Does Slow Efavirenz Metabolism Have Greater Impact on Outcomes in Older HIV+ Africans?

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Abstract

Neurotoxicity occurs frequently in people taking efavirenz (EFV), a medication commonly used in resource limited settings. The cognitive and neuroanatomical changes that occur with advancing age may potentiate these neurotoxic effects in older age, but few data on antiretroviral treatment (ART) toxicity come from sub-Saharan Africa. Certain CYP2B6 single nucleotide polymorphisms are associated with slower EFV metabolism and may also interact with age to increase risk of toxicity and poor outcomes in this population. We examined associations between age, CYP2B6 G516T variants, and clinical outcomes among a cohort of 941 HIV+ adults initiating EFV-based ART in Botswana between 2009 and 2013. Older age was defined as age ≥50 years. CYP2B6 G516T variants were defined as conferring normal, intermediate, and slow metabolism. Neurotoxicity was measured through a symptom severity questionnaire. Age-stratified bivariate analysis was performed to identify association between CYP 2B6 variant and loss to care by age. Older age was associated with loss to care (OR: 2.05, [95% CI: 1.36-3.08]), but not virologic failure (OR: 0.71, [95% CI: 0.34-1.48]). Age modified the effect of CYP 2B6 variants on loss to care with older, slow metabolizers at higher risk than older, normal metabolizers (OR: 7.20, [95% CI: 1.82-28.48]) while younger, slow metabolizers had no increased risk compared to younger, normal metabolizers (OR: 1.03, [95% CI: 0.61-1.74]). Neurotoxicity was not more common in slow EFV metabolizers. Understanding the relationship between older age and genotype is important to improving outcomes in an aging population initiating EFV-based ART.

Introduction

- CYP 2B6 alleles confer slower efavirenz (EFV) metabolism, increasing drug concentration and possibly toxicity
- EFV-associated neurotoxicity is common and may lead to treatment discontinuation and failure
- Pharmacogenetic impact on outcomes in older age is unknown

Objectives

- Primary: Determine association between older age, CYP 2B6 G516T polymorphisms and their impact on treatment outcomes
- Secondary: Determine if EFV-associated neurotoxicity is more pronounced in older participants

Methods

- 941 HIV+ treatment-naïve adults, age ≥ 21 years, initiating EFV-based ART in Botswana were enrolled between 2009 and 2013
- Older age was defined as ≥ 50 years
- CYP2B6 G516T variants were defined as conferring normal (G/G) , intermediate (G/T), or slow (T/T) EFV metabolism[1]
- Neurotoxicity was measured through an EFV symptom severity (ESS) questionnaire[2]
- Loss to care was defined as death or loss to follow-up
- Bivariable analysis stratified by age was completed to determine odds of loss to care by CYP 2B6 variant

Table 1. Characteristics by Age Group

Variable	Age 21-49 years (n=789)	Age ≥50 years (n=125)	p-value
Median age, yrs (Q1, Q3)	36 (32, 41)	54 (52, 57)	--
Sex			
Male	398 (50.4%)	65 (52.0%)	0.75
Female	391 (49.6%)	60 (48.0%)	
BMI			
>18.5	655 (83.6%)	108 (86.4%)	0.42
≤18.5	129 (16.4%)	17 (13.6%)	
Median CD4 count/mL, n (Q1, Q3)	195 (110, 254.5)	194 (111, 242.8)	0.67
Median HIV-1 RNA*, n (Q1, Q3)	4.88 (4.26, 5.38)	5.02 (4.18, 5.48)	0.34
CYP 2B6			
G/G	274 (38.3%)	42 (38.9%)	0.46
G/T	335 (46.8%)	52 (48.2%)	
T/T	107 (14.5%)	14 (12.9%)	
Other	73 (9.2%)	17 (13.6%)	
Depression‡			
No	665 (85.3%)	103 (83.7%)	0.66
Yes	115 (14.7%)	20 (16.3%)	

*$\log_{10}$ copies/mL; †Binge drinking in past year; ‡PHQ-9 positive screen;

