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Sex Hormones, Insulin Resistance, and Diabetes Mellitus among Men with or at Risk for HIV Infection

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Abstract

Objective—To examine the relationship of free testosterone (FT) and sex hormone-binding globulin (SHBG) with insulin resistance and diabetes mellitus (DM) in HIV disease.

Design—Cross-sectional analysis from 322 HIV-uninfected and 534 HIV-infected men in the Multicenter AIDS Cohort Study.

Methods—The main outcomes were DM and Homeostasis model assessment–insulin resistance (HOMA-IR). DM was defined as fasting serum glucose (FG) ≥ 126 or self-reported DM and use of DM medications. Homeostasis model assessment–insulin resistance (HOMA-IR) was calculated from FG and fasting insulin.

Results—Compared with HIV-uninfected men in our sample, HIV-infected men were younger, with lower BMI, and more often black. HIV-infected men had lower FT ($p < 0.001$) and higher SHBG ($p < 0.0001$). The adjusted odds ratio for DM was 1.98 (95% CI 1.04–3.78); mean adjusted log HOMA-IR was 0.21 units higher in HIV-infected men ($p < 0.0001$). Log SHBG, but not log FT, was associated with DM (OR = 0.44, 95% CI 0.25, 0.80) in both groups. Log FT and log SHBG were inversely related to insulin resistance ($p < 0.05$ for both) independent of HIV.

Conclusions—Compared to HIV-uninfected men, HIV-infected men had lower FT, higher SHBG, and more insulin resistance and DM. Lower FT and lower SHBG were associated with insulin resistance regardless of HIV serostatus. This suggests that sex hormones play a role in the pathogenesis of glucose abnormalities among HIV-infected men.

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Keywords

Testosterone; Sex Hormone-Binding Globulin; Insulin Resistance; Diabetes Mellitus; HIV

Introduction

Diabetes mellitus (DM) is a common co-morbidity in individuals with human immunodeficiency virus (HIV) infection. Traditional DM risk factors, including obesity, lack of physical activity, and family history of DM, are common among HIV-infected persons, especially among persons attending urban clinics.¹ In addition to traditional risk factors, use of drugs that comprise highly active antiretroviral therapy (HAART) is also positively associated with DM. A previous report from the Multicenter AIDS Cohort Study (MACS) revealed higher prevalent and incident DM among HIV-infected men receiving HAART compared to HIV-uninfected men.² Other studies have demonstrated a positive association between antiretroviral therapy (ARV) use and DM development among HIV-infected individuals, particularly with longer cumulative exposure to nucleoside reverse transcriptase inhibitors (NRTIs).³

Identification of DM risk factors is important to decrease the burden of disease in this population. One potential risk factor for impaired glucose metabolism is hypogonadism, which has been associated with insulin resistance and DM in men without HIV in several large studies.^{4, 5} Hypogonadism is common in individuals with HIV⁶ and was associated with wasting in the pre-HAART era.⁷ Furthermore, hypogonadism may persist despite effective antiretroviral therapy.⁸ The relationship between hypogonadism and DM and insulin resistance in HIV-infected men has not been examined previously.

Multiple cross-sectional studies have revealed an association between low sex hormone-binding globulin (SHBG) and DM.^{4, 9} Additionally, low SHBG has been associated with worse glycemic control in men with DM, even after adjustment for hyperinsulinemia.¹⁰ Individuals with HIV have increased SHBG with concentrations between 39% and 51% above controls.¹¹ However, the effect of SHBG on DM and insulin resistance in HIV-infected men is unknown.

The primary aim of our study was to investigate the association between FT and SHBG on DM and insulin resistance in HIV-infected men. We hypothesized that, compared to HIV-uninfected men, HIV-infected men would have lower FT, higher SHBG, would be more insulin resistant and have more prevalent DM.

Methods

We used cross-sectional data from a single study visit of participants in the Multicenter AIDS Cohort Study (MACS) to assess the relationship between FT, SHBG, and insulin resistance and prevalent DM among men with and at risk for HIV infection.

