Abstract 0472

# Pharmacogenetics of Weight Gain after Switch from Efavirenz to Integrase Inhibitors

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## INTRODUCTION

- Efavirenz (EFV) is metabolized primarily by hepatic cytochrome P450 (CYP) 2B6.
- Single nucleotide polymorphisms (SNPs) *CYP2B6* 516G→T, 983T→C, 15582C→T, and CYP2A6 -48T→G in combination predict increased plasma EFV exposure [1,2].
- Dolutegravir and raltegravir are primarily metabolized by hepatic UDP glucuronosyltransferase 1A1 (UGT1A1) [3,4].
- *UGT1A1* polymorphisms associated with Gilbert's syndrome result in increased plasma dolutegravir and raltegravir exposure.
- A retrospective cohort analysis showed weight gain after switch from EFV-based to integrase strand transfer inhibitor (INSTI)-based regimen [5].

### Primary Objectives

- To assess whether *CYP2B6* slow metabolizer genotypes were associated with weight gain after switch from EFV- to INSTI-based regimens
- To asses whether *UGT1A1* slow metabolizer genotypes were associated with weight gain after switch from EFV- to INSTI-based regimens

### Hypotheses

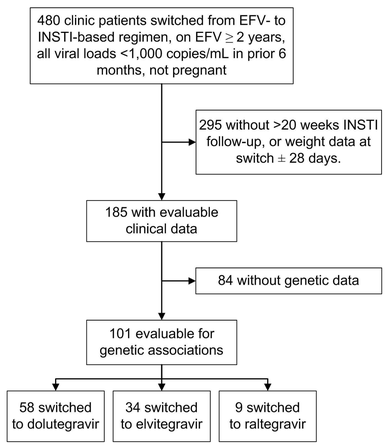
- Individuals with *CYP2B6* slow metabolizer genotypes (i.e. higher plasma EFV exposure) will feel better after switch and therefore gain more weight.
- Individuals with *UGT1A1* slow metabolizer genotypes (i.e. higher plasma INSTI exposure) might gain more weight after switch due to some unknown off-target effect of INSTI.

## METHODS

### Study Design and Participants

- Retrospective, observational genetic association study of HIV+ adults, who switched from EFV- to INSTI-based regimens
- Participants were prescribed an EFV-based regimen for the prior >2 years, had no viral load >1000 copies/mL within 6 the prior months, and were not pregnant during the study period.
- Participants remained on INSTI-based regimen for at least 20 weeks, had weight documented within 28 days of switch, and again at 24 and/or 48 weeks after the switch.
- Eligible participants provided informed written consent to genetic research and had stored DNA available for analysis.

**Figure 1. Derivation of study population.**




### Genetic assays and data

- Some *CYP2B6* and *UGT1A1* genotype data were available from previous HumanCoreExome BeadChip assays
- Additional *CYP2B6* rs28399499, rs4803419, *CYP2A6* rs28399433, and *UGT1A1* rs887829 genotyping by MassARRAY® iPLEX Gold, and *CYP2B6* rs3745274 by Taqman
- *UGT1A1* is in tight linkage disequilibrium with slow metabolizer (Gilbert) genotypes (*UGT1A1* *28/*28, *28/*37 and *37/*37)
- Two participants failed *CYP2B6* genotyping

### Statistical Analyses

- Three *CYP2B6* SNPs and one *CYP2A6* SNP were combined to generate a composite genotype with 12 possible ordinal levels
- The 12 levels were also collapsed into 3 metabolizer levels (normal, intermediate, and slow)
- We treated *UGT1A1* rs887829 as an ordinal variable with 3 levels
- All SNPs were in Hardy-Weinberg equilibrium.
- Covariates in multivariable analyses included weight at switch, age at switch, and sex
- Separate analyses were performed stratified by self-reported race/ethnicity, and by INSTI regimen.
- In sensitivity analyses, an individual with extreme outlier weight change was censored

### Outcomes of interest

- Median weight increased 2.2 kg from baseline to week 24 (IQR: -0.9, 4.8), and 1.7 kg to week 48 (IQR: -1.3, 4.8)
- Median weight changes among white participants at weeks 24 and 48 were 2.1 kg (IQR: -0.3, 4.8) and 1.8 kg (IQR: -1.2, 4.7) respectively.
- Median weight changes among black participants at weeks 24 and 48 were 2.7 kg (IQR: -2.0, 5.3) and 2.8 kg (IQR: -0.3, 7.3), respectively.
- Among the 84 (83.2%) male and 17 (16.8%) female participants, median weight change at week 24 was 2.0 kg (IQR: -0.9, 4.3) and 2.7 kg (IQR: -0.9, 5.4) respectively, and at week 48 was 2.2 kg (IQR: -1.0, 4.8) and 0.7 kg (IQR: -2.5, 8.2), respectively.

