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Impact of Randomized Antiretroviral Therapy Initiation on Glucose Metabolism: AIDS Clinical Trials Group Study A5224s

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Abstract

Objective—Prior studies have found that early HIV protease inhibitors (PIs) contribute to glucose dysregulation. Few randomized trials have evaluated glucose indices in antiretroviral-naïve subjects on newer antiretroviral therapy (ART).

Methods—A5224s was a substudy of A5202, a prospective trial of 1857 ART-naïve participants randomized to blinded abacavir-lamivudine (ABC/3TC) or tenofovir DF-emtricitabine (TDF/FTC) with open-label efavirenz (EFV) or atazanavir-ritonavir (ATV/r). Analyses used 2-sample t-tests, Spearman correlation coefficients and linear regression.

Results—A5224s included 269 non-diabetic subjects: 85% male, 47% white non-Hispanic, baseline median age 38 years, HIV-1 RNA 4.6 log₁₀ copies/mL and CD4 233 cells/μL. Overall, significant 96-week increases occurred in fasting glucose, insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR), *p* 0.004. Assignment to EFV (vs ATV/r) resulted in significantly greater glucose increase (mean difference 4.4; 95% CI 1.3, 7.5 mg/dL; *p*=0.006) but not insulin or HOMA-IR (*p* 0.72). Glucose indices were not significantly different between ABC/3TC or TDF/FTC arms, *p* 0.18. Significant correlations were detected between changes in

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glucose indices and changes in body mass index; all $r = 0.23$, $p = 0.001$. In multivariable analyses, in addition to the EFV effect, higher baseline HIV-1 RNA, and greater BMI change were significant independent factors associated with greater glucose increase.

Conclusions—Changes in glucose metabolism were not significantly different between TDF/FTC- and ABC/3TC-based regimens. A small but significantly greater increase in glucose was observed in those assigned to EFV. As glucose dysregulation may increase with time on ART, longer term studies will be needed to further clarify the clinical significance of these findings.

Keywords

antiretroviral therapy; HIV; glucose; insulin; body composition; randomized clinical trial

INTRODUCTION

Persons living with HIV-infection are more likely to develop diabetes mellitus than the general population, likely the consequence of a multitude of factors including the human immunodeficiency virus (HIV)-1 itself, lipodystrophy, heightened inflammation, an increasing prevalence of obesity, hepatitis C co-infection, and racial/ethnic predilection^{1–4}. Some studies have suggested up to a 4-fold increase in the relative risk of a diabetes mellitus diagnosis compared to HIV-uninfected controls, even after adjusting for differences in obesity^{5,6}.

The role of individual antiretroviral therapy on the development of diabetes mellitus is often difficult to tease out from other confounding factors, and the impact on glucose varies widely. Some of the nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) are associated with diabetes mellitus as a result of inducing lipodystrophy, mitochondrial toxicity, or direct effects on glucose metabolism^{1,3,7–13}. The newer PIs, atazanavir (ATV) and darunavir, appear to have minimal impact on glucose metabolism in either HIV-infected or HIV-uninfected persons^{14–18}. Similarly, the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) has been associated with only very modest changes in glucose metabolism up to 48 weeks^{16,19–21}.

We have previously presented data on changes in total body weight, adipose tissue, and lean mass after ART initiation in AIDS Clinical Trials Group A5224s, a substudy of A5202, in which HIV-infected treatment-naïve participants were randomized in a double-blinded fashion to abacavir/lamivudine (ABC/3TC) or tenofovir DF/emtricitabine (TDF/FTC) with open-label EFV or atazanavir-ritonavir (ATV/r)^{22–26}. Briefly, randomization to TDF/FTC led to less gain in limb fat, and no significant difference in change in visceral fat at week 96 compared to ABC/3TC²⁴. Assignment to ATV/r led to significantly greater increase in total body weight, body mass index (BMI), limb fat and a trend towards greater increase in visceral fat compared to EFV^{24,27}. Here we compare the changes in glucose, insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR) between the NRTI components and NNRTI/PI components. We also explore the association of changes in glucose metabolism with changes in body composition and markers of inflammation.

