Proposed Host Pharmacogenetic Polymorphisms Predict Laboratory Abnormalities, but not Early Treatment Discontinuation in Patients Receiving HAART

20th CROI - Abstract J-161
March 3-6, 2013
Atlanta, GA, USA

Chanson J Brumme[1,2], Celia KS Chui[1], Jeong Eun Min[1], Weiyan Dong[1], Guillaume Colley[1], Benita Yip[1], Katherine Lepik[1], P Richard Harrigan[1,2]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada [2] Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

Presenting Author:
Chanson Brumme
cbrumme@cfenet.ubc.ca

Background

- Host genetic polymorphisms may predict HIV therapy outcome or laboratory abnormalities
- Pharmacogenetic screening other than for HLA-B*57:01 is not routinely used in HIV care

Methods

- Sequenced 12 host polymorphisms in 8 genes reported to influence discontinuation of three common antiretrovirals: tenofovir (TDF), efavirenz (EFV), atazanavir (ATV)
- Study Population: 747 consenting patients who received cART with ≥1 study drugs in British Columbia, Canada between 1998-2010
- Patients treated with TDF (n=475), EFV (n=264), and/or ATV (n=271) were followed for 15 months
- Early treatment discontinuation was estimated from prescription refill records (defined as stopping drug for ≥3 months within the first year of exposure)
- Adverse drug reaction (ADR) data were abstracted from pharmacovigilance reports (June 2008 onwards)
- Rates of discontinuation in the first year of treatment were compared between individuals with and without genetic markers using multivariate Cox proportional hazard models adjusted for non-genetic variables:
  - age, sex, ethnicity, CD4 count, plasma viral load, year of therapy initiation
- Intermediate Phenotypes: Drug-specific laboratory measures collected in the first 6 months of therapy
  - tenofovir: serum creatinine (n=370)
  - efavirenz: randomly timed plasma EFV levels (n=232)
  - atazanavir: bilirubin levels (n=193)

Table 1 - Genotypic Variants Investigated

Drug	Gene	Gene Function	Variant (rs#)	Polymorphism	Minor Allele Freq
TDF	ABCC2	Drug Transport	rs2273697	G>A	17.4%
			rs717620	C>T	22.0%
	ABCC4	Drug Transport	rs899494	C>T	15.0%
EFV	CYP2A6*	Drug Metabolism	rs28399433	T>G	8.4%
	CYP2B6*	Drug Metabolism	rs3745274	G>T	23.6%
			rs35303484	A>G	0.3%
			rs35979566	T>A	0.8%
			rs28399499	T>C	0.1%
	CYP3A4*	Drug Metabolism	rs4646437	C>T	13.5%
ATV	ABCB1	Drug Clearance	rs1045642	C>T	49.3%
	NR1I2	Drug Clearance	rs2472677	T>C	41.2%
	UGT1A1	Bilirubin Conjugation	rs8175347	$A(TA)_6TAA > (TA)_5$, $(TA)_7$ or $(TA)_8$	$(TA)_5$: 0.7% $(TA)_6$: 90.1% $(TA)_7$: 9.0%

*Due to low prevalence of CYP2B6 polymorphisms EFV SNPs were combined into a composite "CYP Score" variable, as defined in Lubomirov et al. *JID*, 2011; 203(2):246-57

Gene	SNP	Total SNP Copies					
		Score 1	Score 2	Score 3	Score 4	Score 5	Score 6
CYP2B6	rs3745274, rs35303484, rs35979566, rs28399499	0	0	1	1	2	2
CYP2A6 CYP3A4	rs28399433 rs4646437	0	1 to 4	0	1 to 4	0	1 to 4

Table 2 - Adverse Drug Reactions Associated with Discontinuation in the First Year of Exposure

Discontinuations	TDF	EFV	ATV
Patients receiving drug	475	264	271
Total drug discontinuations in first year of therapy	81	81	55
Total 1st year drug discontinuations after 1-June-2008†	29	27	25
Any adverse drug reaction reported†	9	18	6

