

Effects of age on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring

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Objectives: The pharmacokinetic and pharmacodynamic effects of antiretroviral therapy may differ in older compared with younger subjects with HIV infection. We aimed to assess factors associated with plasma antiretroviral drug exposure, including age, within a large HIV-infected cohort undergoing therapeutic drug monitoring (TDM).

Methods: Data from the Liverpool TDM Registry were linked with the UK Collaborative HIV Cohort (CHIC) Study. All TDM of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) was included and in order to account for different antiretroviral drugs the plasma concentrations were standardized by group measurements according to drug, dosing and timing of TDM. Regression modelling was used to evaluate associations of drug exposure with age and clinical parameters, including hepatic transaminase results and time to antiretroviral treatment modification.

Results: Data from 3589 TDM samples were available from 2447 subjects. The greatest numbers of plasma concentrations were assessed for lopinavir (22.4%), efavirenz (18.5%), atazanavir (17.0%) and saquinavir (11.6%). As age increased, median standardized NNRTI concentrations remained constant, whereas PI concentrations increased (correlation coefficient 0.04, $P=0.033$). In a regression analysis stratified by antiretroviral drug class, standardized plasma concentrations were significantly associated with age for PIs (0.05 increase in standard deviation of drug concentration with each 10 year increase in age, $P=0.044$), but not for NNRTIs or other clinical parameters, including hepatic transaminase results or time to antiretroviral treatment modification.

Conclusions: With increasing age, statistically significant rises in plasma PI exposure, but not NNRTI exposure, were observed. The clinical relevance of this observation merits further investigation.

Keywords: antiretroviral therapy, pharmacokinetics, ageing, cohort, TDM

Introduction

Combination antiretroviral therapy (cART) for HIV infection is one of the major medical achievements of our time. By preventing HIV disease progression, it has reduced the incidence of AIDS and its associated mortality, and has markedly and sustainably improved survival for patients living with HIV.¹ As a consequence, people with HIV are ageing, including those in low- and middle-income countries.²

Antiretroviral drug exposure and treatment outcomes may differ in older versus younger individuals. Regarding drug exposure, older individuals may experience changes in endogenous drug handling, with several elements of drug pharmacokinetics, including absorption,³ distribution,⁴ metabolism⁵ and elimination,⁶ being subject to change. Data from other disease areas suggest that older individuals may require lower doses to achieve therapeutic efficacy and may experience adverse events at lower concentrations.⁷ In the HIV field, plasma concentrations of some HIV protease inhibitors (PIs) are reported to be higher in those aged >40 years.^{8–10}

Regarding treatment outcomes, older individuals starting cART generally experience better virological, but poorer immunological, responses than their younger counterparts,¹¹ with laboratory abnormalities and temporary discontinuations of cART due to toxicities frequently reported.¹²

The aim of this study was to assess antiretroviral plasma drug exposure in a large cohort of HIV-infected subjects undergoing routine therapeutic drug monitoring (TDM) in clinical practice and to assess the association between plasma drug exposure and clinical factors, including age and measures of toxicity.

Methods

Study cohort

Clinical data for this analysis were obtained from the UK Collaborative HIV Cohort (UK CHIC) Study,¹³ with data extracted in 2010. The UK CHIC Study is a collaboration of some of the largest centres for care of HIV-infected individuals in the UK, with each centre providing electronic data in a standardized format that includes demographic parameters, antiretroviral treatment history and laboratory parameters.

Pharmacokinetic data were obtained from the Liverpool TDM Registry, which contains data on samples from HIV-infected subjects in whom routine TDM was requested between 1996 and 2010. For each sample, details of antiretroviral dose, dosing frequency and time between sampling and last ingestion of medication are routinely available. For the purpose of this analysis, TDM Registry samples from 1999 to 2005 and from 2008 to 2010 were available; it was not possible to obtain results for the intervening time period as cohort data had not been stored in an electronic format. Only TDM samples assessing PIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs) were included. Ethics approval was granted via the National Research Ethics Service with the following reference numbers: UK CHIC (West Midlands, UK), MREC/00/7/47; and Liverpool TDM Registry (North West, UK), 05/MRE08/67.