## RESULTS

### Study participants

- Participant disposition is shown in **Figure 1**
- Participant characteristics at baseline are shown in **Table 1**

**Table 1. Baseline characteristics of study participants**

| ***CYP2B6* group** | Total (n = 101) | Normal (n=30) | Intermed. (n=54) | Slow (n=15) |
|---|---|---|---|---|
| Age | 53.6 (44.8-61.1) | 53.8 (47.8–62.2) | 53.3 (44.4–60.7) | 51.4 (42.2–62.4) |
| Gender | | | | |
| Male | 84 (83.2%) | 23 (28.05%) | 48 (58.54%) | 11 (13.41%) |
| Female | 17 (16.8%) | 7 (41.18%) | 6 (35.29%) | 4 (23.53%) |
| Race/Ethnicity | | | | |
| White | 65 (64.4%) | 20 (66.7%) | 38 (70.4%) | 6 (40.0%) |
| Black | 27 (26.7%) | 6 (20.0%) | 12 (22.2%) | 9 (60.0%) |
| Other | 9 (8.9%) | 4 (7.4%) | 4 (13.3%) | 0 |
| INSTI Regimen | | | | |
| Dolutegravir | 58 (57.4%) | 11 (36.7%) | 36 (66.7%) | 10 (66.7%) |
| Elvitegravir | 34 (33.7%) | 13 (43.3%) | 17 (31.5%) | 3 (20.0%) |
| Raltegravir | 9 (8.9%) | 6 (20%) | 1 (1.9%) | 2 (13.3%) |

| ***UGT1A1* Genotype** | | Normal (38) | Intermed. (n=41) | Slow (n=16) |
|---|---|---|---|---|
| Age | 53.6 (44.8-61.1) | 56.1 (50.4–62.3) | 50.1 (42.6–59.8) | 54.3 (42.3–61.8) |
| Gender | | | | |
| Male | 84 (83.2%) | 38 (43.59%) | 37 (44.87%) | 9 (11.54%) |
| Female | 17 (16.8%) | 4 (23.53%) | 6 (35.29%) | 7 (41.18%) |
| Race/Ethnicity | | | | |
| White | 65 (64.4%) | 34 (80.95%) | 27 (62.79%) | 4 (25.0%) |
| Black | 27 (26.7%) | 6 (14.29%) | 13 (30.23%) | 8 (50.0%) |
| Other | 9 (8.9%) | 2 (4.76%) | 3 (6.98%) | 4 (25.0%) |
| INSTI Regimen | | | | |
| Dolutegravir | 58 (57.4%) | 23 (54.76%) | 26 (60.47%) | 9 (56.3%) |
| Elvitegravir | 34 (33.7%) | 15 (35.71%) | 14 (32.56%) | 5 (31.3%) |
| Raltegravir | 9 (8.9%) | 4 (9.52%) | 3 (6.98%) | 2 (12.6%) |

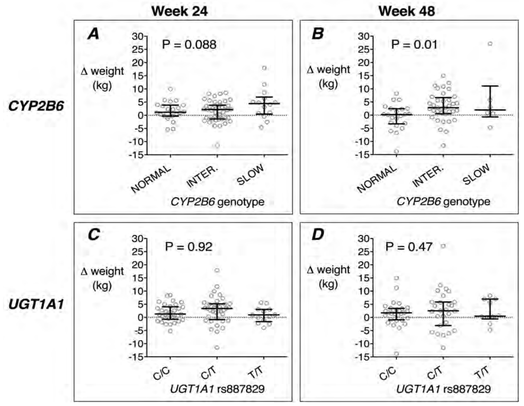
### *CYP2B6* genotype and weight change

- By univariate analysis, *CYP2B6* genotype was not significantly associated with weight change at week 24 (n=81, β=1.2, p=0.088), but was significantly associated with weight change at week 48 (n=61, β=3.3 p=0.01) **(Figure 2 )**
- In sensitivity analysis that censored one participant with extreme weight gain at week 48, *CYP2B6* genotype trended toward significance (n=60, β=2.1 p=0.06).
- In multivariable analysis, *CYP2B6* genotype remained associated with weight change at week 48 (n=61, β=3.25, p=0.009) **(Table 2)**

