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PLASMA NRTI EXPOSURE AND ASSOCIATIONS WITH SERUM ALANINE AMINOTRANSFERASE IN PEOPLE LIVING WITH HIV

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POPPY
Pharmacokinetic and clinical observations in people over 50

BACKGROUND

Nucleoside reverse transcriptase inhibitors (NRTIs) can induce hepatocyte damage through reduced cell proliferation, mitochondrial toxicity and mitochondrial DNA (mtDNA)- loss. Whilst liver abnormalities are observed in people living with HIV (PLWH) on antiretroviral therapy (ART), correlations of NRTI plasma exposure with markers of liver damage are ill-defined.

AIM: To investigate the associations of tenofovir (TFV), emtricitabine (FTC), abacavir (ABC) and lamivudine (3TC) pharmacokinetics (PK) with alanine aminotransferase (ALT) as part of a large cohort of PLWH.

METHODS

PARTICIPANTS

POPPY is a multicentre, prospective, observational study to examine the effects of ageing on the clinical outcomes of PLWH in UK and Ireland (Figure 1) (Bagkeris et al, Int J Epidemiol 2018). In this current study, we included a selection of patients who were on NRTIs.

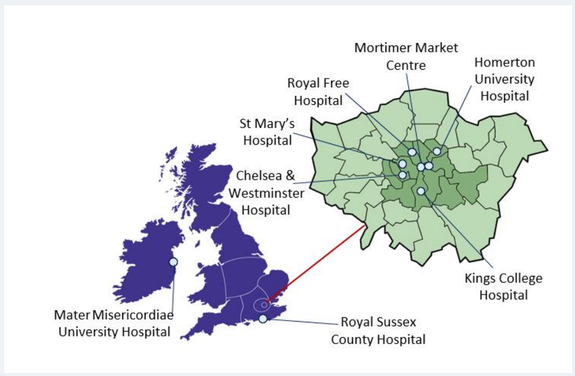

Figure 1: Participating centres in the POPPY study.

ANALYTICAL METHOD TO MEASURE PLASMA NRTIs

One plasma sample from each participant included in the current study was obtained for analysis. Plasma NRTI concentrations were measured by a fully validated method on ultra performance liquid chromatography (ACQUITY, Waters). Briefly, 200 µL plasma were subjected to solid phase extraction (MCX cartridge, Waters) and the elutants were dried under nitrogen stream before being re-constituted in 50 µL water for injection. The NRTI drugs were separated using a C18 BEH column (1.7 µm, 2.1 mm x 100 mm, Waters).

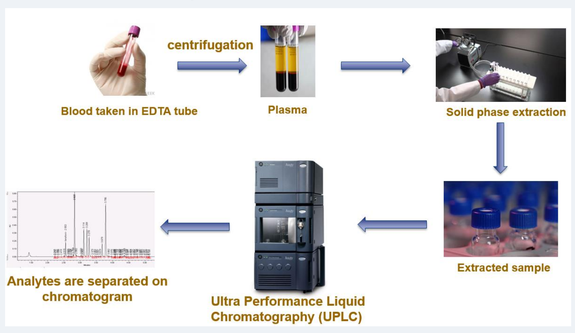

Figure 2: Workflow of analytical method to measure drug concentrations in plasma

POPULATION PHARMACOKINETIC MODELLING

Population PK models were developed to predict PK parameters that included area under the curve (AUC_{24h}), maximum concentration (C_{max}) and trough concentration (C_{24h}). Four covariate factors (weight, age, sex and ethnicity) were assessed in the structural models.

STATISTICAL ANALYSES

Linear regression analysis determined the association between ALT and PK parameters after adjustment for age, gender, ethnicity, current use of boosted protease inhibitors, efavirenz or nevirapine, hepatitis B or C virus co-infection, current use of alcohol, recreational drugs, lipid lowering drugs, and body mass index (BMI).

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RESULTS

BASELINE CHARACTERISTICS

- Most participants were white (90.2%) and male (87.6%) with a median age of 52 (range 23-82) years.
- Of the 488, 452, 92 and 122 participants with PK samples measured for TFV, FTC, ABC and 3TC, median (range) ALT was 30 (6-99), 30 (6-99), 27 (8-89) and 27 (7-89) U/L, respectively.
- A greater proportion of those receiving ABC and 3TC were female compared to those on TFV or FTC. More participants on ABC and 3TC were on boosted PIs compared to those on TFV and FTC. More participants on TFV and FTC were also on efavirenz compared to those on ABC and 3TC, whereas, fewer participants on TFV and FTC were on nevirapine compared to those on ABC and 3TC.
- The remaining characteristics (Table 1) were similarly distributed among participants on each NRTI drug.

