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A Comparative Analysis of Risk Factors Associated With Renal Impairment and Highly Active Antiretroviral Therapy

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Abstract

Background: The effect of boosted protease inhibitors (PI) on renal function is unclear.

Methods: We assessed and compared the risk of developing renal impairment in individuals commencing 3 first line PI-based regimens vs a non-nucleoside reverse transcriptase inhibitor- based regimen. Patients commencing efavirenz, darunavir, atazanavir or lopinavir with 2 nucleos(t)ide reverse transcriptase inhibitors from June 2006 - February 2010, with baseline eGFR>60ml/min per 1.73m^2 were included. Univariate and adjusted Cox's proportional hazards regression models were used to examine likelihood of developing renal impairment (defined as eGFR< 60ml/min per 1.73m^2).

Results: 386 of 2115 treated individuals developed renal impairment over 2680 person years of follow up. By univariate analysis, female gender (HR 1.51, p 0.002), baseline age (p<0.001), baseline eGFR (p<0.001), darunavir (HR 1.53, p<0.001), atazanavir (HR 1.27, p 0.036), lopinavir (HR 1.71, p<0.001), prior tenofovir exposure (HR 1.68, p<0.001), prior indinavir exposure (HR 2.03, p<0.001) and total duration of tenofovir exposure (HR 1.09, p<0.001) were associated with an increased risk of renal impairment. By multivariate analysis, treatment with atazanavir (HR 1.52, p 0.004) and lopinavir (HR 1.61, p<0.017) but not darunavir (HR 1.31, p 0.108) were associated with an increased risk of renal impairment compared with efavirenz.

Conclusion: There was a significantly increased risk of developing renal impairment associated with atazanavir and lopinavir independent of exposure to tenofovir.

Keywords: Boosted protease inhibitors; Renal impairment; Atazanavir; Daruvanvir; Lopinavir; Tenofovir

Introduction

In the era of Highly Active Antiretroviral Therapy (HAART), there has been a reduction in mortality and morbidity associated with renal disease, including HIV-associated nephropathy, HIV-associated immune complex kidney disease and thrombotic microangiopathy [1,2]. Conversely, as those individuals infected with HIV achieve a longer survival, the burden of chronic kidney disease (CKD) is increasing. This is particularly in the context of increased traditional risk factors for CKD including cardiovascular disease, hypertension and diabetes mellitus [3]. There is a complex interplay between HAART and the kidneys, with recovery of kidney dysfunction associated with effective suppression of HIV and associated reductions in immune activation and inflammation. Immune function as measured by the increase in CD4 count has a less straightforward correlation with kidney function over time [4-6]. Several biomarkers are available for monitoring renal function but there is no gold standard which has been validated for use in the context of HIV infection [7]. Although Creatinine based estimates of glomerular filtration rate (eGFR) have not been validated in the HIV population, they have been widely used in clinical practice to measure renal function [8]. There is data to support the use of the MDRD formula for calculation of eGFR in the treated HIV population [9].

Cohort studies have demonstrated that individuals treated with HAART may experience a decline in eGFR over time [6,10,11]. Data from the EUROSIDA cohort has implicated a cumulative exposure to the individual antiretroviral (ARV) agents tenofovir (TFV), indinavir (IND), atazanavir (ATZ) and lopinavir (LPV) with a significantly increased risk of developing chronic kidney disease (CKD) [10]. To date, there has been no data published in the literature on the risk of chronic renal impairment with the newer boosted PI DRV. A meta-analysis of 17 studies has shown TFV to be associated with a statistically significant, but clinically modest, risk of impairment in renal function [12].

An increased risk of TFV associated renal dysfunction with concomitant use of ritonavir boosted protease inhibitors (PIs) has been described [13-15]. Data from the EUROSIDA cohort implicated concomitant use of ATZ and TFV with a 41% increased incidence of CKD per year of exposure [10].

The aim of this study was to assess and compare the risk of developing renal impairment in individuals commencing HAART including the first line ritonavir (r) boosted PIs ATZ, LPV and darunavir (DRV) and to compare this with a non nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) based regimen. We aimed to assess the impact of the PIs on renal function having adjusted for past and total duration of TFV exposure.

