Pharmacogenetics of Weight Gain after Switch to Integrase Inhibitor-Based Regimens

595

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BACKGROUND

- Excessive weight gain affects some persons with HIV (PWH) after switch to integrase strand transfer inhibitor (INSTI)-based ART.
- In a prior study of 101 PWH who switched from efavirenz (EFV)- to INSTI-based ART, *CYP2B6* genotypes (which predict higher plasma EFV levels) were associated with greater post-switch weight gain.
- ACTG protocols A5001 and A5322 are long-term follow-up studies for individuals who had enrolled in prior ACTG randomized ART trials.

OBJECTIVE

- To examine associations between *CYP2B6* genotype and weight change following switch from EFV-containing to INSTI-containing ART.
- *Hypothesis: CYP2B6 slow metabolizer genotype would be associated with excess weight gain following a switch to INSTI-based ART.*

METHODS

- Analyses included all A5001 and A5322 participants who had:
  - Available *CYP2B6* genotype data from past analyses
  - Switched from EFV-containing ART to INSTI-containing ART during A5001 and A5322 follow up
  - At least 1 weight measurement from 4 weeks to 2 years after switch
- *CYP2B6* metabolizer groups were defined by 3 polymorphisms in combination (rs3745274, rs28399499, rs4803419).
- Outcomes of interest were:
  - Weight change (in kg) from switch to 2 years
  - Percent weight change from switch to 48 weeks (±12 weeks)
  - Percent weight change from switch to 96 weeks (±12 weeks)
- Multivariable linear mixed effects models were fit to assess relationships between *CYP2B6* group and estimated rate of weight gain.
- Models were also fit separately for selected subgroups:
  - Sex (male, female)
  - Self-reported race/ethnicity (black, white, Hispanic)
  - INSTI (raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG))
  - Tenofovir disoproxil fumarate (TDF) in pre-switch ART regimen
- Potential confounders considered were age at switch, sex, race/ethnicity, parent ACTG trial, body mass index (BMI) at switch, INSTI, CD4 count at nadir and at switch, history of smoking or diabetes, years of prior D4T/DDI/ZDV use, percent time pre-switch with HIV RNA <200 copies/mL, and psychiatric medications at switch.
- Variables that changed unadjusted effect estimates by ≥10% were retained.

Among individuals who switched from EFV-containing ART to INSTI-containing ART while participating in ACTG cohort studies A5001 and A5322, *CYP2B6* poor metabolizer genotype was associated with greater weight gain after switch from EFV- to INSTI-based ART, but results were inconsistent. Weight gain in this setting is likely complex and multifactorial.

RESULTS

- Of 5,968 participants, a total of 174 met all criteria for these analyses. 153 had pre-switch HIV-1 RNA <200 copies/mL.
- Participant characteristics are shown in **Table 1**.

Table 1: Selected characteristics at time of first INSTI switch by *CYP2B6* metabolizer group in evaluable participants.

		CYP2B6 metabolizer group		
	Total (N=174)	**Normal (N=80)**	**Intermediate (N=75)**	**Poor (N=19)**
Age in years, median (IQR)	41 (35, 48)	40 (35, 47)	41 (35, 51)	43 (35, 46)
Females, n (%)	27 (16%)	10 (13%)	12 (16%)	5 (26%)
Race/ethnicity, n (%)				
White	93 (53%)	45 (56%)	41 (55%)	7 (37%)
Black	51 (29%)	19 (24%)	23 (31%)	9 (47%)
Hispanic	27 (16%)	13 (16%)	11 (15%)	3 (16%)
BMI, kg/m², median (IQR)	26.7 (23.8, 29.9)	27.1 (23.6, 29.4)	26.2 (23.9, 29.9)	28.1 (24.7, 31.4)
INSTI at 1st switch				
RAL	55 (32%)	25 (31%)	25 (33%)	5 (26%)
EVG	41 (24%)	20 (25%)	16 (21%)	5 (26%)
DTG	70 (40%)	32 (40%)	30 (40%)	8 (42%)
BIC	8 (5%)	3 (4%)	4 (5%)	1 (5%)

