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 S166G→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 regimens [5].

Primary Objectives

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

RESULTS

- Of 284 eligible patients switched from EFV- to INSTI-based regimen, on EFV- 2 years, all viral loads <100,000 copies/mL in prior 6 months, not pregnant
- 284 patients participated in the study

- 30 switched to dolutegravir
- 36 switched to raltegravir
- 9 switched to elvitegravir

- 94 without genetic data
- 151 evaluable for genetic associations

- 284 without >2 weeks INSTI follow-up, or weight data at switch < 25 days
- 155 with evaluable circuit data

- 64 with evaluable genotype data

![Figure 1. Derivation of study population.](image)

Study participants

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

![Figure 2: Associations between genotype and weight change after switch from EFV to INSTI-containing regimens](image)

- In multivariable analyses, CYP2B6 genotype was significantly associated with weight gain in white participants at week 48 (n=44, β=0.5, 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= 3.7, p=0.061), but not in the dolutegravir group (n=30, β= 0.28, p=0.87), (Figure 4)

![Figure 4. Associations between CYP2B6 genotype and weight change, stratified by INSTI.](image)

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 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 in the dolutegravir group
- UGT1A1 genotype was not associated with change in weight after switch from EFV-based regimen to 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

This work was supported by the Tennessee Center For AIDS Research (P30 AI110527 and R01 AI077505 (DWH))

References