	Tenofovir (TFV)		Emtricitabine (FTC)		Abacavir (ABC)		Lamivudine (3TC)	
N	488		452		92		122	
ALT (U/l), median (range)	30	(6, 99)	30	(6, 99)	27	(8, 89)	27	(7, 89)
AUC_{0-24} (mg.h/L) (range)	2.754	(1.548, 9.113)	10.246	(7.064, 31.468)	12.376	(4.604, 26.811)	9.865	(1.010, 47.518)
Cmax (mg/L) (range)	0.255	(0.126, 0.525)	1.125	(0.911, 2.212)	4.158	(1.745, 5.192)	2.358	(1.003, 10.559)
Trough (mg/L) (range)	0.053	(0.025, 0.301)	0.073	(0.035, 0.595)	0.003	(0.000, 0.055)	0.012	(0.000, 1.117)
Clearance (L/h) (range)	49.908	(14.924, 86.153)	19.579	(6.356, 28.443)	46.939	(21.496, 77.727)	30.412	(6.313, 297.040)
Age, median (range)	52	(23, 82)	52	(23, 82)	53	(32, 82)	54	(31, 82)
Gender (%)								
Female	54	(11.1)	47	(10.4)	20	(21.7)	22	(18.0)
Male	434	(88.9)	405	(89.6)	72	(78.3)	100	(82.0)
Race (%)								
Black African	48	(9.8)	43	(9.5)	10	(10.9)	12	(9.8)
White	440	(90.2)	409	(90.5)	82	(89.1)	110	(90.2)
Current use of PIs (%)								
Yes	145	(29.7)	127	(28.1)	35	(38.0)	48	(39.3)
HBV (%)								
Negative	323	(66.2)	303	(67.0)	59	(64.1)	74	(60.7)
Positive	70	(14.3)	60	(13.3)	13	(14.1)	19	(15.6)
Unknown	95	(19.5)	89	(19.7)	20	(21.8)	29	(23.8)
HCV (%)								
Negative	383	(78.5)	351	(77.7)	74	(80.4)	93	(76.2)
Positive	49	(10.0)	45	(10.0)	2	(2.2)	7	(5.7)
Unknown	56	(11.5)	56	(12.4)	16	(17.4)	22	(18.0)
Current use of efavirenz (%)								
Yes	163	(33.4)	158	(35.0)	18	(19.6)	19	(15.6)
Current use of nevirapine (%)								
Yes	55	(11.3)	49	(10.8)	18	(19.6)	26	(21.3)
Current alcohol use (%)								
Yes	407	(83.4)	377	(83.4)	74	(80.4)	106	(86.9)
In the past	47	(9.6)	43	(9.5)	8	(8.7)	5	(4.1)
Use of recreational drugs in the past 6 months (%)								
Yes	159	(32.6)	144	(31.9)	28	(30.4)	35	(28.7)
Use of lipid lowering drugs (%)								
Yes	80	(16.4)	74	(16.4)	19	(20.7)	25	(20.5)

Table 1: Summary of baseline characteristics of people living with HIV (PLWH) who are on nucleoside reverse transcriptase inhibitors (NRTIs).

ASSOCIATION BETWEEN NRTI EXPOSURE AND ALT CONCENTRATION

- In univariate analysis, ALT values inversely correlated with TFV AUC_{24h} (p<0.001), C_{max} (p<0.001), and C_{24h} (p=0.003). These associations were substantially attenuated after adjustment for confounders (Figure 3). Post-hoc analysis suggested that adjustment for BMI explained most of the attenuation.
- A weaker association between FTC PK parameters and ALT could be explained by co-administration of TFV in the regimen. Associations with FTC PK parameters were similar, regardless of whether FTC was or was not included in the regimen (Figure 4).
- No associations were observed between ALT and either ABC or 3TC PK parameters.