Study Population

The MACS was initiated in 1984 as a study of men who have sex with men conducted at four study sites in Baltimore/Washington, DC, Chicago, Los Angeles, and Pittsburgh. A total of 6,973 men were enrolled during three time periods. Details of the study design and methods have been published.¹²

Selection Criteria

Data for this analysis came from MACS participants who were at least 40 years old, weighed less than 300 pounds, and had no history of coronary heart disease (including angina, myocardial infarction, or coronary revascularization) who were enrolled in the MACS Cardiovascular Substudy, which has been previously described.¹³ Of the 945 MACS Cardiovascular Substudy participants, 14 were excluded from this analysis because there was no stored serum sample at the time of the substudy visit, 71 were excluded because they were receiving testosterone replacement therapy, and four were excluded because the quantity of stored serum was insufficient to perform hormone assays. Therefore, hormone assays were performed on stored serum from a total of 856 men and their data and was included in the present analysis. The protocol was approved by Institutional Review Boards at each site and each study participant signed informed consent.

Outcomes

DM was defined as a fasting serum glucose ≥ 126 mg/dL or self-reported DM and use of DM medication collected in a standardized fashion at the semi-annual MACS visit. HOMA-IR was calculated using fasting glucose and fasting insulin levels measured from blood samples collected at the same visit using the equation (fasting glucose (mg/dL) $\times$ fasting insulin (μ U/ml))/405.¹⁴

Measures of Interest

All hormone assays were performed using frozen samples in the laboratory of Dr. Shalender Bhasin (Boston University, Boston, MA, USA). Testosterone levels were measured from archived serum using liquid chromatography tandem mass spectrometry (LC-MS/MS). SHBG was measured using radioimmunoassay (RIA). Free T was calculated from total T and SHBG measurements using the Vermeulen equation.¹⁵

Additional variables of interest included race, BMI, intravenous drug use (IVDU) history, Hepatitis C Virus (HCV) infection and, in HIV-infected individuals, CD4 cell count and plasma HIV RNA levels (viral load). Current and prior exposure to antiretroviral medications in the protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitor (NRTI) classes were assessed from semi-annual data. Current and prior exposure histories to individual antiretroviral agents were also collected.

Statistical Analysis

We compared demographic and clinical characteristics of participants with and without HIV infection, using chi-square tests to compare counts and prevalence measurements. To compare continuous variables, we used the two sample t-test or Wilcoxon rank sum test depending on the distribution of the variables.

To examine the relationship between DM and sex hormones, we constructed multiple logistic regression models, using dichotomous DM status as the outcome and log-transformed FT or SHBG as the primary explanatory variable. Other covariates included in the models were HIV infection, age, race (black vs. other), BMI, and HCV status. The models were adjusted for waist circumference to account for adipose tissue distribution. We also adjusted for clinic site to account for the different characteristics of the four sites. As a sensitivity analysis, we built a logistic model including both T and SHBG. The model was similar to those with FT or SHBG, thus is not presented with the results. For models involving SHBG, we adjusted for insulin because hyperinsulinemia can lower SHBG.¹⁰

We examined the relationship between DM status and FT and SHBG in the HIV-infected group only using similar logistic regression models. In addition to the covariates mentioned above for the models including all participants, we adjusted for HIV clinical status and treatment parameters, including CD4 count ≥ 200 cells/ μ L, viral load ≥ 400 copies/mL, and antiretroviral therapy status.

We modeled the relationship between insulin resistance and hormones using multiple linear regression. Similarly to the DM models, we constructed separate models for the entire sample and for the HIV-infected participants only. The dependent variable for the models was log-transformed HOMA-IR, and the primary independent variable was log-transformed FT or log-transformed SHBG. We included age, site, race, BMI, HCV status, and waist circumference in the models. The models for the entire sample set were adjusted by HIV infection status, and the models for HIV-infected individuals also included HIV clinical status and treatment parameters. We then reran all analyses using data only from individuals with hormone assays performed from a blood sample drawn in the morning.

