI-years, PI-years, and NNRTI-years during follow-up among HIV-infected women on any ART regimen. NRTI exposure was associated with a higher median HOMA compared with reporting no NRTI use in the adjusted analysis. Specifically, report of >0 to 3 years of NRTI use had a median HOMA 1.06 times higher (95% CI: 0.98 to 1.16), and report of >3 years of NRTI use had a median HOMA 1.13 times higher (95% CI: 1.02 to 1.25) than the median HOMA of 2.07 when no NRTI was reported. Each additional year of NRTI use was associated with a 2% increase in median HOMA (95% CI: 1.01 to 1.03). Cumulative exposure to PI or NNRTI did not seem to be associated with HOMA. Further adjustment for time-varying changes in hip or waist size did not attenuate the association between cumulative exposure to NRTI and HOMA (results not shown). The effect of the cumulative exposure to each class of ART on HOMA was not modified by age (results not shown).

Cumulative Exposure to Zidovudine, Abacavir, Stavudine, Lamivudine, and Tenofovir

Because cumulative NRTI exposure seemed to be most associated with increased HOMA, we evaluated the association between IR and each of the 5 most commonly used NRTIs: lamivudine, zidovudine, stavudine, abacavir, and tenofovir (Table 4). In the multivariable analysis, cumulative exposures of >0 to 1 year or >1 year to stavudine were associated with median HOMA that were 1.07 (95% CI: 0.98 to 1.16) and 1.15 (95% CI: 1.05 to 1.27) times higher, respectively, than the median HOMA of 2.15 among those reporting no stavudine use. Each additional year of stavudine use was associated with a 6% increase in median HOMA (95% CI: 1.01 to 1.11). Further adjustment for time-varying changes in hip or waist size did not decrease the association between cumulative exposure to stavudine and HOMA (results not shown). No elevated association between cumulative exposure to lamivudine, zidovudine,

abacavir, or tenofovir and HOMA was substantial or were any associations precise enough to rule out chance.

DISCUSSION

In this prospective study of IR as measured by the HOMA, we found that among HIV-infected women, longer cumulative NRTI exposure was associated with greater IR in HIV-infected women. Our findings corroborate the results of small studies which have shown an association between duration of NRTI use and fasting hyperinsulinemia[18] or IR as measured by HOMA[5] and are consistent with those from a large prospective study of HIV-infected men.[4] The latter study, which was one of the few studies to examine the independent associations between specific NRTI and IR in HIV-infected men, observed that cumulative use of stavudine and lamivudine was associated with IR.[4] In our study, cumulative use of the NRTI, stavudine, was associated with greater IR.

An association between NRTI and IR was also suggested in a study that randomized antiretroviral-naive patients to a PI-containing HAART regimen, an NNRTI-containing HAART regimen, or a PI-containing and NNRTI-containing HAART regimen. That study found that IR increased similarly in all 3 treatment groups over a median of 5 years. In that study, the NRTIs most frequently used as part of the HAART regimen were zidovudine plus lamivudine or stavudine plus lamivudine.[19]

NRTI-induced mitochondrial dysfunction has been postulated as a mechanism by which NRTI may cause IR.[20] A recent study in healthy HIV-uninfected volunteers demonstrated that short-term administration of stavudine reduced insulin sensitivity and decreased mitochondrial DNA in muscle, suggesting that altered mitochondrial function in muscle may be an important factor in the development of IR.[21] Stavudine has also been associated with lipoatrophy,[22–27] and lipoatrophy in turn has been associated with IR.[28,29] We observed, however, that after further adjustment for changes in hip (which we have previously demonstrated to be the most affected body site in this cohort[30]), the association between either NRTI or stavudine use and IR was not attenuated. An alternative hypothesis suggested in another study is that elevations in lactate levels (which have been associated with NRTI use and mitochondrial dysfunction) may negatively influence insulin sensitivity.[18]