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Methods

Subjects

We performed a retrospective cohort analysis of HIV-infected individuals at the Chelsea and Westminster Hospital during the study period 1st June 2006 to 28th February 2010. The Chelsea and Westminster Hospital is a large tertiary HIV treatment centre. Demographic and clinical data, treatment history and full laboratory results are held on a central database. This database was interrogated in order to identify individuals commencing HAART containing with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and either EFV, ATZ/r, LPV/r or DRV/r from 1st June 2006 to 28th February 2010. To ensure full case ascertainment, this record was cross checked with a separate database of HIV treatment held by the pharmacy department. Individuals were included in the study if they had 2 available eGFR readings measured which were > 60 ml/min per 1.73m^2 prior to commencement of HAART.

Measurements

Renal impairment was defined as first eGFR < 60 ml/min per 1.73m^2. The modification of diet in renal disease (MDRD) formula was used to calculate eGFR.

CD4 count, HIV viral load, serum creatinine and eGFR were measured 3-6 monthly at routine outpatient follow up care and at the occurrence of clinical events. Viral hepatitis serology was measured on an annual basis and hepatitis B Surface Antigen (Hep B SAg) and Hepatitis C Antibody (Hep C Ab) status was available at the beginning of the study period.

A case notes review was performed to identify traditional risk factors for renal disease in a randomly selected group who developed renal impairment within the study using probability sampling. A simple random sampling without replacement was used to randomly select patients. The traditional risk factors included diabetes mellitus (diagnosis recorded in notes or patient on antihyperglycaemic medications), hypertension (SBP>140mmHg, DBP>90mmHg or patient on antihypertensive medications), renal stones (diagnosis recorded in notes or based on radiology), cardiovascular disease (on medication for symptomatic angina or documented history of myocardial infarction, stroke, angioplasty, coronary artery bypass graft or carotid endarterectomy), peripheral vascular disease (documented history of symptomatic claudication, significant vessel occlusion on arterial dopplers/angiogram, angioplasty, bypass grafting), nephrotoxic drugs, chemotherapy and sepsis.

Statistical analysis

Qualitative data are described as numbers with percentages while quantitative data that were Gaussian normal are described as mean with standard deviations. Quantitative data that were non Gaussian are described as median with inter-quartile range.

Renal impairment was defined as first eGFR < 60 ml/min per 1.73m^2. Univariate and multivariate Cox's proportional hazards regression models were used to derive factors that showed likelihood of eGFR < 60 ml/min per 1.73m^2 since starting HAART with 2NRTI+ATZ/r, 2NRTI+DRV/r, 2NRTI+LPV/r or 2NRTI+EFV.

Person days of follow-up were estimated from first starting either ATZ, DRV, LPV or EFV to either abnormal eGFR (<60ml/min per 1.73m^2) or death. The data were censored at either stopping the PI/EFV based regimen or end of cohort which was defined to time when data were extracted from our cohort (28th Feb 2010). The data were analysed using the PHREG procedure in SAS version 9.1. Baseline CD4 cell count and baseline viral load (VL) were defined as that available at the time of starting 2NRTIs+ PI/EFV based regimen. Previous exposure to TFV or IND was defined as exposure any time prior to starting the PI/EFV based HAART regimen.

Variables with quantitative data were categorised using the median and inter-quartile ranges (IQR) to derive grouped categories. A separate category was created for all variables with missing data. This ensured no degrees of freedom were lost when building multivariate models. Univariate Cox's proportional hazards models with single variables were firstly used to estimate likelihood of abnormal eGFR. All variables found to be significant ($p<0.05$) in univariate Cox's proportional hazards regression model were then used to build a multivariate model, which allowed the risk of a particular prognostic variable to be assessed while controlling for the others in the model. The final multivariate model presented was tested for its proportional hazards distributional assumptions using the complimentary log-log plot where data were plotted on the x-axis of the log of survival function and on the y-axis the log of the negative log of the estimated survivor function [(log(-logS(t)] and the final model was adjusted for gender, age at start of HAART, ethnicity, baseline eGFR, baseline CD4 count, baseline VL, baseline Hep C Ab and Hep B S Ag status, prior exposure to IND / TFV and total ever cumulative duration of TFV exposure, for possible confounding or residual effects.

A χ^2 test was used to test for an association between the EFV and PI group and the traditional risk factors for renal disease in a subgroup of individuals who dropped eGFR less than 60 ml/min per 1.73m^2 and who had been randomly selected.

All statistical analyses were carried out in SAS version 9.1 and all significance tests performed are two tailed.