In order to perform this analysis, the UK CHIC and Liverpool TDM datasets were merged and patients present in both datasets matched using date of birth, HIV centres attended and antiretroviral drugs. Pharmacokinetic data for 1798 subjects from 1999–2006 had previously been linked to UK CHIC patients.¹⁴ When matching patients in the more recent Liverpool TDM dataset, 873 people were matched with UK CHIC patients. Combining these matched patients in the two Liverpool TDM Registry datasets resulted in a total of 2574 matched patients (as some patients

were present in both). Six patients were omitted from the analysis as TDM was for agents other than PIs or NNRTIs. Where repeated measures of a drug were made within a 9 month interval, only the original measurement was retained.

In order to allow assessments for potential toxicity based on the data available within the UK CHIC database, laboratory data (hepatic transaminases) and clinical data (antiretroviral treatment modification) were included in the analysis with the hepatic transaminase measurements [alanine transaminase (ALT) or aspartate transaminase (AST)] recorded nearest in time to each TDM utilized.

Laboratory measurements

Plasma antiretroviral concentrations were measured by validated HPLC–mass spectrometry as previously described by the Department of Pharmacology, University of Liverpool.¹⁵ This laboratory participated in an external quality assurance programme.¹⁶

Statistical analysis

Due to the large variability in plasma concentrations of different antiretroviral drugs and the time of a drug assessment post-dose, plasma concentration was standardized for all analyses. To achieve this, time post-dose was split into five intervals to represent different times in the plasma concentration–time curve (peak, trough etc.). These intervals were defined differently according to whether a drug was being taken on a 12 or 24 h dosing frequency, as shown in Table S1 (available as Supplementary data at JAC Online). Within each of these time intervals, subjects were grouped by antiretroviral drug and values were then standardized within each resulting subgroup by subtracting the group mean concentration and dividing by the standard deviation.

When looking for associations between continuous variables (plasma concentration, age and hepatic transaminases) and time to treatment modification, Spearman's correlation coefficient was calculated. Generalized estimating equations (GEEs) were used, firstly on the complete dataset and then stratified by antiretroviral drug class. GEEs were also used in a linear regression of the effects of standardized concentration on hepatic transaminases (ALT and AST). The use of GEEs allowed us to accommodate correlation arising between outcome measures due to repeated measures in one individual, which would not be possible in a normal linear regression. Finally, a Cox proportional hazards model was fitted to determine whether any effect of plasma concentration on (i) time to treatment discontinuation or switch due to virological failure and (ii) time to treatment discontinuation or switch for reasons other than virological failure could be found.

Results

Study cohort

There were 2447 patients included in the analysis (after omitting patients who were not found to be on any form of cART or who were not reported to be taking the TDM drug for which they were assessed) with a total of 3589 plasma concentration assessments. The characteristics of the group as a whole and by age group, at first plasma drug exposure assessment, are shown in Table S2 (available as Supplementary data at JAC Online).

The majority of TDM measurements were made in those aged between 35 and 50 years, with the fewest made in those aged >50 years, reflecting the characteristics of the HIV population in these centres. The majority of drug exposure assessments were made in men who have sex with men (MSM) of white ethnicity, who were under follow-up in the UK CHIC Study prior to

2000. Approximately 4% of assessments were performed in those found to be positive for hepatitis B prior to a drug exposure assessment and ~5% were in those positive for hepatitis C. Hepatic transaminase results were outside the normal range (≥ 40 IU/L) in almost 30% of individuals.

The median time spent on the drug being assessed in the plasma drug exposure measurement was higher in older age categories. The median (IQR) time on the drug in months in those aged 16–34 years was 4.8 (1.8–14.4) compared with 9.6 (2.4–25.2) and 16.2 (4.2–39) in those aged between 35 and 50 years and those aged >50 years, respectively ($P < 0.0001$).

Plasma drug concentration assessments

Of the 3589 plasma drug exposure assessments, 2562 (71.4%) were performed for drugs that were PIs and 1027 (28.6%) for NNRTIs. The number of plasma concentration measurements for each drug is shown in Table S3 (available as Supplementary data at JAC Online). The most tested drug was lopinavir, with efavirenz being the most tested NNRTI. There were 217 people who had a drug exposure assessment for both a PI and an NNRTI. For all TDM assessments, ritonavir was being utilized as a pharmacoenhancer.