Analyses were conducted using SAS Version 9.2 (Cary, North Carolina), and a p-value <0.05 was considered statistically significant.

Results

Demographics

Table 1 presents the distribution of relevant demographic and clinical characteristics according to HIV status. The HIV-uninfected men (n=322) were older and had higher BMIs than HIV-infected men. The HIV-infected men (n=534) were more likely to be a race other than white and more likely to have HCV infection than the HIV-uninfected men.

Overall DM prevalence

The overall prevalence of DM in all participants was 10.1%. The adjusted odds ratio of DM in HIV-infected men compared with HIV-uninfected men was 1.98 (95% CI 1.04, 3.78) and the adjusted log HOMA-IR was 0.21 units (22.3%) higher ($p < 0.0001$) in HIV-infected men compared with HIV-uninfected men.

Sex hormone levels in HIV-infected and HIV-uninfected men

In our sample, adjusted mean log FT was lower in HIV-infected men, 4.49 v. 4.61 ($p < 0.01$), corresponding to a mean FT of 88.9, and 100.9 pg/mL in HIV-infected and HIV-uninfected men, respectively. Men with HIV had higher adjusted logSHBG than their HIV-uninfected counterparts, 3.98 v. 3.84 ($p < 0.0001$), corresponding to a mean SHBG of 53.4 and 46.5 nmol/L in HIV-infected and HIV-uninfected men, respectively.

Among the HIV-infected men, in adjusted multivariate analysis, log FT decreased with increasing age and HCV infection and increased among individuals with a CD4 count ≥ 200 cells/ μ L. SHBG increased with increasing age, black race, and HCV infection status, and decreased with increasing BMI. (Table 2).

Relationship of sex hormones with insulin resistance and DM

Table 3 shows the adjusted associations between log hormone levels and DM and HOMA-IR in all study participants. In this analysis, FT was inversely associated with HOMA-IR but not associated with DM. SHBG was inversely associated with DM and HOMA-IR, even after adjusting for fasting insulin. In all models, HIV-infected status was positively associated with DM and HOMA-IR. When considering individuals with AM blood draws only (N=532) (Table 3a), FT was inversely associated with DM, and the relationship

achieved statistical significance. SHBG and DM remained inversely associated, but the relationships were no longer statistically significant. FT maintained a statistically significant inverse association with HOMA-IR, but the inverse association between SHBG and HOMA-IR lost statistical significance.

Relationship of sex hormones with DM in HIV-infected men

Table 4 shows the associations between log hormone levels and DM in HIV-infected men. FT was not associated with DM in all HIV-infected participants, however, when the analysis was restricted to individuals with AM samples, the association was statistically significant. SHBG was not associated with DM in either all HIV-infected participants or those with AM blood draws only.

Among the HIV-infected men, in bivariate analysis, current NNRTI use or ever having used an NNRTI or a PI was positively associated with DM (data not shown, $p < 0.10$ for all). For individual agents, ever having used stavudine, high-dose ritonavir, or lopinavir/ritonavir was positively associated with DM ($p < 0.10$ for all). Current NRTI and PI use and ever having used an NRTI, PI, or NNRTI were positively associated with insulin resistance ($p < 0.05$ for all). For individual agents, ever having used stavudine, high- or low-dose ritonavir, or lopinavir/ritonavir was positively associated with insulin resistance ($p < 0.05$ for all) and current use of high- or low-dose ritonavir was positively associated with insulin resistance ($p = 0.01$ for both). These associations held even after adjustment for duration of HIV disease. Ever having used stavudine was the only drug variable positively associated with DM (OR = 4.21, 95% CI 1.84, 9.65 in FT model) in multivariate analysis. The other drug variables were not significant when included in multivariate analysis, alone or in combination. The addition or removal of the other drug variables did not affect the relationship of either FT or SHBG with DM or insulin resistance. Therefore, we included ever having used stavudine in the final multivariate model.