METHODS

A5224s was a sub-study of AIDS Clinical Trials Group A5202, in which ART-naïve persons aged ≥16 years and with an HIV-1 RNA load >1000 copies/mL received blinded TDF/FTC or ABC/3TC, with open label EFV or ATV/r at standard doses. The primary analyses of both A5202 and A5224s have been presented previously^{22,24–26,28}. Specific A5224s exclusion criteria were uncontrolled thyroid disease or hypogonadism; endocrine diseases, including Cushing's syndrome, diabetes mellitus, and the use of growth hormone, anabolic steroids, glucocorticoids, or osteoporosis medications (calcium and/or vitamin D were not included). The duration of the study was 96 weeks after the last A5202 participant enrolled.

Any participant enrolling in A5202 at one of the AIDS Clinical Trials Group sites participating in A5224s and meeting criteria for A5224s was eligible to enroll in the sub-study; A5202 randomization was stratified by willingness to enroll into the substudy. Each participant signed a written informed consent before enrollment. The study was approved by the local institutional review board at each site.

On 18 February 2008, after a median follow-up of 97 weeks (range 0–124 weeks; Q1–Q3 58–108 weeks), the Data Safety and Monitoring Board recommended unblinding the NRTI component of the study for subjects with screening HIV-1 RNA levels ≥100,000 copies/mL because of excess virological failures associated with ABC/3TC; subjects receiving ABC/3TC were permitted to modify their NRTI regimen²⁶.

Clinical Assessment and Bone Density Analysis

At baseline, a complete history was obtained and participants underwent a physical examination, including standardized measurement of height and weight. Development of diabetes mellitus while on study was defined as either a clinical diagnosis by a medical provider or a fasting blood sugar ≥126 mg/dL at 2 separate time points over 1 year. Subjects underwent whole-body dual-energy absorptiometry (DXA) at baseline and at weeks 24, 48, and every 48 weeks until the end of follow-up. Lean body mass was defined as fat-free, bone-free mass as measured by DXA in the anteroposterior view (using Hologic or Lunar scanners). Technicians were instructed to use the same DXA machine on the same participant throughout the study. All DXAs were standardized at the participating sites, then centrally read (Tufts) by blinded personnel.

Measurement of Glucose Metabolism and Biomarker Assays

Fasting samples were obtained after abstaining from food and drink except water for 8 hours. Glucose values were obtained from a metabolic panel run at the individual sites. Serum and plasma were stored at –80°C without prior thawing until analysis. Serum insulin was measured by commercial testing at Quest Diagnostics by radioimmunoassay. Insulin sensitivity by the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin [μIU/mL] x fasting glucose [mg/dL]/405, with higher values indicating lower insulin sensitivity²⁹. Biomarker assays were analyzed as previously described³⁰.

Statistical Analysis

The current study was a pre-specified secondary analysis of A5224s to compare changes from baseline to week 96 in fasting glucose, insulin, and HOMA-IR between pooled, randomized NRTI components (ABC/3TC versus TDF/FTC) and NNRTI/PI components (ATV/r versus EFV). All analyses were performed using the intent-to-treat principle based on randomized treatment assignment in which all available data were included and modifications to randomized treatment were ignored; no imputations were made for missing values. Supplemental as-treated analyses were performed in which values were censored after a change in the randomized NRTI component (when comparing NRTI components) or NNRTI/PI component (when comparing NNRTI/PI components).

Because fasting insulin and HOMA-IR were not normally distributed, data were $\log_{10}$ transformed prior to analysis. The exponential of the estimated mean change in the transformed data was used to obtain the estimated mean fold change; values < 1 correspond to a decrease from baseline. Differences between assigned study arms for glucose are reported as mean differences and differences for log-transformed data (insulin, HOMA-IR) are reported as the % difference in the mean fold change. The unadjusted effects of the NRTI component and the NNRTI/PI component on changes were evaluated separately using two-sample t-tests. Linear regression was used to test for pre-specified interactions between NRTI and NNRTI/PI components and to evaluate a potential interaction between treatment allocation and screening HIV-1 RNA stratum ($< 100,000$ or $\geq 100,000$ copies/mL). Additional sensitivity analyses were done for fasting insulin, glucose, and HOMA-IR which excluded results without confirmed fasting status by a food intake case report form or excluded values where insulin was > 50 uIU/mL. Changes from baseline within study arm or regimen component were assessed with 1-sample t-tests. Correlations of measures of glucose metabolism with inflammatory markers or measures of body composition were evaluated using Spearman's rank correlation test. In addition, a locally weighted least squares (LOWESS) smooth was overlaid on the scatter plot for visual purposes, using only data points between the 2.5th and 97.5th percentiles for both plotted variables. P-values below 0.05 (< 0.10 for assessing interactions) were considered statistically significant. Linear regression was used to adjust for baseline and post-baseline factors and explore associations with baseline and post-baseline factors. Univariate associations with a p-value < 0.20 were included in a multivariable model which utilized backwards selection and only factors with a p-value < 0.05 were retained; NRTI component and NNRTI/PI component were retained regardless of p-value. Analyses were performed using SAS, version 9.2 (SAS Institute).