Standard error in standardized drug concentration assessment was generally higher the longer the TDM assessment was performed post-drug intake [Table S1 (available as Supplementary data at JAC Online)]. This trend was present for both PIs and NNRTIs.

Factors associated with drug exposure

As age increased, the median standardized plasma concentration of NNRTIs remained fairly constant ($P = 0.13$ for differences in age categories 16–34, 35–50 and >50 years). Conversely, a weak linear correlation between age and standardized concentration was observed for PIs (correlation coefficient 0.04, $P = 0.033$; Figure 1).

In a regression analysis using GEEs, a significant effect of age and antiretroviral drug class on drug concentration was detected, which remained when adjusted for other factors ($P = 0.021$, data not shown). When regression analyses were stratified by antiretroviral drug class, a small but statistically significant increase of 0.05 standard deviations in drug concentration with each 10 year increase in age was present for PIs ($P = 0.044$) (Table 1).

Interestingly, for NNRTI exposure female gender and black or unknown/other ethnicities were associated with greater standardized exposure, whereas time on drug being tested was associated with lower standardized exposure. When stratifying for NNRTI drug type, these effects only remained statistically significant for efavirenz (female gender, $P = 0.004$; black ethnicity, $P = 0.003$; unknown ethnicity, $P = 0.032$; and time on drug prior to TDM assessment, $P = 0.002$).

For PIs, unknown/other ethnicity was associated with lower standardized plasma exposure. The strongest associations between age and standardized plasma drug concentrations

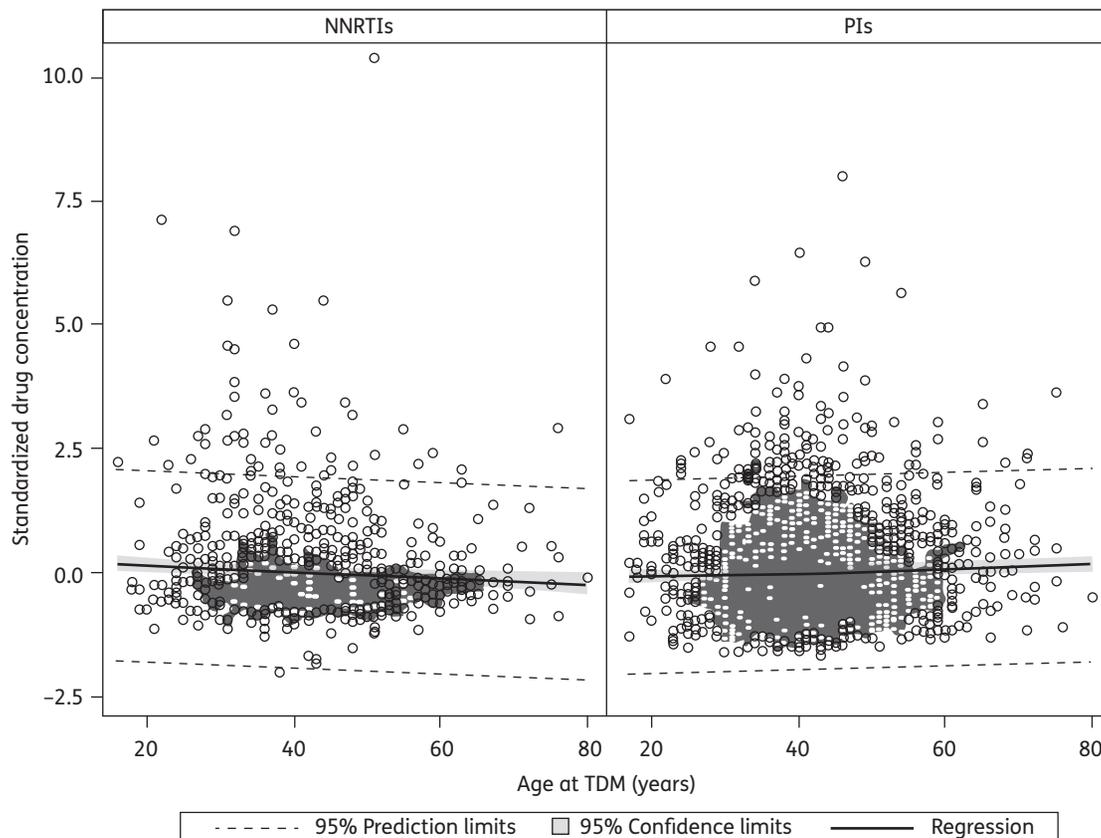


Figure 1. Scatter plot of standardized drug concentration by age for different antiretroviral drug classes.