Relationship of sex hormones with Insulin Resistance in HIV-infected men

Table 5 shows the associations between log hormone levels and HOMA-IR in HIV-infected men. FT was inversely associated with HOMA-IR in a model not adjusted for waist circumference. The addition of waist circumference altered the results in the FT model for HOMA-IR: prior to addition of waist circumference, FT was significantly associated with lower HOMA-IR. However, after addition of waist circumference, the association was no longer significant. SHBG was related to HOMA-IR independent of waist circumference.

SHBG was associated with HOMA-IR in all HIV-infected participants, however, when only individuals with AM blood draws were included in the analysis, the association was no longer statistically significant. Conversely, SHBG remained associated with HOMA-IR in HIV-infected participants when individuals with PM blood draws were considered (data not shown).

Discussion

In this cross-sectional study of a well-characterized population of men either with or at risk for HIV infection, we found that HIV-infected men had lower concentrations of FT and higher concentrations of SHBG than HIV-uninfected men. The adjusted prevalence of DM and the degree of insulin resistance were higher in HIV-infected men compared to HIV-uninfected men. Among HIV-infected men, FT and SHBG were inversely associated with insulin resistance but not with DM. SHBG concentrations were higher in HIV-infected men than uninfected men, a state which should be protective for the development of glucose

abnormalities, however, the prevalence of DM and level of insulin resistance were greater in HIV-infected men than HIV-uninfected men.

Following the introduction of highly active antiretroviral therapy (HAART), DM has been increasingly observed among HIV-infected individuals. Antiretroviral therapy induces insulin resistance and multiple studies have shown that antiretroviral therapy is associated with DM.^{2, 16–19} Although early studies implicated protease inhibitors in the development of insulin resistance, many older protease inhibitors are no longer in use, and recent studies have shown associations between NRTI use and both DM and insulin resistance,²⁰ possibly due to mitochondrial toxicity. Furthermore, traditional DM risk factors such as increasing age and BMI may exert a stronger effect in HIV-infected individuals.¹⁶ We found that the adjusted prevalence of DM and the degree of insulin resistance was higher in HIV-infected versus HIV-uninfected men. In our sample, almost all HIV-infected men (93%) were receiving antiretroviral therapy at the time of the study visit. Of all drug variables examined, the relationship between ever having used stavudine and both DM and insulin resistance was strong, consistent with prior studies.¹⁹ Even short-term administration of stavudine has been shown to increase insulin resistance among healthy volunteers.²¹ There has been conflicting evidence as to whether Hepatitis C virus infection confers increased risk for DM and insulin resistance in individuals with HIV/HCV coinfection.^{17, 22} Hepatitis C was positively associated with insulin resistance among HIV-infected individuals in our sample.

In the general population, low total T concentration is associated with DM in both cross-sectional and prospective studies. Low serum T was associated with impaired fasting glucose and DM, independent of waist circumference and BMI in a large multiethnic cohort.⁴ NHANES III data (1988–1994), showed that among male subjects, those in the lowest testosterone tertile had four times higher odds of DM than those in the highest tertile.⁵ A recent meta-analysis revealed that T was lower among men with incident DM in prospective studies and prevalent DM cases in cross-sectional studies.⁹ Low T has also been associated with metabolic syndrome²³ and both all-cause and cardiovascular mortality.^{24, 25} Potential mechanisms include increased visceral adiposity due to increased lipoprotein lipase activity, polymorphisms of the androgen receptor gene, impaired glucose transport at the cellular level, and less benefit from the antioxidant properties of testosterone.²⁶ The association between FT and DM is inconsistent, with several studies showing weak association^{5, 27, 28} and others revealing no association.^{20, 29} The association between low T and DM and insulin resistance is likely mediated by body fat, specifically by visceral adipose tissue.³⁰ Adipose-derived factors inhibit the hypothalamic–pituitary–gonadal (HPG) axis, which decreases T, which promotes further accumulation of adipose tissue. This in turn promotes further insulin resistance. T may also act independently by decreasing muscle insulin sensitivity.³⁰