RESULTS

Participant Characteristics

A5224s included 271 participants from 37 AIDS Clinical Trials Group sites in the United States and Puerto Rico, randomized to receive ART; 2 participants were excluded from the analysis for eligibility violations. Sixty-nine participants were randomized to receive EFV plus TDF/FTC, 70 to EFV plus ABC/3TC, 65 to ATV/r plus TDF/FTC, and 65 to ATV/r plus ABC/3TC. Baseline characteristics are summarized in Table 1 and were balanced across study arms. The median age of the subjects was 38 years, 85% were male, and 47%

were white, non-Hispanic. The median BMI was 24.9 kg/m², CD4 cell count was 233 cells/ μ L, plasma HIV-1 RNA was 4.6 log₁₀ copies/mL, and 80% had an HIV-1 RNA <100,000 copies/mL at study entry.

Sixty-six (25%) of A5224s participants prematurely discontinued study follow-up, 4 (1%) died, and 122 (45%) modified the randomized treatment regimen. These details have been previously published^{24,25}. Briefly, 36 participants (13%) had a treatment modification before week 12, 12 (4%) between week 12 and 24, 19 (7%) between week 24 and 48, 24 (9%) between week 48–96, and 31 (12%) after week 96. By Kaplan-Meier estimates, 66% of subjects had no modification by week 96²⁴.

Change in Fasting Glucose

Among all participants, the mean glucose change from week 0 to 96 was 2.7 mg/dL (95% confidence interval [CI] 1.1, 4.3), range –41 to 47 mg/dL ($p=0.001$). One hundred and eighty-three participants (83%) had a normal glucose (<100 mg/dL) both at week 0 and week 96. Twenty participants (9%) with normal glucose at week 0 developed impaired fasting glucose (100–125 mg/dL) by week 96; of 17 participants (7%) with impaired fasting glucose at week 0, 8 continued to have impaired fasting glucose, 8 had normal glucose, and 1 had a glucose >125 mg/dL at week 96 ($p=0.024$). The distribution of glucose category changes was not significantly different between the NRTI components ($p=0.89$) or the NNRTI/PI components ($p=0.15$). Six subjects met the definition of diabetes mellitus while on study: 2 on ABC/3TC + EFV, 2 on TDF/FTC + ATV/r, 1 on ABC/3TC + ATV/r, and 1 on TDF/FTC + EFV. The mean change at week 96 in the ABC/3TC arm (3.8; 95% CI 1.5, 6.0 mg/dL) was not significantly different than the mean change in the TDF/FTC arm (1.6; 95% CI –0.6, 3.8 mg/dL) with a difference of 2.2 (95% CI –1.0, 5.3 mg/dL); $p=0.18$ (Figure 1A). No significant differences in glucose were detected between ABC/3TC and TDF/FTC groups in the as-treated analysis (mean difference = 2.9; 95% CI –0.5, 6.3; $p=0.093$).

The mean glucose change in the EFV arm over 96 weeks (4.8; 95% CI 2.6, 7.0 mg/dL) was significantly greater than the mean change in the ATV/r arm (0.4; 95% CI –1.8, 2.6 mg/dL) with a difference of 4.4 (95% CI 1.3, 7.5 mg/dL); $p=0.006$ (Figure 1A). These differences were similar in the as-treated analyses (mean difference= 4.9; 95% CI 1.7, 8.0; $p=0.002$) and sensitivity analysis excluding persons without confirmed fasting status for glucose measurements (mean difference= 4.7; 95% CI 1.4, 8.0; $p=0.005$). There was no significant interaction between the NRTI and NNRTI/PI components ($p=0.61$).

