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Plasma NRTI concentration and their associations with liver and renal parameters in people living with HIV

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Abstract

Associations between markers of liver and renal dysfunction and NRTI plasma exposure are ill-defined. As part of a large cohort study (POPPY), we analysed associations between ALT and eGFR results in people living with HIV on tenofovir (TFV) disoproxil fumarate (TDF), emtricitabine (FTC), abacavir (ABC) and lamivudine (3TC). While we found no associations between NRTI concentrations and ALT, lower eGFR values were associated with greater TFV, FTC and 3TC exposure, whereas ABC showed no associations.

KEY WORDS: antiretroviral therapy, nucleoside reverse transcriptase inhibitors, pharmacokinetics.

Main Text

With the ageing population of people with HIV, clinical priorities are increasingly focused on managing age- and HIV-associated chronic comorbidities, preventing long-term antiretroviral drug toxicity and managing polypharmacy or altered drug exposure due to age-associated physiological changes of drug metabolic pathways [1].

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) constitute the 'backbone' of a typical combination antiretroviral (cART) regimen. NRTIs are pro-drugs and require intracellular phosphorylation in order to be effective against HIV replication [2]. However, NRTI-related toxicities may also be the consequence of their plasma concentrations, as has been clearly shown for tenofovir (TFV) [3]. Importantly, co-administration of tenofovir disoproxil fumarate (TDF) and boosting agents like cobicistat that lead to higher TFV plasma concentrations results in significantly higher TDF discontinuation rates [3,4]. On the other hand, while older NRTIs like zidovudine were associated with hepatotoxicity, newer ones have led to only few cases of NRTI-induced liver toxicities [5,6].

Nevertheless, the association between NRTI plasma exposure and measures of liver and renal dysfunction has rarely been investigated.

In the present study, we investigate the associations between plasma exposure of four frequently used NRTIs (TDF; emtricitabine, FTC; abacavir, ABC; and lamivudine, 3TC) with plasma alanine aminotransferase (ALT) concentrations or estimated glomerular filtration rate (eGFR) results in the large POPPY (Pharmacokinetic and Clinical Observations in People over Fifty) cohort study.

Participants were selected from the POPPY study [7], were receiving at least one of four NRTIs (TDF, FTC, 3TC and ABC) and provided a sample for pharmacokinetic (PK) testing. The latter was analysed by an ultra-performance liquid chromatography (UPLC) (Waters, UK)-validated method [8] and PK models were determined using nonlinear mixed effects (NONMEM v. 7.3) implementing the $PRIOR subroutine to predict NRTI area under the curve (AUC), maximum concentration (C_{max}) and trough concentration (C_{trough}) for each patient as previously described [9].

Univariable and multivariable linear regression models (STATA version 15) were fitted to describe associations between PK parameters and ALT or eGFR (estimated by CKD-EPI -primary analysis-, MDRD and Cockcroft-Gault) results. Models were adjusted for *a priori* selected confounders: age, gender, ethnicity, current use of boosted protease inhibitors (bPI), efavirenz or nevirapine, hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, current use of alcohol, history of recreational drugs in the past six months, current use of lipid lowering drugs. *Post hoc* analyses to estimate the body mass index (BMI) impact on the association between TFV PK parameters and ALT, and stratification of TFV analyses to evaluate the impact of FTC co-administration were also conducted.

The analyses of ALT concentration included 488 participants receiving TDF, 452 receiving FTC, 92 receiving ABC and 122 receiving 3TC. Overall, the median (range) ALT concentration was 30 (6, 99) U/l for those receiving TDF, 30 (6, 99) for those receiving FTC, 27 (8, 89) for those receiving ABC and 27 (7, 89) for those receiving 3TC. In univariate analysis, ALT values were inversely correlated with TFV AUC_{24h} ($p<0.001$), C_{max} ($p<0.001$), and C_{24h} ($p=0.003$) but the associations were attenuated and became non-significant after adjustment for BMI. The concomitant use of FTC showed little impact on the association between TFV PK parameters and ALT levels. Lastly, a weaker association was observed between FTC PK parameters and ALT values and no associations were observed between ALT values and either ABC or 3TC PK parameters (Table).