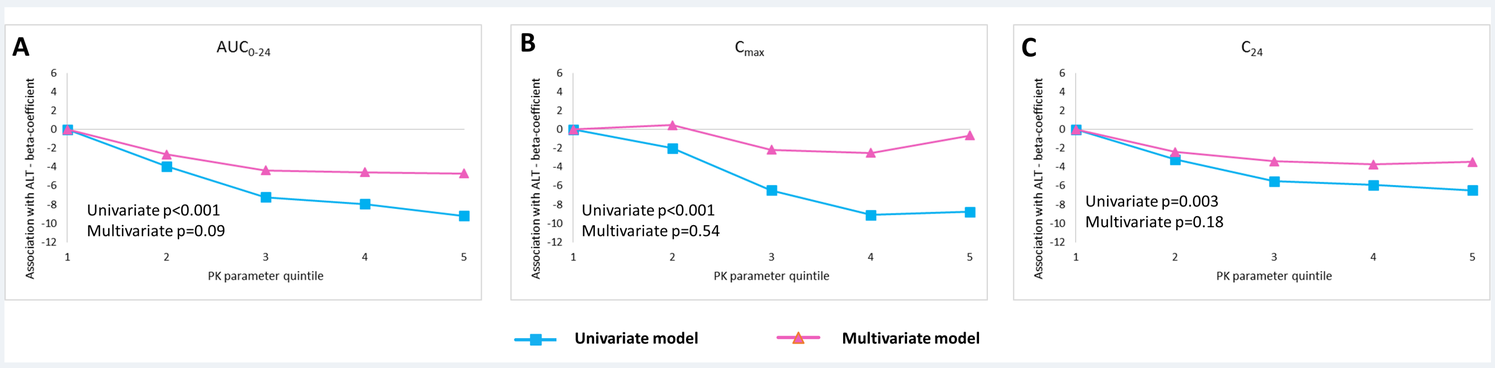

Figure 3: Univariable and multivariable associations between ALT and TFV AUC_{0-24} (A), C_{max} (B) and C_{24} (C) PK parameters. Multivariable model adjusted for age at baseline, gender, ethnicity, body mass index (BMI), use of boosted PIs, efavirenz or nevirapine as part of current regiment, HCV, HBV, current alcohol use, recreational drugs in past 6 months and receipt of lipid lowering drugs

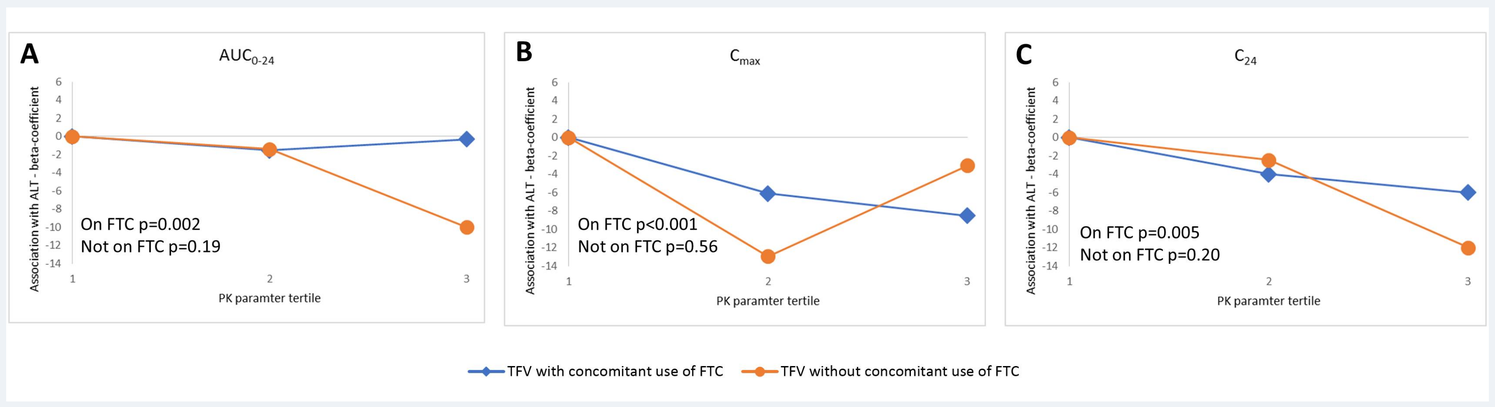

Figure 4: Multivariable association between ALT and TFV PK parameters stratified by concomitant use of FTC in the regimen. (A) TFV with concomitant use of FTC (n=447). (B) FTV without concomitant use of FTC (n=41). Multivariable model adjusted for age at baseline, gender, ethnicity, body mass index (BMI), use of boosted PIs, efavirenz or nevirapine as part of current regiment, HCV, HBV, current alcohol use, recreational drugs in past 6 months and receipt of lipid lowering drugs.

CONCLUSIONS

We have observed a correlation between higher TFV plasma exposure and lower ALT concentrations, but no association between exposure of the other NRTIs and ALT concentration. These observations, however, were strongly attenuated by BMI.