Change in Fasting Insulin

Overall, the median change in insulin from week 0 to 96 was 0 uIU/mL (IQR –2, 4 uIU/mL) and the mean fold change was 1.24 (1.07, 1.44) ($p=0.004$). The subsequent analyses used log₁₀-transformed fasting insulin to account for the skewed distribution of change data. No significant differences in insulin were detected between ABC/3TC and TDF/FTC groups by intent-to-treat (fold change % difference = 3.5; 95% CI –23.0, 39.1; $p=0.82$; Figure 1B) or as-treated analyses (fold change % difference = 17.9; 95% CI –14.6, 62.7; $p=0.31$). Similarly, no significant differences in insulin were detected between ATV/r or EFV groups by intent-to-treat (fold change % difference = 5.5; 95% CI –21.5, 41.9; $p=0.72$; Figure 1B).

or as-treated analysis (fold change% difference =22.8; 95% CI -10.1, 67.8; p=0.19). Similar results were seen in a sensitivity analysis excluding persons without confirmed fasting state (N=71) or with insulin values > 50 uIU/mL (N=62), suggestive of non-fasting state at the time of blood sampling. There was no significant interaction between the NRTI and NNRTI/PI components (p=0.65).

Change in Insulin Sensitivity by HOMA-IR

Overall, the median change in HOMA-IR from week 0 to 96 was 0.09 (IQR -0.28, 0.81) and the mean fold change was 1.30 (1.11, 1.51) (p=0.001). The subsequent analyses used log₁₀-transformed HOMA-IR to account for the skewed distribution of change data. No significant differences in change in insulin sensitivity were detected between ABC/3TC and TDF/FTC groups by intent-to-treat (fold change % difference =2.5; 95% CI -24.7, 39.5; p=0.88; Figure 1C) or as-treated analyses (fold change % difference = 20.6; 95% CI -13.6, 68.3; p=0.27). Similarly, no significant differences in HOMA-IR were detected between ATV/r or EFV groups by intent-to-treat (fold change % difference = 5.2; 95% CI -30.3, 29.1; p=0.73; Figure 1C) or as-treated analysis (fold change % difference = 11.2; 95% CI -20.0, 54.4; p=0.53). There was no significant interaction between the NRTI and NNRTI/PI components (p=0.97). We did detect a differential treatment effect (interaction) between screening viral load strata and NNRTI/PI (p=0.099) such that persons with persons with a VL ≥100,000 copies/mL had less increase in HOMA-IR with ATV/r compared with EFV (difference = -31.9; 95% CI -58.1, 10.7) while persons in the VL <100,000 copies/mL strata had greater increase in HOMA-IR with ATV/r compared to EFV (difference = 15.2; 95% CI -22.4, 71.0)..

Correlation of Change at Week 96 in Glucose and Insulin Sensitivity with Body Composition

Correlation plots were used to investigate the association between week 0 to 96 changes in glucose metabolism and week 0 to 96 changes in body composition that occur with ART initiation. Statistically significant weak to moderate positive correlations were detected between the changes in glucose, insulin, and HOMA-IR with changes in BMI, LBM, limb fat, and trunk fat (Figure 2).

Univariate and Multivariable Linear Regression Analyses

Baseline variables associated with a change in fasting glucose, insulin, and insulin sensitivity are shown in Table 2. In addition to the effect of the NNRTI/PI treatment arm assignment, greater increase in glucose was associated with higher baseline HIV-1 RNA. Similarly, only higher baseline HIV-1 RNA was associated with a greater increase in HOMA-IR (worsened insulin sensitivity), but none of the baseline variables were associated with insulin change (Table 2). To further explore the significant NNRTI/PI treatment effect on change in glucose, in a post-hoc analysis we added post-baseline variables including changes in CD4 cell count, and body composition measures and week 96 viral suppression (<50 copies/mL). In multivariable analyses, assignment to EFV (vs ATV/r), higher baseline HIV-1 RNA, and greater change in BMI remained significant independent factors associated with greater increase in glucose (Table 3).