Hypogonadism is common in HIV disease, and was associated with AIDS wasting in the pre-HAART era.⁷ Prevalence estimates of hypogonadism vary widely between study samples and study conduct, ranging from 29–70%.^{8, 31} Low testosterone in HIV may be related to poor nutritional status, poor clinical status, prescription drug use (opiates, megestrol acetate, steroids), pituitary dysfunction,³² HCV infection or illicit drug use.⁶ In our sample, low FT was associated with insulin resistance, but not DM, in both HIV-uninfected and HIV-infected men. Free T, particularly in young men, demonstrates diurnal variation, with peak levels in the morning and trough levels in the afternoon.^{33, 34} Individuals with DM may lose their diurnal variation in FT, which could account for our findings that FT was significantly associated with DM when the labs were drawn in the AM but not the PM.

In HIV-infected men only, FT was inversely associated with HOMA-IR in a model not adjusted for waist circumference. However, after adjustment for waist circumference, the association was no longer significant. This suggests that the relationship between FT and IR is related to increased central fat. This may reflect that increased central fat both lowers FT and increases IR. Alternatively, low FT may lead to increased central fat leading to insulin resistance. Lipodystrophy, or abnormal fat loss or accumulation, is common among individuals with HIV and is associated with low T.³⁵ Models using T and SHBG rather than FT revealed similar results. Our findings suggest that FT may be an important mediator of glucose metabolism in HIV disease.

Low SHBG is associated with DM in both cross-sectional and prospective studies^{4, 9, 27, 36, 37} in the general population. Previously, SHBG was considered a transport protein only; however, recent research has exposed a broader role. Hammes and colleagues³⁸ showed that SHBG-bound hormone can be transported intracellularly and can be biologically active. Ding and colleagues demonstrated that carriers of the rs6257 variant allele of the SHBG single nucleotide polymorphism had 10% lower plasma SHBG levels and a higher risk for DM.³⁶ Although the exact mechanism for the observed effect is unknown, there is evidence that sex hormones bound to SHBG may be active in cell-surface signaling and exert biologic effect.³⁶ Elevated SHBG in HIV disease has been demonstrated in both pre- and post-HAART era studies, although the exact mechanism is unclear.^{11, 31} Increased SHBG in HIV disease explains the discordance between FT, which is often low in HIV disease, and total testosterone which may be normal.

In a recent study of the relationship between SHBG and fasting glucose, insulin secretion, and insulin sensitivity, increased intrahepatic fat was associated with decreased SHBG.³⁹ Furthermore, SHBG was negatively correlated with fasting glycemia, but not insulin secretion or insulin sensitivity. HIV-infected individuals, who may have chronic inflammation, metabolic derangement, and hepatitis virus coinfection are at higher risk of hepatic steatosis.⁴⁰ Despite this, SHBG levels were still higher among the HIV-infected men in our sample. We did not directly measure intrahepatic fat in this study.

In our model involving only HIV-infected participants, low SHBG was positively associated with increased HOMA-IR but not with DM. There was a trend towards association between low SHBG and DM that did not reach statistical significance. SHBG is typically lowest in the morning and increases by afternoon.^{33, 41} Individuals with DM may lose their diurnal variation in SHBG, which could explain why SHBG was inversely related to DM and IR in all participants but not when restricted to AM draws only. The analysis may have been underpowered, or it may be easier to detect elevated HOMA-IR than DM in individuals with HIV. To diagnose diabetes, we used a fasting serum glucose ≥ 126 mg/dL or self-reported DM and use of DM medication. A prior study by Hadigan and colleagues revealed that HIV-infected individuals with fasting hyperinsulinemia frequently had normal fasting glucose⁴² which may explain why we did not detect more DM. There may be a physiologic difference between the effect of SHBG in HIV-infected and -uninfected men. To examine whether there is a difference in SHBG effect based on HIV infection status, we tested the HIV-SHBG interaction term in the model involving all participants, and this was not statistically significant. There may be a different binding affinity for T among HIV-infected men,¹¹ however, it is unclear what effect, if any, this has on glucose metabolism. Overall, despite having higher SHBG concentrations, which should confer a protective effect against insulin resistance, HIV-infected men in our study were still more insulin resistant and had a higher prevalence of DM than HIV-uninfected men.