Table 1. Factors associated with standardized plasma drug concentration stratified by antiretroviral drug class

	NNRTIs				PIs			
	unadjusted		adjusted		unadjusted		adjusted	
	β (95% CI)	P value						
Age								
per 10 years	-0.06 (-0.13, 0.00)	0.06	-0.002 (-0.06, 0.06)	0.96	0.04 (-0.00, 0.09)	0.064	0.05 (0.00, 0.10)	0.044
Gender								
male	0.00				0.00		—	—
female	0.47 (0.29, 0.64)	<0.0001	0.29 (0.08, 0.51)	0.009	0.01 (-0.09, 0.11)	0.87		
Ethnicity								
white	0.00		0.00		0.00		0.00	
black	0.42 (0.26, 0.57)	<0.0001	0.21 (0.02, 0.40)	0.029	0.03 (-0.07, 0.13)	0.55	0.06 (-0.05, 0.16)	0.29
other/unknown	0.33 (0.12, 0.54)	0.002	0.22 (0.02, 0.42)	0.033	-0.18 (-0.30, -0.05)	0.005	-0.17 (-0.29, -0.04)	0.008
Exposure								
MSM	0.00		0.00		0.00			
heterosexual	0.39 (0.24, 0.53)	<0.0001	0.03 (-0.18, 0.24)	0.79	0.02 (-0.08, 0.11)	0.70		
other/unknown	0.31 (0.10, 0.52)	0.004	0.07 (-0.14, 0.27)	0.53	0.08 (-0.06, 0.22)	0.27		
Year of sample								
1999–2002	0.00				0.00			
2003–05	-0.03 (-0.22, 0.15)	0.74	—	—	-0.04 (-0.13, 0.06)	0.44	—	—
2006–09	-0.08 (-0.26, 0.09)	0.34			-0.09 (-0.20, 0.02)	0.12		
Current viral load								
log ₁₀ copies/mL	-0.01 (-0.09, 0.07)	0.81	—	—	-0.001 (-0.04, 0.04)	0.95	—	—
Current CD4 count								
per 100 cells/mm ³	-0.05 (-0.07, -0.02)	0.0004	—	—	-0.01 (-0.03, 0.01)	0.3	—	—
Hepatitis B								
negative	0.00				0.00			
positive	0.35 (-0.07, 0.77)	0.10	—	—	0.05 (-0.15, 0.24)	0.64	—	—
not tested	0.15 (0.02, 0.29)	0.024			0.06 (-0.03, 0.14)	0.20		
Hepatitis C								
negative	0.00				0.00			
positive	0.29 (-0.16, 0.73)	0.21	—	—	0.20 (-0.02, 0.43)	0.070	—	—
not tested	0.10 (-0.03, 0.24)	0.13			0.05 (-0.04, 0.14)	0.28		
Time on TDM drug								
per 6 months	-0.02 (-0.03, -0.01)	0.003	-0.01 (-0.02, -0.00)	0.048	-0.01 (-0.02, 0.01)	0.35	—	—
Time on antiretroviral therapy								
per 1 year	-0.01 (-0.02, 0.00)	0.14	—	—	0.002 (-0.01, 0.01)	0.63		

β , estimated mean change in standardized plasma concentration.

were for ritonavir measurements compared with other PIs ($P < 0.001$) and saquinavir measurements compared with other PIs ($P = 0.015$).

Associations with markers of toxicities

No correlation was observed between hepatic transaminase results and standardized drug concentration. The Spearman correlation coefficients of ALT and AST with standardized drug concentration were both -0.04 ($P = 0.059$ and $P = 0.24$, respectively).

A large proportion of subjects included in this analysis modified antiretroviral therapy subsequent to a TDM assessment; in total 1774 plasma drug concentration measurements (48.6%) were followed by a treatment modification. Of these, 329 modifications (18.5%) were for reasons other than virological failure.