Correlation with Week 96 Change in Inflammatory Markers

Lastly, we investigated the correlation of changes in glucose metabolism after ART initiation with changes in markers of inflammation. Weak but statistically significant negative relationships were detected between the change in glucose and the change in TNF- α ($r=-0.21$, $p=0.002$), sVCAM-1 ($r=-0.15$, $p=0.037$), sTNF-RII ($r=-0.15$, $p=0.033$), but not IL-6 ($r=0.03$, $p=0.67$), hs-CRP ($r=0.02$, $p=0.73$), sICAM-1 ($r=-0.09$, $p=0.23$), sTNF-RI ($r=-0.12$, $p=0.09$). Changes in insulin and HOMA-IR were not significantly correlated with markers of inflammation ($p>0.074$).

DISCUSSION

Herein, we have demonstrated a significantly larger increase in glucose with assignment to EFV compared to ATV/r. Although modest increases in insulin and HOMA-IR were observed across all treatment arms, differences were not significant between arms. Not surprisingly, the increase in glucose, insulin, and HOMA-IR correlated with increases in BMI, limb fat, and trunk fat. Even after adjusting for changes in body composition in multivariate analyses, the EFV treatment effect on glucose change remained significant. As we have shown previously, persons randomized to EFV had significantly lower gain in BMI compared to those randomized to ATV/r³¹. The Spearman correlation coefficient of 0.23 between glucose and BMI changes indicated a weak positive relationship, and thus, based on the results of the current analysis and our prior work, the change in BMI only explains a small percentage of the glucose change.

We estimated a mean increase in glucose through week 96 of 4.8 mg/dL in the EFV compared to 0.4 mg/dL in the ATV/r arm, similar changes in magnitude as those reported in other studies of shorter duration. Jemsek, et al. demonstrated a mean 1 mg/dL difference in the week 48 change in glucose between 100 HIV-infected persons randomized to EFV (increase of 3 mg/dL) compared to 111 randomized to ATV/r (increase of 4 mg/dL) with identical backbone therapy (zidovudine and lamivudine). Non-significant decreases in insulin and HOMA-IR were observed in the ATV/r arm and non-significant increases were observed in the EFV arm¹⁶. ACTG Study A5095 randomized participants to triple-NRTI, triple NRTI + EFV, or dual-NRTI + EFV and found significant increases in glucose (mean 6–8 mg/dL) and HOMA-IR across all study arms. Due to virologic inferiority, the initial triple-NRTI group underwent intensification with either EFV or TDF after 24 weeks. A trend towards a significantly greater increase from week 24 in glucose (median 3 mg/dL; $p=0.08$) and a significant increase from week 24 in $\log_{10}$ HOMA-IR (0.13; $p=0.03$) was detected in the EFV intensification compared to the TDF intensification arm¹⁹. In STARTMRK, although assignment to EFV was associated with significantly greater 96-week glucose increase (6 mg/dL) compared to the raltegravir arm (2 mg/dL; $p=0.025$), 3 (1.1%) subjects in the raltegravir and none of the EFV group developed a fasting glucose >250 mg/dL while on study²¹. A cross-sectional, observational study in South Africa found a significantly higher prevalence of diabetes or pre-diabetes mellitus among persons receiving EFV compared to nevirapine (73% versus 27%, $p<0.001$), a finding that remained significant in multivariable analysis adjusted for covariates that included body composition, age, and CD4 count²³. Interestingly, a small study switching subjects with lipodystrophy

from PI-based therapy to EFV had a non-significant increase in fasting glucose and insulin after 48 weeks on EFV³².

We had anticipated that inclusion of inflammatory markers would add clinical significance to the changes in glucose, such that increases in markers associated with cardiovascular disease risk (ie, IL-6, hs-CRP) would be associated with increased glucose, insulin, and HOMA-IR. In contrast, we only found significant negative correlations with some inflammatory markers. We hypothesize that our findings reflect that the overall decline in inflammatory markers with ART initiation^{30,33} is greater than changes that might be seen with glucose dysregulation³⁴.