It is unclear whether supplementing testosterone in HIV-infected patients will improve glucose metabolism. Testosterone therapy has been studied in HIV-uninfected diabetic and

non-diabetic men with hypogonadism to determine its effect on insulin sensitivity and glucose levels. Several studies have shown improvement in insulin sensitivity in testosterone-supplemented hypogonadal men with and without DM,^{43, 44} however, other trials have shown no improvement.^{45, 46} A recent study of the efficacy of testosterone in reducing abdominal obesity in hypogonadal HIV-infected men showed decreases in whole body, total, and subcutaneous abdominal fat, but not visceral fat. There were no significant differences in the changes in plasma insulin or fasting glucose between the placebo and treatment groups.⁴⁷ However, testosterone therapy may be more beneficial in individuals with lower baseline FT and in older HIV-infected men. There are potential public health implications in screening for hypogonadism and treating with testosterone to decrease DM risk in HIV-infected if future studies reveal that T replacement decreases DM risk. Another possible mechanism to improve T in HIV-infected men is to improve insulin sensitivity or reduce liver fat. Metformin reduces insulin resistance among people with HIV with lipodystrophy,⁴⁸ but it is unclear if this has an effect on T. Lifestyle intervention to promote weight loss may be effective in decreasing hepatic steatosis, and weight loss would certainly improve both insulin sensitivity and T levels.

A major strength of our study was the use of an internal HIV-uninfected comparison group which allowed us to examine the effect of HIV status on our outcomes. Most of the HIV-infected participants were on HAART, however, so our results are not generalizable to antiretroviral naive individuals. Furthermore, it is difficult to determine the relative contributions of HIV infection and antiretroviral therapy on insulin resistance and diabetes in HIV-infected participants. Our ability to determine temporality is limited by the study's cross-sectional design. Furthermore, the DM diagnosis was based only on one fasting blood glucose measurement or self report of a DM diagnosis and use of DM medications.

To our knowledge, this is the first examination of the association between sex hormones, insulin resistance, and diabetes in men with and at risk for HIV infection. Diabetes is a common problem among HIV-infected persons with serious related complications, including increased morbidity and mortality from cardiovascular and renal disease. Additional research should be conducted to determine whether all HIV-infected men should be screened for hypogonadism and then treated in order to decrease diabetes risk. Planned analysis of MACS data will include serial testosterone measurements and evaluation of their association with insulin resistance and diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Clinical Characteristics of HIV-uninfected and HIV-infected Participants