Increased age was associated with an increased time to treatment modification for treatment changes due to viral failure and modifications for other reasons, with a median (IQR) time to treatment modification of 5.2 (1.6–14), 7.2 (2.3–20) and 7.6 (2.6–23) months for those aged 16–34, 35–50 and >50 years, respectively ($P < 0.001$). A statistical interaction between age and standardized drug concentration was investigated, but was not found to be present when treatment modifications were due either to viral failure or to other causes.

Discussion

In HIV-infected subjects undergoing routine TDM in a clinical setting, we have observed a statistically significant association between standardized plasma drug concentration of PIs and age, with greater drug exposure associated with increasing age, albeit with a low correlation coefficient, but no association between standardized plasma concentration of NNRTIs and age. However, this association was not associated with any blunt markers of antiretroviral drug toxicity, such as hepatic transaminase results or time to treatment modification and hence the clinical relevance of this observation remains to be determined.

However, we postulate that this effect of age on PI plasma drug exposure may have clinical relevance in specific circumstances. For instance, in a subject with other risk factors for increased plasma drug exposure, such as a subject receiving concomitant medication that may interact and potentially increase the exposure of other agents such as the HIV PIs, the effects of increasing PI drug exposure with age may be of clinical relevance.

Data on comorbidities, non-antiretroviral concomitant medication and several clinical parameters that may affect plasma drug exposure, such as body mass index, are not available from the databases we have analysed, which limits the interpretation of our results. Future work incorporating these and other such clinical parameters may allow further modelling in order to ascertain the specific clinical scenarios, similar to the hypothetical scenario outlined above, where the effects of age on plasma drug exposure may have the greatest clinical relevance. Our analysis is also limited by the observational nature of the TDM dataset, whereby subject selection is inherently biased. However, given the large nature of this dataset, our novel observation reporting a signal of ageing being associated with PI plasma exposure sets the scene for future work to confirm these observations in formal pharmacokinetic studies. On the other hand, due to the large size of our dataset, associations

we have observed may have arisen by chance. However, given that these findings are scientifically plausible, we consider they justify further investigation.

We did not observe any correlation between measures of drug toxicity, such as hepatic transaminase results or time to treatment modification, and antiretroviral drug exposure. We chose to assess these markers of potential drug toxicity as they were readily available parameters within the datasets that were utilized for this analysis. Although this lack of observation could be due to a true lack of toxicity being present, other, more sensitive markers of toxicity, such as patient-reported side effects and adverse events captured in real time, may have revealed associations with drug exposure.

Female gender and black ethnicity were associated with greater standardized plasma efavirenz exposure. Such associations between gender and ethnicity with plasma efavirenz exposure have previously been described.^{14,17,18} Longer duration of efavirenz therapy was associated with lower standardized exposure, which we hypothesize may be due firstly to an early autoinduction effect of some NNRTIs whereby an agent, via induction of hepatic CYP isoenzymes, increases its own clearance,¹⁹ secondly to the possibility that individuals with greater plasma exposure may have switched efavirenz therapy owing to toxicity without TDM, and thirdly to the potential for weight gain following initiation of cART.

As recommended by current treatment guidelines,²⁰ in clinical practice most HIV PIs are administered with a pharmacoenhancer, generally ritonavir, which acts as a CYP450 enzyme inhibitor, creating a more favourable dosing profile and increased antiretroviral activity of the PI. Hepatic metabolism of drugs may wane with ageing.^{5,21} Therefore, the effects of CYP450 enzyme inhibition may be greater in older individuals. We hypothesize that our observation of an association with increasing age and greater PI plasma exposure, but not NNRTI exposure, may be due to this potential for greater pharmacoenhancement of PIs in older subjects, such effects being less relevant to antiretroviral agents whose plasma exposure is less dependent on CYP450 enzyme inhibition. Strengthening this hypothesis is our observation that a stronger effect of age was observed between standardized plasma concentration of ritonavir measurements compared with other PIs.

In summary, by linking a well characterized and established clinical cohort with our TDM Registry we have been able to evaluate important associations between plasma drug exposure and age, which may assist in the design of future work assessing the effects of lifelong antiretroviral therapy in subjects ageing with HIV infection.

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UK Collaborative HIV Cohort Study

Steering committee

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Transparency declarations

None to declare.

Disclaimer

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Supplementary data

Tables S1, S2 and S3 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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