We also found an association between higher HIV-1 RNA at treatment initiation and greater glucose increase. Higher HIV-1 RNA (>400 copies/mL versus <400 copies/mL) has previously been reported as a risk for metabolic syndrome both in observational^{35,36} and treatment initiation studies³⁷. The impact of HIV-1 RNA tends to be more apparent through abnormalities in the metabolic syndrome components of blood pressure, triglycerides, and HDL rather than glucose^{35,38}. Nonetheless, this is yet another factor to support initiation of ART at lower HIV-1 RNA levels.

We acknowledge several limitations of the current study. We excluded persons with a diagnosis of diabetes mellitus at baseline, thus the effect on blood glucose in persons with known diabetes mellitus cannot be evaluated in the context of this study. Our participant population was relatively young, and greater rates of insulin resistance may be observed in older cohorts. Second, we may underestimate the true changes in glucose metabolism through measuring only fasting glucose and insulin. Prior studies have demonstrated that 15% of subjects with normal fasting glucose had evidence of diabetes mellitus or impaired glucose tolerance on a 75 g glucose tolerance test, suggesting that fasting glucose may be relatively insensitive to the diagnosis of diabetes mellitus among HIV-infected persons^{39,40}. Nonetheless, our study measured concomitantly fasting insulin level, and the derived HOMA-IR index has been shown to correlate well with more expensive and cumbersome methods of measuring insulin sensitivity such as hyperinsulinemic-euglycemic clamps⁴¹. Also, no physical activity data or diary of specific food or drink intake was collected, and these could confound insulin sensitivity. Although sensitivity analyses excluding persons without confirmed fasting state or with insulin levels >50 uIU/mL did not show significant differences, we did not confirm fasting state with measurement of C-peptide. Lastly, a large proportion of subjects modified the ART regimens while on study, and week 96 data was not available for all participants: 82% of participants had week 96 fasting glucose available, 78% fasting insulin, and 75% HOMA-IR.

The primary strengths of this study lie in the randomized design including four contemporary ART regimens, all with a presumably low risk of metabolic adverse effects. Additionally, the inclusion of the two different NRTI backbone arms allowed for analysis of a potential NRTI interaction with PI/NNRTI treatment, although this substudy was not specifically powered to detect interactions. The inclusion of body composition data, CD4 count, and HIV-1 RNA allowed for interpretation of changes in glucose metabolism between study arms while considering the effects of individual ART on body composition.

In summary, we detected significantly greater glucose increases among persons treated with EFV compared to those treated with ATV/r that persisted in multivariable analyses and was not explained through an increase in BMI. Although the glucose differences that we detected were statistically significant, the clinical significance of an approximately 4 mg/dL difference in glucose between the EFV and ATV/r treatment arms is unclear. However, in the era of HIV as a chronic disease, even modest increases in glucose in the context of concurrent increase in BMI and insulin resistance could have important consequences over decades of treatment. Furthermore, this reinforces the need for healthy lifestyle choices including diet and exercise, as the added impact of EFV may be yet another risk factor for diabetes mellitus in a population of increasing age and obesity^{13,42,43}. The impact of long-term EFV use on the development of diabetes mellitus should be explored in randomized studies of longer duration.

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Figure 1.

Changes in measures of glucose metabolism by treatment arms (intent-to-treat). Mean and 95% confidence intervals are represented by symbols and error bars; P value from comparison between arms at 96 weeks; TDF/FTC, tenofovir-emtricitabine; ABC/3TC, abacavir-lamivudine; EFV, efavirenz; ATV/r, atazanavir-ritonavir. **A.** Changes in glucose between the nucleoside reverse transcriptase inhibitor (NRTI) components and non-nucleoside reverse transcriptase inhibitor/protease inhibitor (NNRTI/PI) components. **B.** Changes in insulin between NRTI components and NNRTI/PI components. **C.** Changes in

homeostatic model assessment of insulin resistance (HOMA-IR) between NRTI components and NNRTI/PI components.

Figure 2.

Correlation of changes in glucose (top row), insulin (middle row), homeostatic model assessment of insulin resistance (HOMA-IR; bottom row) with body mass index (BMI), lean body mass (LBM), limb fat, and trunk fat.