### *UGT1A1* genotype and weight change

- *UGT1A1* slow metabolizer genotype was not associated with weight change at either week 24 (n=83, β =-0.06, p=0.92) or week 48 (n=63, β=0.78, p=0.47) **(Figure 2)**

**Figure 2: Associations between genotype and weight change after switch from EFV- to INSTI-containing regimens**




(univariate P-values are shown)

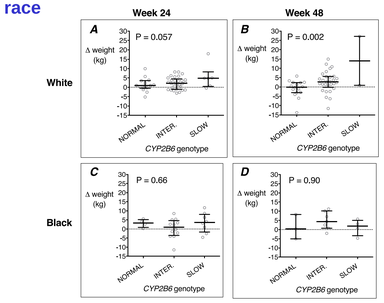
**Table 2. Multivariable linear regression models for association between *CYP2B6* genotype and weight change**

| | Variable | Coefficient | p-value |
|---|---|---|---|
| Week 24 | CYP2B6 genotype (loss of function) | 1.32 | 0.067 |
| | Female Sex | 1.70 | 0.203 |
| | Age at Switch (years) | -0.05 | 0.901 |
| | Weight at Switch (kg) | -0.04 | 0.079 |
| Week 48 | CYP2B6 genotype (loss of function) | 3.25 | 0.009 |
| | Female Sex | 3.16 | 0.120 |
| | Age at Switch (years) | -0.07 | 0.306 |
| | Weight at Switch (kg) | -0.01 | 0.857 |

### Analyses stratified by race and INSTI

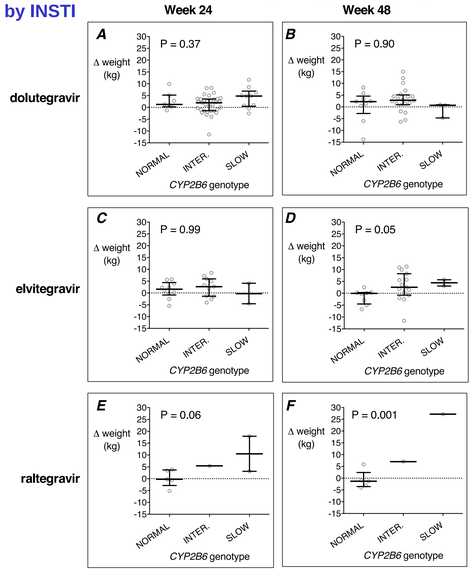
- In multivariable analyses, *CYP2B6* genotype was significantly associated with weight gain in white participants at week 48 (n=44, β=5.0, p=0.003), but not in black participants (n=14, β= -0.9, p=0.68). **(Figure 3)**
- In multivariable analyses, *CYP2B6* genotype trended toward association in the elvitegravir group at week 48 (n=25, β= 3.73, p=0.061), but not in the dolutegravir group (n=30, β= 0.28, p=0.87). **(Figure 4)**

**Figure 3. Associations between *CYP2B6* genotype and weight change, stratified by race**




(univariate P-values are shown)

**Figure 4. Associations between *CYP2B6* genotype and weight change, stratified by INSTI**




(univariate P-values are shown)

## CONCLUSIONS

- *CYP2B6* slow metabolizer genotypes were associated with greater weight gain at week 48, with a trend at week 24, in patients who switched from EFV- to an INSTI-containing regimens
- These associations were present in white participants but not in black participants at week 24 and 48
- The association with *CYP2B6* were seen in the elvitegravir and raltegravir groups, but not the the dolutegravir group
- *UGT1A1* genotype was not associated with change in weight after switch from EFV-based regimen to an INSTI-based regimen
- These findings suggest that genotypes that affect plasma EFV exposure affect weight gain after switch from EFV- to INSTI-based regimens.

### Acknowledgments

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### References

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