eGFR analyses included 533 participants receiving TDF, 495 receiving FTC, 104 receiving ABC and 135 receiving 3TC. Overall, the median (range) eGFR CKD-EPI value (mL/min/1.73m^2) was 91 (42,

145) for those receiving TDF, 90 (42, 145) for those receiving FTC, 91 (35, 144) for those receiving ABC and 90 (35, 143) for those receiving 3TC.

eGFR CKD-EPI values strongly correlated with AUC, C_{max}, and C_{trough} for TFV and FTC, both before and after adjusting for confounding factors (Table). In patients receiving both TDF and FTC (n=436), both TFV and FTC PK parameters were independently associated with eGFR CKD-EPI values, suggesting that the associations between eGFR and FTC PK parameters are independent of the concomitant administration of TDF.

Weaker but significant associations were observed between eGFR values and AUC (p=0.03) and C_{trough} (p=0.03) for 3TC, but no clear associations were seen with any of the ABC PK parameters and eGFR values (Table).

Although this is the first study to investigate the plasma exposure of NRTIs in a large cohort of patients who are ageing with HIV and are on stable cART, it has some limitations. Firstly, we used only ALT and eGFR to assess liver dysfunction and renal function, respectively. These surrogate biomarkers may not fully reflect changes in liver and renal function. Furthermore, this is a cross-sectional study; therefore, we cannot establish the direction of the associations or identify whether the higher TFV concentrations were leading to eGFR changes or *vice versa*. However, the population studied was stable on their cART, suggesting that manifestations of drug toxicity leading to drug switch/discontinuation were not imminent.

In conclusion, while we observed no consistent associations between plasma concentrations of NRTIs and ALT results after adjusting for confounding factors, higher plasma PK parameters of TFV, FTC and 3TC but not ABC were associated with lower eGFR. This suggests that altered liver function tests, which are a common finding in people living with HIV (PLWH) [10] may not be a consequence of increased NRTI plasma concentrations. However, a decreased eGFR indicating reduced (glomerular or tubular) excretory capacity of the kidney leads to higher plasma concentrations of renally excreted NRTIs (TFV, FTC and 3TC) and this may be taken into consideration when providing clinical care to ageing PLWH on polypharmacy and experiencing drug toxicity.

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Multivariate associations with ALT concentrations	TFV		FTC		ABC		3TC	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
AUC_{24h} (mg.h/L)		<0.001		0.006		0.60		0.73
≤2.355	Ref.	-	Ref.	-	Ref.	-	Ref.	-
2.356-2.612	-5.06 (-9.64, -0.48)		3.84 (-1.14, 8.81)		1.85 (-9.07, 12.77)		-8.00 (-17.27, 1.26)	
2.613-2.928	-7.84 (-12.47, -3.22)		1.65 (-3.46, 6.75)		5.87 (-5.19, 16.92)		1.84 (-7.34, 11.02)	
2.929-3.410	-9.51 (-14.29, -4.73)		-3.11 (-8.38, 2.16)		0.07 (-11.32, 11.47)		-0.72 (-9.74, 8.31)	
≥3.411	-9.94 (-14.82, -5.05)		-2.36 (-7.90, 3.17)		-3.42 (-15.11, 8.28)		-1.31 (-10.64, 8.02)	
C_{max} (mg/L)		<0.001		0.11		0.18		0.92
≤0.219	Ref.	-	Ref.	-	Ref.	-	Ref.	-
0.220-0.241	-2.61 (-7.16, 1.94)		3.76 (-1.24, 8.76)		-6.32 (-17.19, 4.54)		-1.77 (-10.79, 7.26)	
0.242-0.263	-7.13 (-11.66, -2.59)		1.90 (-3.17, 6.98)		-0.23 (-11.11, 10.65)		1.50 (-7.70, 10.70)	
0.264-0.289	-8.74 (-13.36, -4.11)		-2.42 (-7.76, 2.92)		-7.13 (-18.39, 4.13)		-4.54 (-13.97, 4.90)	
≥0.290	-8.46 (-13.27, -3.64)		-2.01 (-7.61, 3.58)		-8.73 (-20.40, 2.94)		1.72 (-7.49, 10.92)	
C_{24h} (mg/L)		0.003		0.05		0.94		0.77
≤0.042	Ref.	-	Ref.	-	Ref.	-	Ref.	-
0.043-0.049	-3.62 (-8.33, 1.09)		3.11 (-1.86, 8.08)		-0.58 (-11.69, 10.53)		-7.97 (-17.23, 1.30)	
0.050-0.057	-5.99 (-10.70, -1.28)		0.94 (-4.05, 5.94)		0.26 (-10.67, 11.19)		1.85 (-7.33, 11.03)	
0.058-0.072	-6.89 (-11.86, -		-2.78 (-8.00,		-2.93 (-14.58,		-0.37 (-9.51, 8.78)	