Table 1

Baseline characteristics of study participants

Characteristic	EFV + TDF/FTC N=69	EFV + ABC/FTC N=70	ATV/r + TDF/FTC N=65	ATV/r + ABC/3TC N=65	Total N=269
Age (years)	40 (33–44)	39 (31–46)	38 (30–44)	37 (29–43)	38 (31–44)
Female	11 (16%)	14 (20%)	9 (14%)	6 (9%)	40 (15%)
Race/Ethnicity					
White non-Hispanic	37 (54%)	34 (49%)	26 (40%)	29 (45%)	126 (47%)
Black non-Hispanic	22 (32%)	20 (29%)	21 (32%)	27 (42%)	90 (33%)
Hispanic	8 (12%)	14 (20%)	14 (22%)	8 (12%)	44 (16%)
CD4 T-cell count (cells/ μ L)	250 (132–334)	213 (106–350)	247 (114–319)	222 (75–332)	233 (106–334)
HIV-1 RNA (log ₁₀ copies/mL)	4.7 (4.2–4.9)	4.7 (4.2–4.9)	4.5 (4.2–4.9)	4.6 (4.3–5.1)	4.6 (4.2–4.9)
HIV-1 RNA 100,000 copies/mL	13 (19%)	11 (16%)	13 (20%)	17 (26%)	54 (20%)
Fasting glucose (mg/dL)	82 (77–88)	84 (78–90)	88 (80–93)	82 (78–89)	84 (78–90)
Fasting insulin (uIU/mL)	3 (1–7)	5 (1–11)	4 (1–9)	5 (1–8)	4 (1–9)
Fasting HOMA-IR	0.6 (0.2–1.4)	0.9 (0.2–2.4)	0.7 (0.2–1.8)	0.9 (0.2–1.8)	0.8 (0.2–1.8)
Family history of diabetes	20 (34%)	23 (40%)	20 (35%)	21 (36%)	84 (36%)
Hepatitis B/C co-infection	10 (14%)	11 (16%)	3 (5%)	8 (13%)	32 (12%)
Body mass index (kg/m ²)	24.9 (21.6–27.1)	24.7 (22.6–28.3)	24.9 (21.8–28.8)	25.3 (21.8–28.9)	24.9 (21.8–28.2)
Lean body mass (kg)	53.1 (48.5–61.3)	54.0 (46.6–58.9)	55.0 (48.0–60.0)	56.6 (50.6–61.7)	54.6 (48.1–61.1)
Limb fat (kg)	7.3 (4.7–9.4)	7.8 (4.9–10.5)	7.4 (5.0–11.6)	6.8 (4.3–10.5)	7.4 (4.7–10.1)
Trunk fat (kg)	8.5 (5.4–12.6)	10.0 (5.5–13.6)	9.6 (5.5–14.5)	9.9 (4.9–12.9)	9.4 (5.3–13.0)

Data presented as median (25th, 75th quartile) or number (%). HOMA-IR, homeostatic model assessment of insulin resistance

Table 2
Univariate Association with Baseline Variables and Change in Glucose, Insulin and Insulin Sensitivity

Baseline Covariate	Change in Glucose		Change in Insulin		Change in HOMA-IR	
	Estimated Mean Change (95% CI)	P	Estimated Mean Fold Change (95% CI)	P	Estimated Mean Fold Change (95% CI)	P
ABC/3TC (versus TDF/FTC)	2.2 (−1.0, 5.3)	0.18	1.03 (0.77, 1.39)	0.82	1.02 (0.75, 1.39)	0.88
ATV/r (versus EFV)	−4.4 (−7.5, −1.3)	0.006	1.06 (0.78, 1.42)	0.72	0.95 (0.70, 1.29)	0.73
Male	−0.5 (−4.8, 3.8)	0.83	0.32 (−0.74, 1.37)	0.55	1.04 (0.68, 1.59)	0.84
Age*	0.1 (−0.1, 0.3)	0.25	−0.99 (0.97, 1.00)	0.097	0.99 (0.97, 1.0)	0.15
Race/Ethnicity (vs White non-Hispanic)		0.94		0.52		0.87
Black non-Hispanic	−0.7 (−4.3, 3.0)		0.86 (0.61, 1.20)		0.92 (0.65, 1.31)	
Hispanic	−0.3, (−5.1, 4.5)		1.09 (0.71, 1.66)		1.02 (0.65, 1.60)	
Other	−7.5 (−16.6, 1.7)		1.12 (0.38, 3.34)		1.04 (0.34, 3.15)	
Baseline HIV-1 RNA†	3.2 (0.8, 5.5)	0.009	1.20 (0.97, 1.50)	0.25	1.30 (1.03, 1.63)	0.025
Baseline CD4 count§	−0.1 (−0.5, 0.4)	0.79	1.00 (0.96, 1.05)	0.99	1.00 (0.95, 1.05)	0.95
Baseline BMI¶	0.0 (−0.3, 0.3)	0.95	1.00 (0.97, 1.03)	0.93	1.00 (0.97, 1.03)	0.92
Baseline trunk fat (kg)††	0.2 (−0.1, 0.4)	0.21	1.01 (0.98, 1.03)	0.55	1.01 (0.98, 1.03)	0.56

