# Impact of Randomized Antiretroviral Therapy Initiation on Glucose Metabolism: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202

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## Abstract

**Background:** Prior studies have found that early HIV protease inhibitors (PIs) and lipodystrophy contribute to glucose dysregulation. Few randomized trials have evaluated glucose indices in antiretroviral therapy (ART)-naïve subjects on newer ARTs.

**Methodology:** A5202 randomized 1857 ART-naïve HIV+ subjects to blinded abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) with open-label efavirenz (EFV) or atazanavir/ritonavir (ATV/r). A pre-specified secondary analysis of the metabolic substudy A5224s compared fasting glucose, insulin, and homeostatic model assessment-insulin resistance (HOMA-IR) using 2-sample t-tests, linear regression, and Spearman correlation. Diabetes was defined as 2 fasting glucose values >126 or a clinical definition of diabetes.

**Results:** Overall, 269 non-diabetic subjects enrolled: 85% male, 47% white non-Hispanic, median baseline age 38 years, HIV-1 RNA 4.6 $\log_{10}$ copies/mL, CD4 236 cells/mm$^3$, glucose 84 mg/dL, insulin 4 µIU/mL, and HOMA-IR 0.77. At 96 weeks, the mean (95% CI) glucose increased by 2.7 (1.1, 4.3) mg/dL, insulin by 0.09 (0.03, 0.16) $\log_{10}$ µIU/mL, and $\log_{10}$ HOMA-IR by 0.11 (0.05, 0.18); p<0.05 for all. Six subjects developed diabetes; glucose changes ranged from -41 to +47 mg/dL. No interaction was detected between nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI)/PI for any glucose index (p≥0.61). Changes in indices were not significantly different between NRTI arms (p≥0.18). Assignment to EFV resulted in greater glucose increase (mean 4.8; 2.6-7.0 mg/dL) compared to ATV/r (0.4; -1.8-2.6 mg/dL); p=0.006. Insulin and HOMA-IR changes were not significantly different (p≥0.72). Multivariable analyses are shown in the table. Glucose change positively correlated with changes in BMI (r=0.23, p=0.001), lean body mass (r=0.19, p=0.006), and trunk fat (r=0.18; p=0.010).

**Conclusions:** Changes in glucose metabolism were minimal and not significantly different between TDF/FTC- and ABC/3TC-based regimens. The small but significantly greater increase in glucose in those assigned to EFV has not been previously reported in a randomized setting of ART-naïve persons and were not explained by change in BMI. As glucose dysregulation may increase with time on ART, longer studies will be needed to further clarify the clinical significance of these findings.

## Acknowledgements

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**A5202 and A5224s Publications:**

Sax PE, et al. N Engl J Med 2009; 361: 2230-40.
Daar ES, et al. Ann Intern Med 2011; 154: 445-56.
Sax PE, et al. J Infect Dis 2011; 204: 1191-201.
McComsey GA, et al. Clin Infect Dis 2011; 53: 185-96.
McComsey GA, et al. J Infect Dis 2011; 203: 1791-801.
McComsey GA, et al. AIDS 2012; 26:1371-85.
McComsey GA, et al. J Infect Dis 2013; 207: 604-11
Erlandson KM, et al. AIDS 2013; 27: 2069-79.

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## Background

- The risk of developing diabetes mellitus (DM) is higher among people with HIV than in the general population (Brown 2005)
- Causes are multifactorial including HIV, ART, obesity, racial/ethnic predilection
- Goals of this study:
  - Compare changes in glucose metabolism between randomized NNRTI/PI and between NRTIs
  - Explore association between changes in glucose metabolism with changes in body composition

## Methods

### Study Participants and Design

- Pre-specified analysis of A5224s (n=269), a metabolic substudy of A5202 in which ART-naïve subjects ≥16 years old with HIV-1 RNA>1,000 copies/mL were randomized in a double-blinded fashion to co-formulated TDF/FTC or ABC/3TC with open-labeled EFV or ATV/r
- Exclusion criteria included uncontrolled endocrine diseases, diabetes mellitus, use of growth hormone, osteoporosis medications or anabolic steroids
- Study duration was 96 weeks after the last subject enrolled into A5202

