Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV+ persons with a normal baseline eGFR : A prospective international cohort study

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Abstract

Background

There is continued controversy whether the association between some antiretrovirals used in HIV-infection and chronic kidney disease (CKD) is cumulative, particularly among those with initially normal renal function.

Methods

D:A:D study participants with first eGFR > 90 mL/min/1.73m^2 were followed from baseline (first eGFR after 1/1/2004) until earliest of CKD, last eGFR, 1/1/2014 or last visit plus 6 months. CKD was defined as confirmed (>3 months apart) eGFR <60 ml/min/1.73m^2. Poisson regression was used to estimate the incidence of CKD associated with cumulative exposure to tenofovir (TDF), ritonavir-boosted atazanavir (ATV/r), lopinavir/ritonavir (LPV/r), other ritonavir-boosted protease inhibitors (other PI/r) or abacavir (ABC).

Findings

23560 persons were included with median baseline eGFR 110ml/min/1.73m^2 (IQR 100–125), age 39 years (IQR 33–45) and CD4 440/mm^3 (IQR 293–629). During a median follow-up of 6.3 years (IQR 4.4–8.0), 210 persons developed CKD (0.9%; incidence 1.48/1000 PYFU; 95% CI 1.28–1.68). After adjustment, there was a significant increase in CKD associated with each additional year of exposure to TDF (adjusted incidence rate ratio [aIRR] 1.14; 95% CI 1.10–1.19), ATV/r (aIRR 1.20; 95% CI 1.13–1.26) and LPV/r (aIRR 1.11; 95% CI 1.06–1.16) but not other PI/r or ABC.

Interpretation

In persons with normal renal function, the yearly incidence of CKD was increasing for up to 6 years of follow-up after starting TDF, ATV/r or LPV/r. Although the absolute number of new events was modest, treatment may result in an increasing and cumulative risk of CKD.

Funding

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Research in context

Evidence before this study

Certain antiretrovirals used to treat HIV-infection may be associated with an increased risk of chronic kidney disease (CKD) or a decline in estimated glomerular filtration rate (eGFR). We performed a review of available literature on 20th April 2014 via PubMed from 2004 searching for clinical trials and observational (cohort) studies reporting changes in eGFR or CKD and individual antiretrovirals. Evidence from clinical trials, especially for tenofovir, suggest that any decreases in eGFR occur within the first few months of treatment, with little further change after this. Evidence from observational studies have suggested a cumulative effect of antiretrovirals, including atazanavir/ritonavir or lopinavir/ritonavir and tenofovir. Clinical trials in HIV-positive persons tend to be short in duration and may exclude those at higher risk of CKD, and therefore not follow persons for long enough to observe CKD, while observational studies have not focused on persons with an initially normal eGFR > 90 mL/min/1.73m^2, or have not used a confirmed eGFR < 60 mL/min/1.73m^2 to define CKD.

Added value of this study

23560 study participants with first eGFR > 90 mL/min/1.73m^2 were included, of whom 210 developed CKD. After adjustment for potential confounding variables, both HIV-associated and traditional risk factors for CKD, there was a 14%, 20% and 11% increase in CKD associated with each additional year of exposure to tenofovir, atazanavir/ritonavir and lopinavir/ritonavir, but no increased incidence of CKD associated with either abacavir or other ritonavir-boosted protease inhibitors.

Implications of all the available evidence

Our findings suggest that the yearly incidence of CKD was increasing for up to 6 years of follow-up after starting TDF, ATV/r or LPV/r in HIV-positive persons with an initially normal eGFR. Although the absolute number of CKD events was modest, the incidence of CKD continued to increase with up to 5+ years of exposure; after 5 years it was equivalent to an increased incidence of CKD of 1.94-fold, 2.44-fold and 1.66-fold for tenofovir, atazanavir/ritonavir and lopinavir/ritonavir respectively. The continued increase in risk of CKD that we observed with exposure suggests a cumulative toxic effect of these medications. The benefits of potentially nephrotoxic antiretrovirals, even in persons with an initially normal renal function, should be weighed against the risks in those at highest risk of CKD.