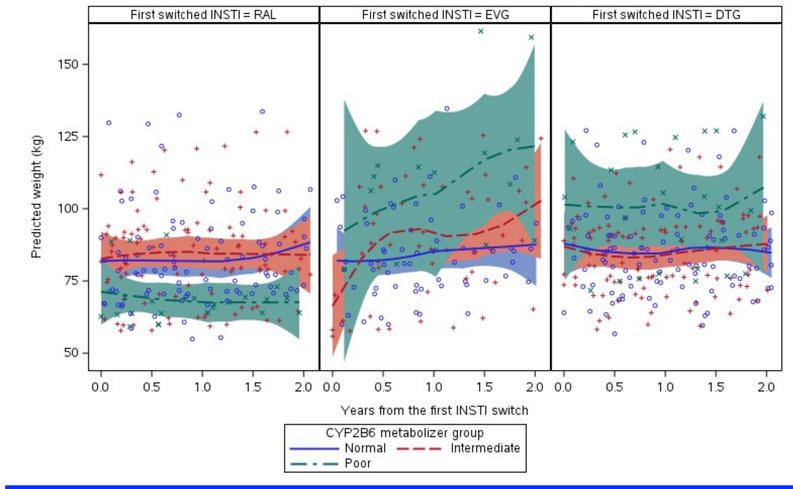
- Weight increased over time in each of the 3 *CYP2B6* groups.
- Overall, we found no consistent association between *CYP2B6* group and rate of weight gain among all participants (**Table 2**), or when stratified by sex, race/ethnicity, or INSTI (data not shown).
- Among 153 participants with VL <200 copies/mL at switch, rate of weight gain was greater in *CYP2B6* poor than in *CYP2B6* normal metabolizers, and within 8 subgroups analyzed separately (male, female, white, black, Hispanic, DTG, EVG, RAL).
- Only in Hispanic and EVG subgroups was P < 0.05 (**Table 2**),
- *CYP2B6* intermediate metabolizer group was not consistently associated with rate of weight gain.
- LOESS curves of weight by *CYP2B6* group, stratified by INSTI, are shown in the **Figure.**

Table 2 : Estimated rate of weight gain (kg/year) by *CYP2B6* group*

	Slope of weight change in kg/year			
	All	**P-value (vs. normal metabolizers)**	**VL <200 at switch**	**P-value (vs. normal metabolizers)**
All participants	**N=174**		**N=153**	
CYP2B6 normal	2.54 [1.86,3.21]		2.33 [1.59,3.07]	
CYP2B6 intermediate	1.48 [0.78,2.18]	0.03	1.11 [0.36,1.86]	0.02
CYP2B6 poor	3.19 [1.89,4.48]	0.4	3.67 [2.25,5.10]	0.1
Hispanic participants	**N=27**		**N=25**	
CYP2B6 normal	1.97 [0.61,3.33]		2.26 [0.76,3.76]	
CYP2B6 intermediate	1.97 [0.81,3.14]	0.9	1.75 [0.47,3.03]	0.6
CYP2B6 poor	5.57 [3.49,7.66]	**0.004**	5.63 [3.49,7.76]	**0.01**
Switched to EVG	**N=41**		**N=38**	
CYP2B6 normal	2.66 [1.66,3.65]		2.73 [1.83,3.63]	
CYP2B6 intermediate	2.15 [1.07,3.24]	0.5	1.40 [0.33,2.46]	0.06
CYP2B6 poor	5.56 [3.83,7.28]	**0.004**	5.75 [4.19,7.31]	**0.001**

* Based on mixed effects models adjusted for race/ethnicity, CD4, age, BMI, and INSTI unless factor was used to stratify.

Figure: LOESS curves of weight over time by *CYP2B6* group, stratified by INSTI (with 95% confidence bands)



CONCLUSIONS

- *CYP2B6* poor metabolizer genotype was associated with greater weight gain after switch from EFV- to INSTI-based ART, but results were inconsistent.
- Weight gain in this setting is likely complex and multifactorial.

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