When compared with HIV-uninfected women, HIV-infected women who reported using any HAART regimen at the last visit had greater IR. The strongest association was observed in those reporting recent use of a PI-containing HAART regimen. These findings suggest that both an HAART-associated restoration to health phenomenon and a direct effect of PI may play a role in the observed greater IR in HIV-infected women. Indeed, the association between recent (but not cumulative) PI use and IR is noteworthy. PI use has been associated with IR in HIV-infected individuals in several studies.[1,2,31,32] Acute decreases in insulin sensitivity were observed in HIV-uninfected volunteers after a single dose of either indinavir[33] or lopinavir/ritonavir,[34] a commonly used PI in our study population. However, more recent data suggest that longer PI use may ameliorate the acute induction of IR observed in HIV-uninfected volunteers. In one study, although an acute decrease in insulin sensitivity was observed after a single dose of lopinavir/ritonavir, no change in insulin sensitivity from baseline was observed after 4 weeks on lopinavir/ritonavir.[34] Similarly, the acute decrease in insulin sensitivity observed after a single dose of indinavir was ameliorated after 4 weeks of indinavir.[35] A possible explanation for the amelioration of IR in these studies was the observed increases in levels of the adipocyte hormone, adiponectin from baseline after 4 weeks of therapy. Adiponectin is associated with increased insulin sensitivity.

Although we found that ART, including class of drug and specific drug, was associated with IR, several non–HIV-related factors were also associated with IR. Factors including family history of diabetes, increased BMI, and HCV seropositivity are recognized risk factors for IR, and these risks are replicated here. We also observed an association between menopause and greater IR; menopause has been associated with increased visceral adipose tissue, a key risk factor for IR. Interestingly, African American race, which has been shown to be associated with decreased insulin sensitivity in HIV-uninfected women,[36] was not associated with higher IR compared with white women. A recent study in HIV-infected women found that African American women had less visceral fat than white women,[23] which may partly explain our findings. On the other hand, being Hispanic was associated with higher IR when compared with African American or white women.

There are limitations of the current study. First, we defined IR using the HOMA, a surrogate marker, and not the gold standard euglycemic insulin clamp technique.[37] Given the nature of our large, multicenter, prospective cohort, detailed testing using a clamp technique was not feasible. Furthermore, HOMA has been shown to be a reasonable marker of IR in large epidemiologic studies.[38,39] Second, as with all prospective studies, our findings are subject to possible informative censoring. Third, as with all observational studies, our findings are subject to possible unmeasured confounding. Finally, the design of this cohort study, which examines participants every 6 months, only allows us to coarsely define cumulative exposure to specific ART.

In summary, we conclude that in HIV-infected women, recent use of any HAART regimen was associated with higher IR when compared with HIV-uninfected women. Among HIV-infected women, cumulative exposure to NRTI, but not PI or NNRTI, was independently associated with higher IR. Study of the biologic mechanisms by which exposure to individual ART and classes of ART might induce disorders in glucose metabolism is needed. In addition to antiretroviral drug effects, non–HIV-related factors must also be considered in the development of IR among HIV-infected persons.

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TABLE 1

Characteristics at the Study Visit Immediately Before the Index Visit by HIV Status of 2218 Participants of the WIHS*

Characteristics	HIV-Infected Women, n = 1614	HIV-Uninfected Women, n = 604	*P*†
Age, yrs	38.8 (33.0, 44.8)	33.9 (27.0, 41.7)	<0.001
Race, % (n)			
African American	56.2 (907)	58.1 (351)	0.69
Hispanic	27.9 (451)	27.2 (164)	
White‡	15.9 (256)	14.7 (89)	
Current smoker, % (n)§	47.6 (766)	51.8 (313)	0.07
BMI, kg/m^2 §	26.6 (23.3, 31.1)	27.7 (23.4, 32.9)	<0.01
Waist size, cm §	87.3 (79.2, 98.2)	86.3 (77.6, 99.0)	0.39
Hip size, cm §	99.0 (91.3, 107.8)	102.0 (94.9, 112.2)	<0.001
Menopausal, % (n)§	15.2 (245)	8.1 (49)	<0.001
HCV antibody positive, % (n)§	29.4 (465)	15.6 (93)	<0.001
Family history of diabetes, % (n)	29.5 (454)	27.0 (156)	0.27
Clinical AIDS, % (n)	31.9 (515)	NA	NA
Log_{10}HIV RNA, copies/mL§	2.93 (1.90, 4.04)	NA	NA
CD4 count, cells/mm^3 §	431 (270, 633)	NA	NA
Nadir CD4 count, cells/mm^3 §	257 (130, 389)	NA	NA
ART-naive, % (n)	17.7 (285)	NA	NA

*All values are median (interquartile range) unless otherwise noted; if data were missing at visit immediately before index, then data concurrent with index visit were used; ART-naive was determined from WIHS baseline through the index visit.