CI, confidence interval; ABC/3TC, abacavir-lamivudine; TDF/FTC, tenofovir-emtricitabine; ATV/r, atazanavir-ritonavir; EFV, efavirenz; BMI, body mass index;

* per 1 year older;

† per log10 copies/mL higher;

§ per 50 cells/mm³ higher;

¶ per 1 kg/m² higher,

†† per 1 kg higher. 82% of participants had week 96 fasting glucose available, 78% fasting insulin, and 75% HOMA-IR.

Table 3

Univariate and Multivariable Linear Regression to Assess the Association Between Baseline and Post-baseline Factors and Change in Glucose

Baseline Covariate	Univariate Analyses		Multivariable Analyses	
	Estimated Mean Change (95% CI)	P	Estimated Mean Change (95% CI)	P
ABC/3TC (versus TDF/FTC)	2.2 (−1.0, 5.3)	0.18	2.1 (−1.0, 5.1)	0.18
ATV/r (versus EFV)	−4.4 (−7.5, −1.3)	0.006	−5.7 (−8.7, −2.6)	<0.001
Male	−0.5 (−4.8, 3.8)	0.25		
Age [*]	0.1 (−0.1, 0.3)	0.83		
Race/Ethnicity (vs White non-Hispanic)		0.94		
Black non-Hispanic	−0.7 (−4.3, 3.0)			
Hispanic	−0.3 (−5.1, 4.5)			
Other	−7.5 (−16.6, 1.7)			
Hepatitis B or C co-infection	2.9 (−2.3, 8.0)	0.27		
Family history of diabetes	−0.9 (−4.4, 2.7)	0.63		
Baseline HIV-1 RNA [†]	3.2 (0.8, 5.5)	0.009	2.4 (0.0, 4.9)	0.047
Week 96 virologic suppression	0.0 (−4.9, 4.9)	0.99		
Baseline CD4 count [§]	−0.1 (−0.5, 0.4)	0.79		
96 week CD4 change [§]	−0.2 (−0.6, 0.3)	0.50		
Baseline BMI [¶]	0.0 (−0.3, 0.3)	0.95		
96 week BMI change [¶]	0.9 (0.3, 1.4)	0.002	0.8 (0.3, 1.4)	0.005
Baseline trunk fat (kg) ^{††}	0.2 (−0.1, 0.4)	0.21		
96 week trunk fat change ^{††}	0.7 (0.2, 1.2)	0.005		
Baseline limb fat (kg) ^{††}	0.2 (−0.1, 0.5)	0.27		
96 week limb fat change ^{††}	0.8 (0.1, 1.5)	0.018		
Baseline total body lean mass ^{††}	0.0 (−0.1, 0.2)	0.76		
96 week total body lean mass change ^{††}	0.7 (0.2, 1.2)	0.008		

CI, confidence interval; ABC/3TC, abacavir-lamivudine; TDF/FTC, tenofovir-emtricitabine; ATV/r, atazanavir-ritonavir; EFV, efavirenz; BMI, body mass index;

^{*} per 1 year older;[†] per log10 copies/mL higher;

§ per 50 cells/mm³ higher;
¶ per 1 kg/m² higher,
‡‡ per 1 kg higher