	1.93)		2.44)		8.71)			
≥0.073	-7.05 (-12.15, -1.95)		-3.38 (-8.89, 2.12)		0.79 (-11.14, 12.73)		-1.66 (-10.92, 7.60)	
Multivariate associations with eGFR CKD-EPI values	**TFV**		**FTC**		**ABC**		**3TC**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
AUC_{24h} (mg.h/L)		<0.001		<0.001		0.11		<0.001
≤2.355	Ref.	-	Ref.	-	Ref.	-	Ref.	-
2.356-2.612	-3.33 (-6.91, 0.25)		-6.30 (-10.42,-2.18)		5.12 (-5.02,15.25)		3.28 (-7.74,14.31)	
2.613-2.928	-3.42 (-7.06, 0.21)		-9.75 (-13.86,-5.65)		4.26 (-5.94,14.46)		-2.12 (-12.72,8.49)	
2.928-3.407	-5.05 (-8.84, -1.27)		-14.97 (-19.09,-10.85)		0.83 (-9.76,11.43)		-10.59 (-21.29,0.11)	
≥3.408	-12.78 (-16.61, -8.94)		-22.40 (-26.53,-18.27)		-8.79 (-19.41,1.84)		-17.98 (-29.01,-6.96)	
C_{max} (mg/L)		0.003		<0.001		0.25		0.09
≤0.219	Ref.	-	Ref.	-	Ref.	-	Ref.	-
0.220-0.241	1.82 (-1.88, 5.52)		-6.26 (-10.35,-2.17)		1.57 (-8.63,11.77)		4.99 (-6.00,15.99)	
0.242-0.263	-0.41 (-4.09, 3.26)		-9.67 (-13.73,-5.61)		4.60 (-5.56,14.76)		17.37 (6.48,28.26)	
0.264-0.289	0.09 (-3.68, 3.85)		-14.95 (-19.06,-10.83)		3.12 (-7.45,13.70)		1.99 (-9.36,13.33)	
≥0.290	-4.32 (-8.24, -		-22.81 (-		-9.12 (-19.83,1.59)		11.80 (0.91,22.70)	

	0.40)		26.92,-18.71)					
C_{24h} (mg/L)		<0.001		<0.001		0.06		<0.001
≤0.042	Ref.	-	Ref.	-	Ref.	-	Ref.	-
0.043-0.050	-1.77 (-5.23,1.68)		-7.14 (-11.22,-3.05)		6.21 (-3.73,16.16)		2.52 (-8.49,13.52)	
0.051-0.058	-6.09 (-9.80,-2.37)		-10.18 (-14.21,-6.14)		6.08 (-3.63,15.78)		-1.00 (-11.59,9.59)	
0.059-0.072	-7.07 (-10.84,-3.29)		-15.14 (-19.16,-11.12)		-0.97 (-11.75,9.82)		-10.69 (-21.48,0.09)	
≥0.073	-15.23 (-19.11,-11.36)		-22.90 (-27.00,-18.80)		-9.09 (-19.61,1.42)		-18.10 (-28.99,-7.20)	

Table 1. Multivariable association between pharmacokinetic (PK) parameters for each drug and alanine transaminase (ALT) concentrations[1] and between PK parameters for each drug and estimated glomerular filtration rate (eGFR) CKD-EPI* values[2].

*Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

[1]Multivariate models adjusted for age at baseline, gender, ethnicity, use of boosted PIs, efavirenz or nevirapine as part of current regimen, HCV, HBV, current alcohol use, recreational drugs in past 6 months and receipt of lipid lowering drugs.

[2]Multivariate models adjusted for age, gender/race, use of any concomitant medication and use of boosted PIs.