	HIV-uninfected N= 322 (37.6%)	HIV-infected N= 534 (62.4%)	p-value
Mean Age (years)	52.6 ± 7.8	48.9 ± 6.4	<0.0001
Race - White (%)	237 (73.6%)	324 (60.7%)	0.0001
BMI (kg/m ²)	26.0 [23.7, 29.1]	25.1 [22.8, 27.7]	0.0001
Hepatitis C Virus (HCV) Positive (%)	28 (8.7%)	93 (17.4%)	<0.001
Nadir CD4 cell count (cells/μL)	--	273 [163, 383]	--
Median CD4 cell count (cells/μL)	--	510 [349,693]	--
HIV RNA ≥ 400 copies/mL	--	174 (32.7%)	--
DM prevalence (%)	8.0	11.4	0.16
Adjusted log HOMA-IR	1.06	1.30	<0.0001
Mean duration of HIV disease (years)	--	10.4 ± 8.2	--
On Antiretroviral therapy (%)	--	498 (93.3%)	--
Nucleoside Reverse Transcriptase Inhibitor (NRTI)*			
Current NRTI	--	365 (69.1%)	--
Ever NRTI	--	469 (87.8%)	--
Current zidovudine	--	113 (21.4%)	--
Ever zidovudine	--	340 (63.7%)	--
Current stavudine	--	59 (11.2%)	--
Ever stavudine	--	282 (52.8%)	--
Protease Inhibitor (PI)**			
Current PI	--	214 (40.5%)	--
Ever PI	--	367 (68.7%)	--
Current indinavir	--	34 (6.4%)	--
Ever indinavir	--	172 (32.2%)	--
Current ritonavir, high dose	--	3 (0.6%)	--
Ever ritonavir, high dose	--	38 (7.1%)	--
Current ritonavir, low dose	--	159 (30.1%)	--
Ever ritonavir, low dose	--	228 (42.7%)	--
Current lopinavir/ritonavir	--	87 (16.5%)	--
Ever lopinavir/ritonavir	--	123 (23.0%)	--
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)[‡]			
Current NNRTI	--	223 (42.2%)	--
Ever NNRTI	--	345 (64.6%)	--

Data are expressed as mean ± SD or median [interquartile range]

* retrovir (AZT), epivir (3TC), didanosine (ddI), stavudine (d4T), abacavir, emtricitabine (FTC), tenofovir

** saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, lopinavir, atazanavir, darunavir, tipranavir

[‡] nevirapine, delavirdine, efavirenz

Table 2

Relationship between demographic and clinical characteristics and mean log hormone levels in HIV-infected participants

	Outcome: log free T β (p-value)	Outcome: log SHBG β (p-value)
Age	-0.01 (<0.01)	0.01 (<0.0001)
Race (Black v. other)	-0.10 (0.08)	0.13 (0.01)
BMI	-0.01 (0.08)	-0.03 (<0.0001)
HCV-infected	-0.15 (0.03)	0.39 (<0.0001)
CD4 $\geq$ 200 cells/ μ L	0.22 (0.01)	-0.08 (0.29)
HIV RNA $\geq$ 400 copies/mL	-0.03 (0.54)	0.04 (0.41)
AM v. PM (ref.) draw	-0.19 (<0.001)	0.17 (<0.001)

Table 3
Log hormone levels and DM/HOMA-IR in HIV-infected and HIV-uninfected participants*

	Outcome: DM			Outcome: HOMA-IR		
	FT Model OR (95% CI)	SHBG Model OR (95% CI)	SHBG Model** OR (95% CI)	FT Model β (p)	SHBG Model β (p)	
Log hormone‡	0.77 (0.44, 1.36)	0.44 (0.25, 0.80)	0.39 (0.21, 0.74)	-0.11 (0.04)	-0.14 (<0.01)	
HIV-infected/HIV-uninfected	1.98 (1.04, 3.78)	2.30 (1.20, 4.38)	2.16 (1.08, 4.31)	0.21 (<0.0001)	0.24 (<0.0001)	

Table 3a. AM blood draws only (N=532)

	Outcome: DM			Outcome: HOMA-IR		
	FT Model OR (95% CI)	SHBG Model OR (95% CI)	SHBG Model** OR (95% CI)	FT Model β (p)	SHBG Model β (p)	
Log hormone‡	0.46 (0.22, 1.00)	0.71 (0.34, 1.48)	0.64 (0.30, 1.38)	-0.17 (0.02)	-0.11 (0.10)	
HIV-infected/HIV-uninfected	2.00 (0.84, 4.76)	2.19 (0.93, 5.16)	2.32 (0.89, 5.60)	0.19 (0.01)	0.21 (0.002)	

* All models adjusted for log hormone, HIV, age, center, black race, BMI, HCV status, and waist circumference

** Adjusted for insulin

‡ Odds ratio corresponds to each 1-log increase in either FT or SHBG.