### Substudy Evaluations

- Fasting samples were obtained for measurement of glucose, insulin, and insulin sensitivity by the homeostatic model assessment of insulin resistance (HOMA-IR), with higher values indicating lower insulin sensitivity.
- DM was defined as diagnosis by a medical provider or fasting blood sugar ≥126 mg/dL at 2 separate time points over 1 year
- Body mass index (BMI) was calculated; whole body densitometry (DXA) was used to measure lean and fat mass

### Data Analysis

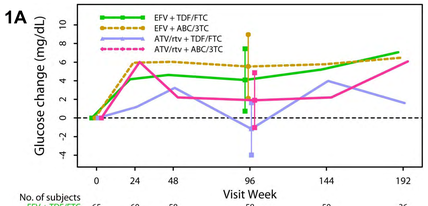
- Statistical analyses included 2-sample t-tests, Spearman's rank correlation, and linear regression, and were intent-to-treat.
- In linear regressions, covariates included ART regimen, sex, age, race/ethnicity, baseline and 96-week change in CD4 count and HIV-1 RNA, family history of diabetes, and baseline and 96-week change in body weight, BMI, lean body mass, limb/trunk fat

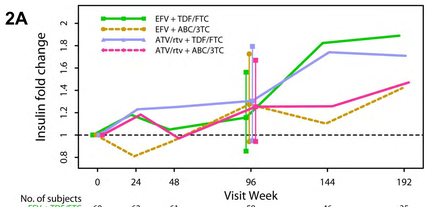
## Results

### On-Study Diabetes Mellitus:

6 subjects (2%) developed DM:
- 1 subject on EFV + TDF/FTC
- 1 subject on ATV/r + ABC/3TC
- 2 subjects on EFV + ABC/3TC
- 2 subjects on ATV/r + TDF/FTC

**Figures 1-3: Mean (95% confidence interval) changes in fasting glucose (1), insulin (2), and HOMA-IR (3); across treatment arms (A) and by randomized components (B)**



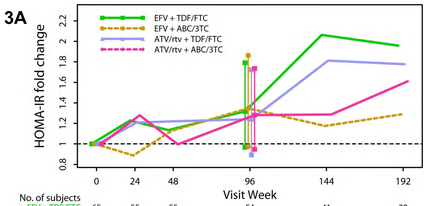




**Table 1.**

| Baseline Subject Characteristics | Total N=269 |
|---|---|
| **Age (years)** | **38 (10)** |
| **Female** | **40 (15%)** |
| **Race/ethnicity** | |
| **White non-Hispanic** | **126 (47%)** |
| **Black non-Hispanic** | **90 (33%)** |
| **Hispanic** | **44 (16%)** |
| **Other** | **9 (3%)** |
| **CD4 count (cells/µL)** | **236 (165)** |
| **Family history DM** | **84 (36%)** |
| **HIV-1 RNA ≥100,000 copies/mL** | **54 (20%)** |
| **Glucose (mg/dL)** | **84 (10)** |
| **Insulin (uIU/mL)** | **6.5 (8.1)** |
| **HOMA-IR** | **1.4 (1.7)** |
| **BMI (kg/m$^2$)** | **25.5 (4.7)** |
| **Lean body mass (kg)** | **54.5 (9.3)** |
| **Limb fat (kg)** | **8.3 (5.0)** |
| **Trunk fat (kg)** | **10.1 (6.1)** |