Results

2115 individuals had an eGFR > 60 ml/min per 1.73m^2 at baseline and were commenced on a HAART regimen containing EFV, ATZ/r, LPV/r or DRV/r with two NRTIs during the study period. Table 1 illustrates baseline demographics of the overall cohort. The cohort contained a majority of Caucasian men and a high proportion of individuals already treatment experienced as shown by a proportion of 60% who had a VL<50 copies at baseline. 86% of the cohort had TFV included in their NRTI backbone.

386 (18%) individuals developed renal impairment during a total of

Baseline Demographics	Overall Cohort n= 2115
Gender: n (%) Male Female	 1842 (87) 273 (13)
Ethnicity: n (%) Caucasian Black African Other	 1520 (72) 259 (12) 336 (16)
Age (yrs) : mean (SD)	43 (9.5)
Median baseline CD4 (cells/mm^3)(IQR)	383 (259 to 550)
% with VL<50 copies/ml at baseline	60

Table 1: Baseline demographics of overall cohort.

Risk factor for renal impairment (unit)	Total number of Subjects=2115		No. subjects who dropped eGFR<60 ml/min per 1.73m^2 (%)	Hazard Ratio (95% CI)	P value
Sex	Female Male	273 1842	68 (24.9) 318 (17.3)	1.51 (1.16 to 1.96) 1	<0.001
Baseline age (years)	>48.19 42.48-48.19 36.75-42.49 <36.76	528 529 529 529	4 (17.4) 70 (22.4) 56 (10.6) 256 (16.8)	2.75 (2.03 to 3.73) 2.06 (1.50 to 2.82) 1.30 (0.92 to 1.82) 1	0.002
Ethnicity	Other Black Africans Caucasian	336 259 1520	74 (22) 56 (21.6) 256 (16.8)	1.29 (0.98 to 1.68) 1.28 (0.96 to 1.71) 1	0.090
Baseline CD4 (cells/mm^3)	Missing <258 258-381 382-549 >550	11 526 528 525 525	1 (9.1) 106 (20.2) 83 (15.7) 103 (19.6) 93 (17.7)	0.47 (0.07 to 3.40) 1.12 (0.85 to 1.48) 0.88 (0.65 to 1.18) 1.12 (0.84 to 1.48) 1	0.356
Baseline viral load (copies/ml)	Missing >500 50-500 <50	24 456 368 1267	2 (8.3) 73 (16) 63 (17.1) 248 (19.6)	0.43 (0.11 to 1.75) 0.79 (0.61 to 1.03) 0.85 (0.64 to 1.12) 1	0.155
Baseline eGFR ml/min per 1.73m^2	61-69 69-78 79-84 >84	528 550 479 558	251 (47.5) 69 (12.6) 35 (7.3) 31 (5.6)	10.42 (6.96 to 15.60) 2.42 (1.54 to 3.79) 1.38 (0.83 to 2.30) 1	<0.001
Baseline hepatitis C Ab status	Positive Negative	170 1945	32 (18.8) 354 (18.2)	1.11 (0.78 to 1.60) 1	0.174
Baseline hepatitis B Surface Antigen status	Positive Negative	71 2044	25 (35.2) 361 (17.7)	1.41(0.88 to 2.26) 1	0.180
Previous indinavir exposure	Yes No	230 1885	75 (32.6) 311 (16.5)	2.03 (1.58 to2.62) 1	<0.001
Previous tenofovir exposure	Yes No	835 1280	190 (14.8) 196 (23.5)	1.68 (1.38 to 2.05)	<0.001
Tot duration tenofovir exposure ¥	Median exposure 2years (IQR 1-4yrs)			1.09 (1.06 to 1.12)*	<0.001
ATZ/r exposure	Yes No	488 1627	276 (17.0) 110 (22.5)	1.2 (1.02 to 1.58) 1	<0.036
DRV/r exposure	Yes No	415 1700	283 (16.7) 103 (24.8)	1.54 (1.22 to 1.92) 1	<0.001
LPV/r exposure	Yes No	214 1901	321 (16.9) 65 (30.4)	1.71 (1.38 to 2.24) 1	<0.001
EFV exposure	Yes No	1245 870	204 (23.5) 182 (14.6)	0.6 (0.47 to 0.73) 1	<0.001
Combinations with	Combination LPV/r DRV/r ATZ/r EFV	227 369 287 111 1121	68 (30.0) 80 (21.7) 61 (21.3) 27 (24.3) 150 (13.4)	1.97 (1.48 to 2.62) 2.07 (1.38 to 3.12) 1.71 (1.27 to 2.31) 1.65 (1.26 to 2.17) 1	<0.001