Table 4

Log hormone levels and DM in HIV-infected participants*

	FT Model OR (95% CI)	FT Model: AM ONLY OR (95% CI)	SHBG Model OR (95% CI)	SHBG Model: AM ONLY OR (95% CI)
Log hormone **	0.72 (0.37, 1.40)	0.39 (0.17, 0.92)	0.53 (0.26, 1.09)	0.83 (0.35, 1.94)
Age	1.06 (1.00, 1.12)	1.04 (0.97, 1.11)	1.07 (1.01, 1.14)	1.06 (0.99, 1.13)
Race (Black v. other)	2.60 (1.10, 6.11)	2.20 (0.74, 6.50)	3.07 (1.29, 7.27)	2.46 (0.83, 7.27)
Current CD4 $\geq$ 200	0.75 (0.19, 2.96)	1.43 (0.24, 8.68)	0.69 (0.18, 2.69)	0.98 (0.18, 5.28)
BMI	1.08 (0.94, 1.24)	1.05 (0.85, 1.29)	1.07 (0.93, 1.23)	1.04 (0.85, 1.28)
HCV-infected	1.20 (0.47, 3.08)	1.70 (0.51, 5.63)	1.61 (0.61, 4.23)	2.02 (0.62, 6.60)
Viral load $\geq$ 400	0.27 (0.09, 0.75)	0.24 (0.07, 0.87)	0.29 (0.10, 0.80)	0.24 (0.07, 0.89)
Ever stavudine therapy	4.53 (1.91, 10.76)	5.50 (1.77, 17.13)	4.10 (1.74, 9.64)	4.54 (1.55, 13.30)
Waist circumference	0.99 (0.94, 1.05)	0.99 (0.93, 1.07)	0.99 (0.94, 1.05)	1.00 (0.93, 1.07)

* All models adjusted for log hormone, age, site, black race, BMI, HCV status, CD4, viral load, ever used d4T, and waist circumference

** Odds ratio or β corresponds to each 1-log increase in either FT or SHBG

Table 5

Log hormone levels and HOMA-IR in HIV-infected participants*

	FT Model β (p)	FT Model β (p)	FT Model: β (p)	SHBG Model: β (p)	SHBG Model: β (p)
Log hormone**	-0.12 (0.04)	-0.08 (0.20)	-0.14 (0.09)	-0.13 (0.03)	-0.12 (0.11)
Age	0.00 (0.40)	0.00 (0.90)	-0.01 (0.35)	0.00 (0.67)	.00 (0.73)
Race (Black v. other)	-0.06 (0.42)	-0.03 (0.73)	-0.10 (0.31)	0.00 (0.99)	-0.07 (0.47)
Current CD4 $\geq$ 200	0.03 (0.79)	0.01 (0.95)	-0.07 (0.59)	-0.03 (0.79)	-0.12 (0.36)
BMI	0.05 (<0.001)	0.01 (0.26)	0.02 (0.17)	0.01 (0.38)	0.02 (0.26)
HCV-infected	0.28 (<0.01)	0.25 (0.01)	0.22 (0.06)	0.31 (0.001)	0.27 (0.02)
Viral load $\geq$ 400	-0.09 (0.17)	-0.13 (0.05)	-0.15 (0.08)	-0.13 (0.06)	-0.15 (0.08)
Ever stavudine therapy	0.26 (<0.001)	0.28 (<0.001)	0.29 (<0.001)	0.28 (<0.001)	0.29 (<0.001)
Waist circumference	--	0.02 (<0.01)	0.01 (0.03)	0.02 (<0.01)	0.01 (0.02)

* All models adjusted for log hormone, age, site, black race, BMI, HCV status, CD4, viral load, ever used ddT, and waist circumference, unless marked with --.

** Odds ratio or β corresponds to each 1-log increase in either FT or SHBG