Relative genetic contribution to the pharmacokinetics of commonly prescribed antiretrovirals

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Introduction

• Pharmacokinetics (PK) is influenced by several absorption, distribution, metabolism and elimination (ADME) processes.

• Inter-patient variability (SD_b) in PK can be influenced by host genetic factors in addition to environmental factors, both of which are known to influence ADME processes (Figure 1).

• Conversely, intra-patient variability (SD_w) in PK is assumed to be determined only by environmental factors that influence ADME processes since DNA sequence doesn't change between individuals (Figure 1).

• The role of genetics can be quantified through the calculation of a "relative genetic contribution" score (rGC = 1-(1/ (SD_b^2/SD_w^2) and an rGC of 0.904 (0.64 – 0.97) was recently reported for nevirapine (NVP) $AUC_{0\text{-}6h}$ (Micheli *et al*, *Pharmacogenet Genomics*, 2013).

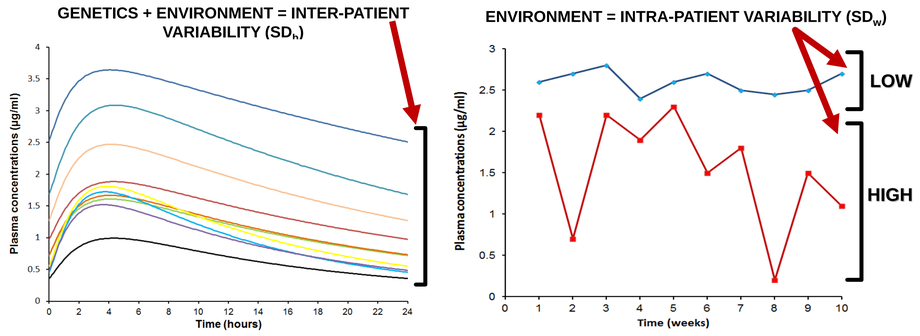


Figure 1. Role of the environment and genetics in the definition of inter and intra-patient pharmacokinetic variability

• The aim of this study was to assess the rGC of a panel of antiretroviral drugs to assess the degree by which heritability influences their pharmacokinetics

Methods

• Patients from the Therapeutic Drug Monitoring Registries at the University of Turin and the University of Liverpool were included in the analysis.

• Inclusion criteria: receiving lopinavir/ritonavir (LPV/r; 300/100 mg b.i.d.), atazanavir/ritonavir (ATV/r; 300/100 q.d.), unboosted ATV (400mg q.d.), efavirenz (EFV; 600 mg q.d.), nevirapine (NVP; 400 mg q.d.), raltegravir (RAL; 400 mg b.i.d), etravirine (ETR; 200 mg b.i.d), tenofovir disoproxil fumarate (TDF; 300 mg q.d), maraviroc, (MVC; 300mg b.i.d.), age>18 years, not receiving drugs known to be involved in drug-drug interactions (e.g. enzyme inhibitors/inducers).

• Plasma drug concentrations had been determined using validated HPLC-UV or LC-MS/MS methods.

• Intra-patient (SD_w) and inter-patient (SD_b) variability were measured in patients with C_{min} or C_{12} available from more than one visit. The rGC was calculated using the following equation: 1-(1/F) where F= SD_b^2/SD_w^2. Statistical significance for genetic contribution was calculated using F-test, α = 0.05.

• Patient demographics are summarised in Table 1.

Table 1. Patient demographics

ARVs (number of patients)	Age (years ± SD)	Weight (kg ± SD)	Height (cm ± SD)	Gender (% of male)
Efavirenz (n=41)	44 ± 10	74 ± 20	174 ± 10	70%
Tenofovir (n=92)	42 ± 8	66 ± 11	171 ± 9	73%
Nevirapine (n=31)	45 ± 8	72 ± 12	170 ± 7	60%
Etravirine (n=42)	45 ± 12	69 ± 10	171 + 6	90%
Atazanavir (n=63)	46 ± 10	66 ± 13	169 ± 8	60%
Atazanavir/r (n=31)	44 ± 8	69 ± 14	170 ± 9	63%
Maraviroc (n=32)	47 ± 9	73 ± 5	170 ± 8	75%
Lopinavir/r (n=61)	42 ± 8	66 ± 12	172 ± 9	78%
Raltegravir (n=67)	48 ± 9	72 ± 12	172 ± 9	80%

Results

• A total of 460 patients were included. Mean rGC, SD_w and SD_b are presented in table 2.

• Mean with 95% CI rGC was calculated to be 0.81 (0.72 – 0.88) for EFV, 0.74 (0.61 – 0.84) for NVP, 0.74 (0.63 – 0.85) for TDF, 0.67 (0.49 – 0.78) for ETV, 0.59 (0.38 – 0.74) for ATV, 0.47 (0.27 – 0.60) for ATV/r, 0.36 (0.01 – 0.48) for MVC, 0.15 (0.01 – 0.44) for LPV/r and 0 (0 – 0.33) for RAL (Table 2 and Figure 2A).

• All patients were of Caucasian ancestry and demographics were not significantly associated with C_{min} or C_{12}. Insufficient females were included to robustly assess influence of gender.

• No relationship between inter-patient variability (SD_b) and rGC was observed (Figure 2B) but intra-patient variability (SD_w) was significantly correlated with rGC (Figure 2C).

• A positive correlation between inter-patient variability (SD_b) and intra-patient variability (SD_w) was also observed (Figure 2D).