Symptom Category (primary symptom)	TDF (n=9)	%	EFV (n=18)	%	ATV (n=6)	%
Central Nervous System	0	0%	**16**	**89%**	0	0%
Gastrointestinal upset	1	11%	1	6%	5	83%
Isolated hyperbilirubinemia	0	0%	0	0%	**1**	**17%**
Hepatic (excluding isolated hyperbilirubinemia)	0	0%	1	6%	0	0%
Renal	**8**	**89%**	0	0%	0	0%

Drug discontinuation (defined as an interruption of study drug for ≥3 months) was inferred from prescription refill histories
† Adverse drug reaction (ADR) data were only available from 1-Jun-2008 onwards

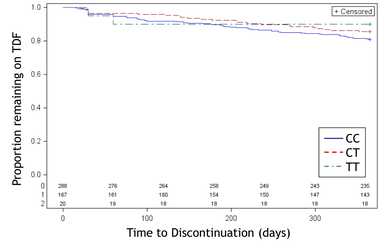
Table 3 - SNP Associations with Therapy Discontinuation

Drug	Variant (rs#)	Genotype	Unadjusted HR (95% CI)	Unadj. p-value	Adjusted HR (95% CI)	Adj. p-value	Discontinuation Rate (%) †
TDF	rs2273697	GG (0)	1	-	-	-	17.0
		GA (1)	0.89 (0.53-1.48)	0.65	-	-	14.8
		AA (2)	1.30 (0.47-3.57)	0.62	-	-	22.2
	rs717620[a]	CC (0)	1	-	1	-	18.4
		CT (1)	0.73 (0.45-1.18)	0.20	0.75 (0.45-1.23)	0.26	14.4
		TT (2)	0.51 (0.13-2.10)	0.35	0.66 (0.16-2.74)	0.57	10.0
	rs899494	CC (0)	1	-	-	-	17.4
		CT (1)	0.86 (0.52-1.44)	0.57	-	-	15.4
		TT (2)	0.95 (0.23-3.87)	0.94	-	-	9.1
EFV	rs28399433	TT (0)	1	-	-	-	30.2
		TG (1)	1.18 (0.65-2.13)	0.59	-	-	33.3
	rs3745274	GG (0)	1	-	-	-	30.6
		GT (1)	0.99 (0.64-1.53)	0.96	-	-	30.8
	rs4646437	CC (0)	1	-	-	-	32.1
		CT (1)	0.78 (0.46-1.34)	0.37	-	-	26.2
		TT (2)	1.29 (0.18-9.29)	0.80	-	-	33.3
	CYP Score	Score 1	1	-	-	-	32.9
		Score 2	0.82 (0.44-1.54)	0.54	-	-	27.3
		Score 3	0.91 (0.53-1.57)	0.74	-	-	30.9
		Score 4	0.89 (0.46-1.72)	0.73	-	-	30.2
ATV	rs1045642[b]	CC(0)	1	-	1	-	13.2
		CT(1)	1.75 (0.82-3.71)	0.15	1.82 (0.82-4.05)	0.14	21.8
		TT(2)	1.88 (0.85-4.15)	0.12	2.08 (0.90-4.80)	0.085	24.1
	rs2472677[c]	TT(0)	1	-	1	-	14.9
		TC(1)	1.96 (1.01-3.61)	0.032	2.02 (1.04-3.92)	**0.037**	26.2
		CC(2)	1.15 (0.49-2.70)	0.76	1.35 (0.56-3.29)	0.51	16.7
	rs8175347	$(TA)_5$	1	-	-	-	25.0
		$(TA)_6$	0.75 (0.10-5.40)	0.77	-	-	19.3
		$(TA)_7$	1.27 (0.16-10.3)	0.83	-	-	30.4