†The *P* value from Pearson χ^2 test of overall association when percentages are compared and *P* value from Wilcoxon rank sum test when medians are compared.

‡Includes 3% (n = 54) and 4% (n = 25) Asian, Pacific Islander, Native American, Alaskan, and other among HIV-infected and HIV-uninfected women, respectively.

§Current smoking was missing for 3 HIV-infected women; BMI was missing for 12 HIV-infected women and 3 HIV-uninfected women; waist size was missing for 215 HIV-infected women and 79 HIV-uninfected women; hip size was missing for 216 HIV-infected women and 80 HIV-uninfected women; menopausal status was missing for 4 HIV-infected women and 1 HIV-uninfected woman; HCV infection status was missing for 33 HIV-infected women and 9 HIV-uninfected women; family history of diabetes was missing for 73 HIV-infected women and 27 HIV-uninfected women (women who reported not being familiar with health history of family members were classified as not having a family history of diabetes); HIV RNA was missing for 6 HIV-infected women; CD4 was missing for 11 HIV-infected women; and nadir CD4 was missing for 92 HIV-infected women.

TABLE 2

Comparison of HOMA Values Among 2218* Women by HIV Infection Status, Most Recent ART Reported, and Demographic and Clinical Factors†

			Estimated Relative Difference in Medians‡ (95% CI)	
	No. Person-Years	Median HOMA	Unadjusted Analyses	Adjusted Analysis§
HIV-uninfected women	1598	1.91	1 (reference)	1 (reference)
HIV-infected women				
No therapy	1325	2.11	1.11 (1.03 to 1.19)	1.05 (0.96 to 1.15)
Mono/combination	199	2.07	1.07 (0.94 to 1.21)	1.05 (0.93 to 1.19)
HAART with PI	1491	2.30	1.21 (1.13 to 1.30)	1.20 (1.11 to 1.30)
HAART—no PI	1215	2.18	1.13 (1.05 to 1.22)	1.10 (1.01 to 1.20)
Race				
African American	3268	2.11	1 (reference)	1 (reference)
Hispanic	1710	2.25	1.08 (1.02 to 1.15)	1.13 (1.06 to 1.19)
White‖	850	1.91	0.95 (0.87 to 1.02)	1.00 (0.93 to 1.08)
HCV				
Negative	4296	2.05	1 (reference)	1 (reference)
Positive	1423	2.39	1.16 (1.10 to 1.24)	1.17 (1.09 to 1.24)
Family history of diabetes				
No	3934	2.05	1 (reference)	1 (reference)
Yes	1647	2.28	1.11 (1.04 to 1.17)	1.05 (1.00 to 1.11)
Age (per 10 yrs)	—	—	1.06 (1.03 to 1.09)	1.01 (0.98 to 1.05)
Smoking				
No	3051	2.17	1 (reference)	1 (reference)
Yes	2773	2.05	0.96 (0.91 to 1.02)	0.98 (0.93 to 1.03)
BMI (per 5 units)	—	—	1.17 (1.15 to 1.19)	1.18 (1.16 to 1.20)
CD4 count (per 100 cells)¶	—	—	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.02)
Reported menopause				
No	5112	2.09	1 (reference)	1 (reference)
Yes	699	2.46	1.19 (1.10 to 1.28)	1.11 (1.02 to 1.21)

*Two thousand one hundred twenty-eight women (1614 HIV-infected and 604 HIV-uninfected) contributed a total of 11,017 person-visits (7981 HIV-infected and 3036 HIV-uninfected) of follow-up including the index visit.

†Data on demographic and clinical factors assessed at visit immediately before index; if data for a particular variable were missing at visit immediately before index, then data concurrent with index visit were used.

‡Antilog of coefficient of exposure group from regression model.

§Two thousand forty-seven women (1482 HIV-infected and 565 HIV-uninfected) contributing 10,436 person-visits (7529 HIV-infected and 2907 HIV-uninfected) were included in adjusted analysis.

‖Includes Asian, Pacific Islander, Native American, Alaskan, and other.

¶Only assessed among HIV-infected women in unadjusted analysis and assessed via an interaction with HIV status in adjusted analysis (ie, set to zero for HIV-uninfected women).