Introduction

Following the widespread introduction of combination antiretroviral therapy (cART) and the rapid decline in mortality associated with HIV infection [1], there has been a shift in focus to chronic diseases such as cardiovascular, liver and renal disease, where there is a complex relationship between immunodeficiency, chronic inflammation, aging and long term toxicities of antiretrovirals [2]. The prevalence of chronic kidney disease (CKD) in HIV-positive persons treated with cART varies considerably, ranging from 2 to over 30% [3], depending on the prevalence of other risk factors, including both HIV-related and more traditional risk factors for CKD [4;5]. There have been a number of studies focusing on the role of antiretrovirals, including work from the D:A:D study[6]. Tenofovir disoproxil fumarate (TDF) has been widely demonstrated to be associated with decreases in estimated glomerular filtration rate (eGFR) and progression to CKD[7], while some studies suggested similar associations with ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r) [6;8], together with reports of crystalluria, urolithiasis and interstitial nephritis[9;10] . In addition, a number of antiretrovirals, including dolutegravir, ritonavir, and rilpivirine, can reduce creatinine clearance (thereby decreasing eGFR) without changing actual glomerular filtration rate[11].

Results from some large cohort studies have demonstrated nephrotoxic effects of some antiretrovirals, in persons with both a normal and impaired eGFR at start of follow-up [6;8;12]. Some clinical trials, with mostly short follow-up, have suggested that exposure to TDF was associated with an initial decline in eGFR that does not continue with increasing exposure[13;14], others have reported no initial decline in renal function[15;16]Despite the many studies of renal function in HIV, no study to date has been adequately powered to formally assess the exact nature of the association between exposure to antiretrovirals and CKD in those with an initially normal eGFR. It therefore remains unclear, especially in those with an initially normal renal function, whether the 'early-hit' phenomenon remains true after extended exposure to antiretrovirals. As treatment with cART can extend over many years, it is crucial to determine whether the risks of CKD will be self-limiting, to aid clinical decision making and monitoring of HIV-positive persons.

The aim of this study was therefore to investigate the relationship between duration of exposure to antiretrovirals and the development of CKD in persons with an initially normal eGFR.

Study Population and Methods

Study population

The Data Collection on Adverse events of Anti-HIV Drugs Study (D:A:D) is a prospective cohort collaboration established in 1999 following more than 49,000 HIV-1-positive persons in Europe, the United States and Australia; details have been published previously[17]. Data on routine clinical care, including demographic factors, antiretroviral therapy, laboratory values, cardiovascular risk factors and AIDS events are collected electronically at enrolment and annually thereafter. Serum creatinine measurements have been collected systematically in participating cohorts since January 2004.

Statistical methods

Baseline was defined as the first eGFR measured during prospective follow-up after 1/1/2004; eGFRs were calculated via creatinine clearance using Cockcroft-Gault and standardised for body surface area, using weight measured within 1 year of serum creatinine. Where there was >1 eGFR measured within a 28 days period, the median of all measurements over that period was used and assigned to the median date. Persons were excluded if their baseline eGFR was <90 mL/min/1.73m^2, had no CD4 or viral load measured within 6 months of baseline (closest before or if not available, closest after), or less than 2 eGFRs 3 months apart after baseline. cART was defined as 3 or more antiretrovirals from any drug class. CKD was defined as confirmed (> 3 months apart) eGFR < 60 mL/min/1.73m^2. Follow-up for each individual was calculated to the earliest of CKD, last visit plus 6 months, last eGFR date plus 6 months, or 1/2/2014, to allow for reporting delays.

Exposure to TDF, LPV/r, ATV/r, other PI/r (i.e., all other ritonavir boosted PIs except LPV/r and ATV/r) and abacavir (ABC) was investigated as cumulative exposure, as previously described and including exposure prior to baseline[17] , and additionally as never exposed, exposed but off antiretroviral (including time since stopping) and currently exposed. Poisson regression was used to model incidence rates of CKD according to antiretroviral exposure, after adjustment for confounding variables (race, HIV exposure group, D:A:D enrolment cohort, D:A:D participating cohort, gender, nadir CD4, date of baseline, eGFR at baseline, and hepatitis B, C serostatus, smoking status, hypertension, diabetes, prior cardiovascular disease, body mass index (BMI), family history of cardiovascular disease, viral load, CD4, a new AIDS diagnosis within the past 12 months, all as time updated variables). As indinavir is known to be associated with

urolithiasis , but is not currently widely used, models were adjusted for previous cumulative exposure to indinavir but associations with indinavir are not explicitly presented.