Table 2. Intra and inter patient variability and rGC

ARVs (number of patients)	Intra patient variability (SDb)	Inter patient variability (SDw)	Mean rGC (95%CI)
Efavirenz (n=41)	25%	58%	0.81 (0.72-0.88)
Tenofovir (n=92)	57%	112%	0.74 (0.63-0.85)
Nevirapine (n=31)	21%	43%	0.74 (0.61-0.84)
Etravirine (n=42)	45%	79%	0.67 (0.49-0.78)
Atazanavir (n=63)	75%	128%	0.59 (0.38-0.74)
Atazanavir/r (n=31)	56%	86%	0.47 (0.27-0.60)
Maraviroc (n=32)	81%	102%	0.36 (0.01-0.48)
Lopinavir/r (n=61)	47%	51%	0.15 (0.01-0.44)
Raltegravir (n=67)	91%	90%	0.00 (0.00-0.33)

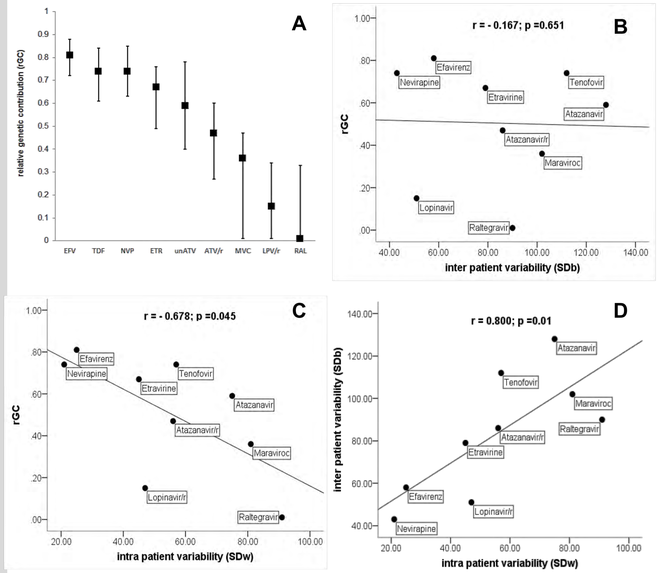


Figure 2. A) rGC for antiretrovirals (mean with 95% CI). B) Correlation between SD_b variability and rGC. C) Correlation between SD_w and rGC. .D) Correlation between SD_w and SD_b.

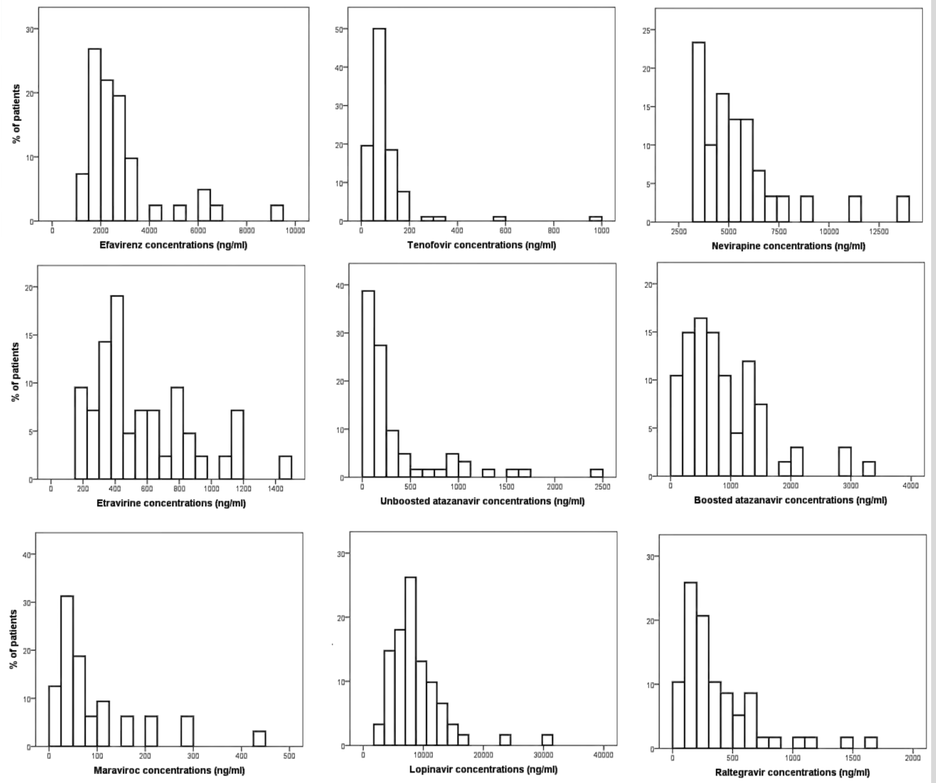


Figure 3. Bar charts representing the distribution of mean plasma concentrations for each of the drugs within the study population.

Discussion

• The rank order for rGC score for the included drugs was EFV > TDF > NVP > ETR> > ATV > ATV/r > MVC > LPV/r > RAL. An indication of class-specific differences was also evident (N(t)RTI/NNRTI > PI > II).

• These data indicate that ritonavir reduces the rGC for ATV plasma concentrations, presumably through inhibition of ADME proteins such as CYP3A4 and ABCB1.

• The correlation of SDw with rGC illustrates a higher genetic contribution for drugs with lower environmental influences.

• Plasma concentrations were not normally distributed for any of the ARVs, suggesting an influence from an interplay of factors.

• Drugs with high rGC scores may represent good candidates for genetic studies.

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