¥ Includes current TFV exposure

* For every additional year of TFV exposure, risk of developing eGFR<60 ml/min per 1.73m^2 increased by 9%

HAART highly active antiretroviral therapy NRTI nucleos(t)ide reverse transcriptase inhibitor ATZ atazanavir DRV darunavir LPV lopinavir EFV efavirenz r ritonavir TFV tenofovir IND indinavir eGFR estimated glomerular filtration rate

Table 2: Univariate Cox's proportional hazards regression model showing likelihood of eGFR< 60 ml/min per 1.73m^2 since starting HAART with 2NRTI+ATZ/r, 2NRTI+DRV/r, 2NRTI+LPV/r or 2NRTI+EFV.

2680 person years of follow up. Table 2 contains the results of univariate analyses and reveal that female gender, older age, lower baseline eGFR, previous TFV exposure, previous IND exposure, total TFV exposure, ATZ/r, LPV/r and DRV/r exposure during the study were all associated with a significantly increased hazard of renal impairment. EFV was associated with a decreased hazard of renal impairment on univariate analysis when compared with the PI group as a whole. Ethnicity, baseline CD4, baseline VL, positive Hep B S Ag status and Hep C Ab status were not associated with renal impairment.

A case note review of 160 randomly selected individuals who developed renal impairment during the study, revealed no significant differences in traditional risk factors for renal disease between those receiving EFV and those treated with PIs (Table 3).

On multivariate analysis, LPV/r (HR 1.69 [95% CI 1.1 to 2.6], p 0.017) and ATZ (HR 1.52 [95% CI 1.14 to 2.03] p 0.004) but not

DRV/r (HR 1.31 [95% CI 0.94 to 1.81], p 0.108) were associated with a significantly increased risk of the development of renal impairment (Table 4).

Discussion

Renal disease associated with HIV infection is often insidious with an initial asymptomatic stage. Measurement of eGFR and urine dipstick for protein is routinely performed in the HIV outpatient setting to aid early diagnosis of renal disease. This study confirmed that individuals treated with HAART could develop renal dysfunction and that the risk appeared to be greater in those treated with LPV/r and ATZ/r. This risk was still significant when baseline eGFR, baseline age, previous exposure to TFV and total duration of TFV exposure was adjusted for in the multivariate model. In this study, traditional risk factors for renal disease were thought not to be a confounding factor as evidenced by the non-significant difference in traditional risk factors seen between the EFV and the PI treated groups who developed renal impairment during the study (Table 3).

Data from the randomized controlled trial ACTG 5202 showed a statistically significant modest increase risk in creatinine clearance over 96 weeks with TFV and emcitrabine (Truvada) and ATZ/r taken in combination compared with the truvada/ EFV arm of the study [15]. In a non-randomised clinical trial including both naive and treatment experienced patients commencing a new PI or non- nucleoside reverse transcriptase inhibitors (NNRTI) based regimen, Goicoechea et al. [14] showed that over 48 weeks, those on TFV/PI (PI choice was LPV/r in 75% of cases) had a 3.7 times increased risk developing significant renal function decline compared with those on TFV/NNRTI combination.

	n (%)		
Traditional risk factor	#EFV group n=50	#PI group n=110	p value
Diabetes	10 (20)	14 (13)	0.34
Hypertension	16 (32)	22 (20)	0.15
Renal stones	0 (0)	7 (6)	0.16
Cardiovascular disease s	2 (4)	11 (10)	0.33
Peripheral vascular disease	3 (6)	6 (5)	0.82
Nephrotoxic drugs	22 (44)	45 (41)	0.84
Chemotherapy	1 (2)	14 (13)	0.06
Sepsis	0 (0)	6 (5)	0.22

#out of the 386 who developed renal impairment during the study EFV

Table 3: Comparison of traditional risk factors for renal impairment in the efavirenz (EFV) vs protease inhibitor (PI) group.