We assumed a linear relationship between ARV exposure and CKD based on the crude incidence rates; different ways of modelling this relationship, including quadratic terms or categorical variables, but the continuous model provided the best statistical fit and was easily interpreted. We included variables in multivariate analyses based on those routinely recorded in D:A:D and commonly adjusted for D:A:D or in renal disease, and included all potential confounders, rather than those that were significant in univariate analyses. All variables were included as categorical in the first instance, then were included as the best fitting continuous variable (eg age was included as liner, CD4 was included on $\log_2$ scale) where the categorical variables indicated a linear trend. Goodness of fit was assessed by comparing the Akaike Information Criterion between different models and by adding and removing confounding variables to assess how their inclusion or exclusion altered the fit of the model and the variables remaining in the model.

The analyses were repeated using chronic renal impairment (CRI) as an alternative endpoint reflecting renal impairment and the point at which persons with decreasing eGFR may be switched away from potentially nephrotoxic antiretrovirals [6]. CRI was defined as confirmed (> 3 months apart) eGFR < 70 mL/min/1.73m^2. The relationship between ATV/r and CKD could be confounded by the use of TDF, as the antiretrovirals are often used together. The analysis was therefore repeated among persons not exposed to TDF (i.e., right-censoring follow-up at starting TDF). An additional sensitivity analysis assessed the cumulative effect of antiretrovirals after excluding person-years of follow-up and events occurring in persons not exposed to the antiretroviral of interest. This was extended by additionally excluding person-years and follow-up among persons currently off the antiretroviral in question, similar to an 'on-treatment' type analysis.

All analyses were performed using SAS (Statistical Analysis Software), Version 9.3.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval

All participating cohorts followed local national guidelines/regulations regarding patient consent and/or ethical review. In particular, of the countries represented by the participating cohorts, only Switzerland and Australia require specific ethical approval for D:A:D in addition to that required for their national cohorts (Swiss HIV Cohort Study and AHOD), France, Italy, and Belgium do not require specific ethical approval over-and-above that required for the individual cohorts (Nice/Aquitaine, Brussels St. Pierre and IcoNA, respectively), and the Netherlands do not require any specific ethical approval as data is provided as part of HIV care (ATHENA). For the EuroSIDA study (which includes the data from the BASS and Swedish cohorts), which contains participants from across many European countries, each participating site has a contractual obligation to ensure that data collection and sharing is done in accordance with national legislation; each site principal investigator either maintains appropriate documentation from an ethical committee (if required by law) or has a documented written statement to say that this is not required.

Results

Of 37,022 persons with at least 1 eGFR > 1/1/2004, 25,933 had a baseline eGFR > 90 mL/min/1.73m^2. 1,792 were excluded because they did not have 2 additional eGFRs > 3 months apart during follow-up, and 236 were excluded due to missing viral load and/or CD4 counts. Those with a baseline eGFR but excluded from analyses (n=2028) had a later baseline, a higher eGFR, were older, had a lower baseline CD4 count, were less likely to be of white ethnic origin, and more likely to be hepatitis C coinfected. 9003 persons (37.7%) follow-up were censored at last visit plus 6 months, 5607 (23.5%) at last eGFR plus 6 months, and 9010 (37.7%) at 1/2/2014. The characteristics of the 23,905 included persons are shown in Table 1. 285 (1.2%) persons developed CKD during 161,628 person-years of follow-up (PYFU) (median 7.2; interquartile range [IQR] 5.1–8.9 years), giving an incidence of CKD of 1.76/1000 PYFU (95% CI 1.56–1.97). From Kaplan-Meier estimation, the percentage experiencing CKD by 2 years was 0.11% (95% confidence interval (CI 0.07–0.15%), increasing to 0.49% (95% CI 0.39–0.57%) and 1.46% (95% CI 1.26–1.66%) by 5 and 8 years respectively. The analyses included 382,733 eGFRs, a median of 16 (IQR 9–22) per person with a median time of 3.9 between measurements (IQR 2.9–5.8 months). Persons developing CKD were older, had lower eGFRs at baseline, had more cardiovascular risks such as smoking, hypertension and diabetes, and were more likely to have started cART.

Figure 1A and Figure 1B summarises the use of the potentially nephrotoxic antiretrovirals at baseline. For example, 5,844 (24.5%) of persons had ever started TDF at or before baseline, and 87.0% of these were taking TDF at baseline (Figure 1A), with a median exposure of 0.8 years (IQR 0.3–1.6; Figure 1B) . Among the 761 who had stopped TDF prior to baseline, the median time since stopping was 0.7 years (IQR 0.3–1.5; Figure 1B). While a considerable proportion had ever used indinavir and other PI/r, current use of either of these regimens was low at baseline. Further, time since stopping other PI/r or indinavir was considerably longer compared to the other antiretrovirals.