Table 2. Outcome by Age and CYP 2BG G516T Variant

Variable	Age 21-49 years	Age ≥50 years	OR (95% CI)*	p-value
OVERALL				
Loss to care	172 (22.3%)	44 (37.0%)	2.05 (1.36, 3.08)	0.001
Death	27 (3.4%)	11 (8.8%)	2.70 (1.31, 5.60)	0.007
Loss to follow-up	145 (19.2%)	33 (29.0%)	1.72 (1.07, 2.72)	0.016
Virologic failure†	94 (15.4%)	9 (11.5%)	0.71 (0.34, 1.48)	0.37
BY CYP 2B6				
Loss to care				
G/G	64 (23.4%)	10 (23.8%)	1.00 (0.42, 2.24)	0.99
G/T	64 (19.1%)	20 (38.5%)	2.95 (1.46, 5.80)	<0.001
T/T	26 (24.3%)	9 (64.3%)	7.01 (1.74, 33.14)	<0.001
Virologic failure†				
G/G	24 (8.8%)	4 (9.5%)	1.11 (0.26, 3.56)	0.87
G/T	47 (14.0%)	5 (9.6%)	0.98 (0.28, 2.82)	0.98
T/T	18 (16.8%)	0 (0%)	--	--

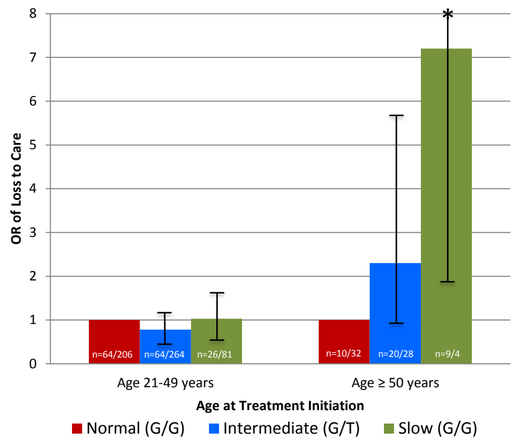
*Odds of outcome in people ≥50yrs versus odds of outcome in people age 21-49yrs
†≥25 copies/mL @ Month 6

Table 3. EFV Toxicity by Age and CYP 2B6 G516T Variant

	Mean ESS* (SD) Month 1			Mean ESS (SD) Month 6		
	Age 21-49 yrs	Age ≥50 years	p-value	Age 21-49 yrs	Age ≥50 years	p-value
Overall	4.1 (6.6)	4.9 (7.7)	0.26	1.8 (4.0)	3.8 (6.8)	0.0001
CYP 2B6						
G/G	4.4 (7.0)	7.4 (11.2)	0.02	2.0 (4.2)	3.9 (6.9)	0.02
G/T	4.0 (6.5)	3.9 (5.0)	0.97	1.6 (3.7)	4.0 (7.7)	0.001
T/T	3.0 (5.2)	1.8 (2.0)	0.50	1.4 (3.2)	1.8 (2.5)	0.81

*ESS: Efavirenz symptoms severity questionnaire, score range 0-140

Figure 1. Loss to Care by Age and CYP 2B6 G516T Variant



Results

- Older age increased odds of loss to care (OR: 2.0, p=0.001), including death (OR: 2.7, p=0.007), but not virologic failure (OR: 0.71, p=0.36) (Table 2)
- The effect of CYP 2B6 variants on loss to care differed by age group (Figure 1, test of homogeneity: p=0.016)
- Loss to care was increased in older, intermediate (G/T) variants (OR: 2.29, p=0.076) and older, slow (T/T) variants (OR: 7.2, p=0.011) compared to older, normal variants (G/G) (trend: p=0.003)
- No association was observed between the CYP 2B6 variants and loss to care in younger people
- EFV-associated neurotoxicity was rare, and not consistently greater in older adults (Table 3)

Conclusion

- Older participants are at increased risk for loss to care, particularly in slow EFV metabolizers
- Altered pharmacokinetics and unmeasured toxicity may explain the association between slow EFV metabolism and loss to care in older people
- Understanding why slow EFV metabolism might cause loss to care in older adults will be critical for interventions to improve retention and allow providers to tailor HIV therapy in similar settings

Strengths and Limitations

- This is the largest study of the impact of EFV pharmacogenetics and older age on clinical outcomes in resource-limited settings.
- This study is a post hoc analysis, thus results need to be interpreted with caution

References

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