TABLE 3

Comparison of HOMA Values Among 1614* HIV-Infected Women by Cumulative Amount of Exposure to Each Class of ART Reported At Each Visit

	No. Person-Visits	Median HOMA	Estimated Relative Difference in Medians† (95% CI)	
			Unadjusted Analyses	Adjusted Analysis‡
Cumulative number of NRTI-years				
0	1910	2.07	1 (reference)	1 (reference)
>0 to 3.0	3039	2.25	1.06 (0.99 to 1.13)	1.06 (0.98 to 1.16)
>3.0	3032	2.22	1.09 (1.01 to 1.19)	1.13 (1.02 to 1.25)
Cumulative number of PI-years				
0	4309	2.15	1 (reference)	1 (reference)
>0 to 1.5	1837	2.22	1.07 (1.01 to 1.14)	1.03 (0.96 to 1.10)
>1.5	1835	2.25	1.06 (0.98 to 1.13)	1.01 (0.93 to 1.10)
Cumulative number of NNRTI-years				
0	4586	2.21	1 (reference)	1 (reference)
>0 to 1.0	1699	2.17	0.99 (0.93 to 1.06)	0.96 (0.89 to 1.03)
>1.0	1696	2.20	1.00 (0.93 to 1.08)	0.95 (0.86 to 1.03)

* One thousand six hundred fourteen HIV-infected women contributed a total of 7981 person-visits of follow-up including the index visit.

† Antilog of coefficient of exposure group from regression model.

‡ Adjusted for cumulative number of NRTI, PI, or NNRTI reported from WIHS baseline through the visit before index, WIHS cohort status (1994–1995 or 2001–2002), race, baseline HCV antibody status, family history of diabetes, age, smoking status, BMI, CD4 count, and menopause assessed at visit immediately before index; if data for a particular variable were missing at visit immediately before index, then data concurrent with index visit were used; 1482 women contributing 7529 person-visits were included in analysis.

TABLE 4

Comparison of HOMA Values Among 1614* HIV-Infected Women by Cumulative Amount of Zidovudine, Abacavir, Stavudine, Lamivudine, and Tenofovir Reported at Each Visit

			Estimated Relative Difference in Medians† (95% CI)	
	No. Person-Visits	Median HOMA	Unadjusted Analyses	Adjusted Analysis‡
Cumulative number of person-years reporting lamivudine				
0	2915	2.11	1 (reference)	1 (reference)
>0 to 1.1	2539	2.20	1.04 (0.98 to 1.11)	1.04 (0.96 to 1.12)
>1.1	2527	2.34	1.10 (1.02 to 1.18)	1.06 (0.97 to 1.17)
Cumulative number of person-years reporting zidovudine				
0	4508	2.17	1 (reference)	1 (reference)
>0 to 1.0	1717	2.15	1.00 (0.94 to 1.07)	1.03 (0.95 to 1.11)
>1.0	1756	2.34	1.06 (0.99 to 1.14)	1.08 (0.98 to 1.19)
Cumulative number of person-years reporting stavudine				
0	5622	2.15	1 (reference)	1 (reference)
>0 to 1.0	1179	2.25	1.06 (0.98 to 1.14)	1.07 (0.98 to 1.16)
>1.0	1180	2.41	1.15 (1.05 to 1.25)	1.15 (1.05 to 1.27)
Cumulative number of person-years reporting abacavir				
0	5772	**2.20**	1 (reference)	1 (reference)
>0 to 1.0	1099	2.15	0.97 (0.91 to 1.05)	0.96 (0.89 to 1.03)
>1.0	1110	2.19	1.00 (0.92 to 1.09)	0.99 (0.90 to 1.07)
Cumulative number of person-years reporting tenofovir				
0	5904	2.23	1 (reference)	1 (reference)
>0 to 1.0	1043	2.17	0.97 (0.91 to 1.04)	1.00 (0.94 to 1.07)
>1.0	1034	2.05	0.93 (0.86 to 1.01)	0.91 (0.91 to 1.07)

*One thousand six hundred fourteen HIV-infected women contributed a total of 7981 person-visits of follow-up including the index visit.

†Antilog of coefficient of exposure group from regression model.

‡Adjusted for cumulative number of NRTI, PI, and NNRTI reported from WIHS baseline through the visit before index, time-updated cumulative number of PI-years and NNRTI-years from index through visit immediately before current visit, WIHS cohort status (1994–1995 or 2001–2002), race, baseline HCV antibody status, family history of diabetes, age, smoking status, BMI, CD4 count, and menopause assessed at visit immediately before index; if data for a particular variable were missing at visit immediately before index, then data concurrent with index visit were used; 1482 women contributing 7529 person-visits were included in analysis.