Incidence of CKD and antiretroviral exposure

For TDF, ATV/r and LPV/r, there was a clear trend of increasing incidence of CKD and CRI as exposure increased (Figure 2). There was insufficient data to consider ATV without ritonavir-boosting. For example, in those never exposed to TDF, the incidence of CKD was 0.84/1000 PYFU (95% CI 0.62–1.06), increasing steadily to 4.84/1000 PYFU (95% CI 3.66–6.03) in persons with >6 years exposure to TDF. The increase in CKD as exposure to other PI/r and ABC increased was less clear. Figure 3 summarises the crude and adjusted incidence rates of CKD per 12 months additional exposure to

each ARV. After adjustment, increasing exposure to TDF, ATV/r and LPV/r was associated with an increased incidence of CKD. For example, in univariate analyses, each additional year of exposure to TDF was associated with a 23% increased incidence of CKD (incidence rate ratio [IRR] 1.23; 95% CI 1.18–1.27) and after adjustment, each additional year exposure to TDF was associated with a 14% increased incidence of CKD (adjusted incidence rate ratio [aIRR] 1.14; 95% CI 1.10–1.19). Cumulative exposure to other PI/r or ABC was not associated with an increased incidence of CKD after adjustment.

The increased incidence of CKD per year of exposure to certain antiretrovirals (Figure 3 and Table 2; model a, CKD) were all fairly modest in size, but antiretroviral treatment extends over many years. To illustrate this, the increased incidence after 5 years of exposure is also shown in Table 2. After 5 years exposure to TDF, there was a 1.94-fold increased incidence of CKD (aIRR 1.94; 95% CI 1.57–2.39). The corresponding figures for ATV/r were 2.44 (95% CI 1.86–3.21) and 1.66 for LPV/r (95% CI 1.32–2.09).

Sensitivity analyses

The results of various sensitivity analyses are also shown in Table 2, with the results of the main analysis from Figure 3 included for comparison. There were 57 CKD events in 67971 PYFU after excluding follow-up and events occurring after starting TDF (Model b, CKD). This model assesses the relationship between ATV/r or LPV/r and CKD among those never exposed to TDF or prior to starting TDF. The association between ATV/r and LPV/r and CKD was similar compared to the main analysis (adjusted IRR [aIRR]/ year exposure 1.22; 95% CI 1.05–1.41 and 1.13; 95% CI 1.02–1.25 respectively), although with wider confidence intervals, reflecting that there were significantly fewer events and person-years of follow-up, especially for ATV/r. In addition, there was a significant association between TDF and CKD in persons never exposed to ATV/r, LPV/r or other PI/r, including 55 events and 72468 PYFU (aIRR 1.28/year exposure; 95% CI 1.17–1.39).

As seen in Figure 2, those not exposed to the antiretroviral of interest had considerably lower event rates than those exposed, which may suggest a different underlying risk for CKD. Excluding the follow-up and events occurring in those exposed to TDF shows a weaker association between ATV/r, LPV/r and CKD (model c, CKD), but increasing exposure remained statistically significant. The final model for CKD assesses the increased incidence of CKD for those currently on the antiretroviral of interest, comparable to an on-treatment type analysis (model d, CKD). The results from this analysis were consistent with the main analysis for TDF, but in this analysis, additional exposure to ATV/r (aIRR/year

exposure 1.05; 95% CI 0.92–1.19) or LPV/r (aIRR/year exposure 1.09; 95% CI 0.98–1.21) was not associated with a significantly increased incidence of CKD.

Incidence of CRI and antiretroviral exposure

Analyses were repeated using CRI as an endpoint . 923 persons developed CRI during 159,881 PYFU, an incidence of CRI of 5.77/1000 PYFU (95% CI 5.40–6.15). Results are shown in the lower half of Table 2. Increasing exposure to TDF (aIRR/year exposure 1.18; 95% CI 1.15–1.22), ATV/r (aIRR/year exposure 1.14; 95% CI 1.10–1.17) and LPV/r (aIRR/year exposure 1.06; 95% CI 1.03–1.09) were all associated with an increased incidence of CRI. Cumulative exposure to other PI/r or ABC was not associated with an increased incidence of CRI.

Discussion

This large study of almost 24,000 HIV-positive persons with an initially normal eGFR demonstrates clearly, for the first time, that the association between TDF, ATV/r and LPV/r and CKD was cumulative in nature. This suggests that persons starting these antiretrovirals have a small, but significantly increasing, incidence of CKD with increasing exposure. The incidence of CKD continued to increase with up to 5+ years of exposure; after 5 years it was equivalent to an increased incidence of CKD of 1.94-fold, 2.40-fold and 1.67-fold for TDF, ATV/r and LPV/r respectively. The continued increase in risk of CKD that we observed with exposure suggests a cumulative toxic effect of these medications.