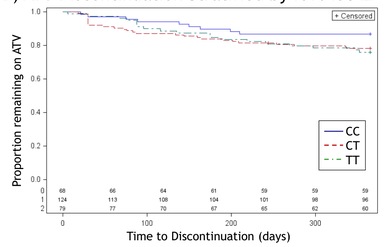
[a] rs717620 : Adjusted for plasma viral load, CD4 count, injection drug use history, sex, European ancestry, year of TDF initiation
[b] rs1045642: Adjusted for sex, plasma viral load and injection drug use history
[c] rs2472677: Adjusted for CD4 count, sex, European ancestry, year of ATV initiation
† The cumulative discontinuation rate was computed by crude Kaplan-Meier estimates at the first year

Figure 1 - Cumulative Rates of Treatment Discontinuation

A) TDF Discontinuation Stratified by rs717620



B) ATV Discontinuation Stratified by rs1045642



C) ATV Discontinuation Stratified by rs2472677

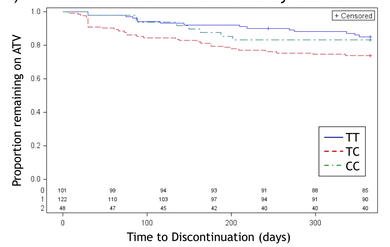


Table 4 - Associations with Lab Measures of Drug Toxicity

A) No association with highest observed serum creatinine level in first 6 months of TDF (n=370)

Variant	Genotype	Median (IQR)	p-value
rs2273697	GG (0)	87 (76-100)	0.64
	GA (1)	86 (75-97)	
	AA (2)	88 (86-95)	
rs717620	CC (0)	86 (76-97)	0.55
	CT (1)	90 (76-100)	
	TT (2)	84 (78-95)	
rs899494	CC (0)	88 (76-99)	0.30
	CT (1)	86 (77-97)	
	TT (2)	72 (68-87)	

B) Variants associated with highest observed plasma EFV level in first 6 months of EFV (n=232)

Variant	Genotype	Median (IQR)	p-value
rs28399433	TT (0)	1970 (1410-2960)	0.60
	TG (1)	2040 (1480-2690)	
rs3745274	GG (0)	1595 (1300-2270)	**<0.001**
	GT (1)	2545 (1760-3750)	
rs4646437	CC (0)	1890 (1360-2830)	0.062
	CT (1) or TT (2)	2235 (1690-2910)	
CYP Score	Score 1	1495 (1205-2050)	**<0.001**
	Score 2	1965 (1480-2350)	
	Score 3	2495 (1830-3750)	
	Score 4	2725 (1750-3715)	

C) *UGT1A1* variant associated with highest observed bilirubin level in first 6 months of ATV (n=193)

Variant	Genotype	Median (IQR)	p-value
rs1045642	CC(0)	39 (27-56)	0.020
	CT(1)	38 (24-49)	
	TT(2)	49 (34-68)	
rs2472677	TT(0)	42 (28-55)	0.88
	TC(1)	39 (25-54)	
	CC(2)	38 (30-54)	
rs8175347	$(TA)_5$	38 (23-73)	**<0.001**
	$(TA)_6$	39 (25-52)	
	$(TA)_7$	86 (41-116)	

Conclusions

- Screening for host polymorphisms may predict laboratory abnormalities, but not cART discontinuation in this cohort
- Investigation of additional variants with longer-term followup is warranted. For example, renal (creatinine) abnormalities may develop only after several years of exposure to tenofovir
- Current data are not sufficient to recommend expanded pharmacogenetic screening as a method for routinely identifying patients at risk of early treatment discontinuation in British Columbia

BRITISH COLUMBIA CENTRE for EXCELLENCE in HIV/AIDS
Providence HEALTH CARE How you want to be treated.
UBC
CIHR IRSC
Bourses d'études supérieures du Canada Vanier Canada Graduate Scholarships