	Total duration of follow up (patient years)	¶ Hazard Ratio (95% CI)	P Value
LPV/r	267	1.69 (1.1 to 2.60)	0.017
ATZ/r	562	1.52 (1.14 to 2.03)	0.004
DRV/r	451	1.31 (0.94 to 1.81)	0.108
EFV	1400	1	

¶ adjusted for Gender, Age at start of HAART, ethnicity, baseline eGFR, baseline CD4 count, baseline viral load, baseline Hepatitis C Antibody status, Hepatitis B Surface Antigen status and prior exposure to tenofovir/indinavir and total duration of tenofovir exposure

HAART highly active antiretroviral therapy NRTI nucleos(t)ide reverse transcriptase inhibitor ATZ atazanavir DRV darunavir LPV lopinavir EFV efavirenz r ritonavir eGFR estimated glomerular filtration rate

Table 4: Multivariate cox's proportional hazards regression model showing likelihood of eGFR < 60 ml/min per 1.73m^2 since starting HAART with 2NRTI+ATZ/r, 2NRTI+DRV/r, 2NRTI+LPV/r or 2NRTI+EFV.

Of note, DRV/r was not significantly associated with the risk of development of renal impairment by multivariate analysis. In the ARTEMIS trial, TFV was included in the background regimen of treatment naive patients commencing HAART containing either LPV/r (n=346) or boosted DRV 800mg once daily (n=343). No serious renal adverse events and no treatment discontinuations due to renal adverse events were reported in over 96 weeks in either treatment arm [16].

The mechanism of potential chronic renal toxicity associated with LPV/r and ATZ/r is unclear. There are case reports of renal stones and acute interstitial nephritis associated with ATZ/r but this is relatively rare [17-19]. It is known that co-administration of DRV, LPV and ATZ lead to increase in TFV plasma levels up to 30% [20]. There is conflicting data regarding the role of ritonavir induced inhibition of the tubular efflux of TFV through interference with MRP2/4 function in proximal tubule cells, as a mechanism for PI induced TFV toxicity [21-23]. Bierman et al. [24] showed that ATZ, LPV and ritonavir are potent blockers of other transporters including multidrug resistance 1 p glycoprotein and multidrug resistant protein 1 which are normally involved in efflux of drugs from cells. This may explain a mechanism of accumulation of drugs including TFV in cells leading to nephrotoxicity. Tong et al. [20] reported that ATZ/r and LPV/r induced suppression of P glycoprotein in enterocytes may increase absorption and systemic exposure of TFV.

Our study did not examine the effects on eGFR of switching from one PI to another or to an appropriate other class of ARV. However previous data from Mocroft et al. [10] revealed that on multivariate analysis, the incidence rate ratio of those who had previously taken but were not currently receiving ATZ and LPV, there was no significantly increased incidence of CKD compared with those who had never taken ATZ and LPV. Due to the high proportion of individuals that had TFV as part of the NRTI backbone in our study at baseline, and the limited long term follow up, we were unable to assess the effect of TFV exposure on subsequent recovery of renal function. Wever et al. [25] presented data suggesting TFV related renal toxicity was incompletely reversible in up to 58% of cases. Campbell et al. [26] examined eGFR slopes prior to, during and post TFV exposure and observed that older patients with lower baseline eGFR and other risk factors for CKD, including co-morbidities, were less likely to recover renal function post cessation of TFV. They suggested that patients with insidious onset drug related kidney injury, particularly in the context of long term drug exposure, may have developed chronic kidney disease, the natural history of which could be progressive in nature.

Overall, our cohort was relatively small and significant trends will need to be followed up in further larger cohort studies with longer periods of follow up. Clinical trials may not be able to supply such data due to the small numbers involved and exclusion of individuals with or at risk of renal impairment. The chief limitation of our study was the potential risk of hidden confounding factors although we found no such evidence in a subset of patients analyzed for factors associated commonly with renal disease.

Another limitation of the study was that eGFR was only calculated using the MDRD formula without corroboration using other formulae such as the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula. There is evidence in the HIV negative population that MDRD formula underestimates calculation of eGFR at higher levels of GFR [27]. However, at present, no formulae have been

formally validated in the HIV population and it is important to note we were aiming to capture the threshold of eGFR<60 ml/min per 1.73m^2. The use of MDRD formula for assessment of renal function for management of chronic kidney disease in HIV- infected patients is also recommended by the HIV Medicine Association of Infectious diseases Society of America [28].

In conclusion, 18% of the studied cohort developed renal impairment over 2680 patient years of follow up. ATZ/r and LPV/r, but not DRV/r were associated with an increased risk of renal impairment when compared with EFV in a multivariate analysis. This was independent of both previous and total duration of TFV exposure. These data are of clinical significance when choosing a PI in those at risk of or who have developed renal impairment.

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