***Data are shown as mean (SD) or number (%)***

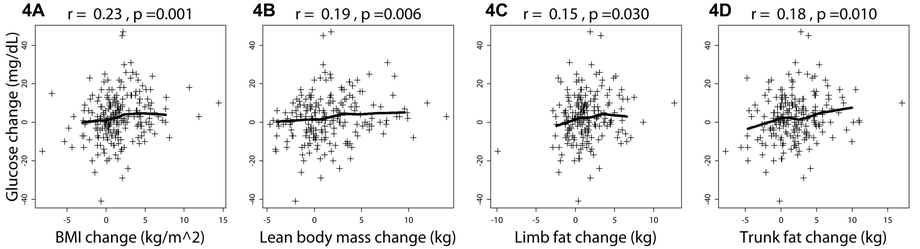
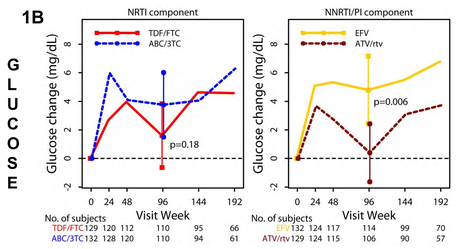
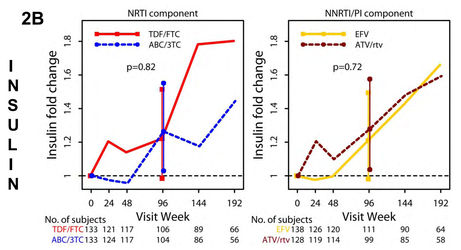
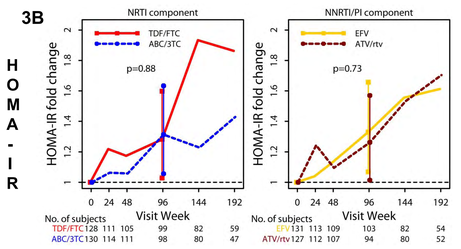



**Figure 4 A-D. Spearman Rank Correlation between week 0 to 96 change in glucose and change in BMI (4A), lean body mass (4B), limb fat (4C), and trunk fat (4D).**

*line represents a locally weighted least squares (LOWESS) smooth, using only data points between the 2.5th and 97.5th percentiles for both plotted variables




### Univariate and Multivariable Linear Regression

**Table 2. Univariate and Multivariable Linear Regression to Assess the Association Between Baseline and Post-baseline Factors and Change in Glucose**

| Baseline Covariate | Univariate Analyses Estimated Mean Change Difference (95% CI) | P | Multivariable Analyses Estimated Mean Change Difference (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** |
| **Baseline HIV-1 RNA†** | **3.2 (0.8, 5.5)** | **0.009** | **2.4 (0.0, 4.9)** | **0.047** |
| **96 week BMI change¶** | **0.9 (0.3, 1.4)** | **0.002** | **0.8 (0.3, 1.4)** | **0.005** |
| **96 week trunk fat change††** | **0.7 (0.2, 1.2)** | **0.005** | | |
| **96 week limb fat change††** | **0.8 (0.1, 1.5)** | **0.018** | | |
| **96 week LBM change††** | **0.7 (0.2, 1.2)** | **0.008** | | |

Covariates included ART regimen, sex, age, race/ethnicity, baseline CD4 and HIV-1 RNA, hepatitis B/C, family history of DM, baseline/change in body mass index (BMI) and measured lean body mass (LBM), limb and trunk fat. After adjusting for treatment, only variables that remained significant in the univariate or multivariable model are shown above. † per $\log_{10}$ copies/mL higher; ¶ per 1 kg/m$^2$ higher, †† per 1 kg higher

- Other regression results:
  - Higher baseline HIV-1 RNA was associated with a greater increase in HOMA-IR (worsened insulin sensitivity) in univariate analysis only. No baseline variables were associated with insulin change in univariate or multivariable analyses.

***Interpretation**: With everything else held constant, a 1log higher baseline HIV-1 RNA was associated with a mean 2.4 mg/dL higher change in glucose from baseline to week 96*

## Summary of Results

- Overall increases in fasting glucose, insulin, and HOMA-IR were observed across nearly all study arms.
- A significantly greater increase in fasting glucose was seen in the EFV compared to ATV/r arm.
- Change in glucose correlated positively and significantly, but weakly, with changes in body composition (Figure 4).
- Assignment to EFV (compared to ATV/r), higher baseline HIV-1 RNA, and greater gain in BMI over 96 weeks were independently and significantly associated with a greater increase in fasting glucose from week 0 to week 96.

## Conclusions

- We detected significantly greater increase in glucose among persons treated with EFV compared to ATV/r that persisted in multivariable analyses and was not explained through an increase in BMI.
- The small but significantly greater increase in glucose in those assigned to EFV in comparison to a newer protease inhibitor has not been previously reported in a randomized setting of ART-naïve persons.
- Even modest increases in glucose in the context of concurrent increase in BMI and insulin resistance could have important consequences over decades of treatment.
- These findings reinforce the need for healthy lifestyle choices such as diet and exercise, as the added impact of EFV may be another risk factor for DM among HIV-infected persons.
- The impact of long-term EFV use on the development of DM should be explored in randomized studies of longer duration.