The increased incidence of CKD per year exposure to each of the considered antiretrovirals was consistent with previous data from EuroSIDA[8], one of the cohorts contributing data to this analysis. This previous work was not focused on those with an initially normal eGFR, and was only able to show the cumulative effect of 2 years antiretroviral exposure. Further, this study adds to the earlier publication from D:A:D[6] by focusing on CKD alone, more than doubling the number of events, adding almost 3 years to median duration of follow-up, and considering the role of antiretrovirals in much greater detail (cumulative and current exposure). Treatment with cART can extend over many years, and this is the first well-powered study, to our knowledge, to show the risks of CKD were not self-limiting and extended up to 5 years of ARV exposure. The relationship between TDF and CKD was similar among persons never exposed to any ritonavir-boosted PI. TDF is widely recommended and used as first line antiretroviral treatment in developed and developing countries, both ATV/r and LPV/r are suggested as a suitable alternative first-line regimen for some individuals and are recommended as second line therapy in developing countries [18]. The so-called 'early hit' phenomenon of TDF is largely a result of short term clinical trials, suggesting an early reduction in serum creatinine, with few changes after the first months of therapy [13;19-22]. Preliminary data from a novel pro-drug of TDF, Tenofovir Alafenamide Fumarate, suggests it has a lower risk of causing renal injury [23], but long term follow-up will be required to conclude whether it is more weakly associated with CKD or other renal adverse events.

Cumulative exposure to either ATV/r or LPV/r was associated with an increased incidence of CKD, independently of exposure to TDF, and among those not exposed to TDF. TDF has been associated with proximal renal tubular dysfunction related to mitochondrial toxicity[24] and both LPV/r and ATV/r have been associated with interstitial nephritis, urolithiasis and urinary stones [9;10], although the exact mechanism is unclear. Evidence from other studies between ATV/r, LPV/r and CKD or other markers of renal function are contradictory[7;12;25] and there is conflicting evidence

whether the precipitation of protease inhibitor crystals leads to interstitial nephritis and a decrease in eGFR[26]. Since recent studies demonstrated that many antiretroviral medications, including ritonavir, reduce tubular creatinine secretion[11] and reductions in eGFR associated with antiretroviral medications may not be due to renal toxicity per se. However, if changes in eGFR were simply due to reduced tubular secretion, one would expect a rapid decrease in eGFR after starting antiretroviral medications without further changes in renal function. The association between CKD and ATV/r or LPV/r was somewhat weaker and not statistically significant when limiting the analysis to those 'on treatment' where, by definition, CKD only occurred in those currently on ATV/r or LPV/r and CKD events occurring after discontinuation of ATV/r or LPV/r as eGFR declined were excluded This could suggestsome selection bias by clinicians of those thought to be at lower risk of CKD to remain on drugs as eGFR declined.

We found no evidence that other PI/r were associated with an increased incidence of CKD, suggesting no large effect of ritonavir-boosting on CKD when not used to boost ATV or co-formulated as LPV/r. The other PI/r group was comprised of predominantly older boosted combinations. The number of persons taking tipranavir/r or darunavir/r either at baseline or during follow-up was low, less than 1000 PYFU and 10 CKD events for each of these antiretrovirals. Darunavir/r was more commonly used during follow-up, with similar PYFU and CKD events as ATV, but there was insufficient data to stratify the events according to duration of exposure. Further data is required to explore the relationship between CKD and newer or lesser used ritonavir-boosted protease inhibitor regimens such as tipranavir/r, darunavir/r or other antiretroviral combinations such as elvitegravir, boosted with cobicistat.

The increase in CKD incidence per year of exposure to TDF, ATV/r or LPV/r was modest, and the risk:benefit of any antiretroviral regiment should be considered for all persons initiating treatment. The relationship between TDF, ATV/r or LPV/r effect was cumulative and after 5 years of exposure CKD incidence increased 2-3-fold. Of note, the effect per year of additional TDF exposure was smaller than previously reported by other studies [8;12], and was similar across various sensitivity analyses. This difference in effect size between studies may be explained by differences in baseline eGFR, HIV-independent risk factors, greater awareness of TDF-associated renal toxicities with active selection of low-risk patients for TDF exposure as well as increased switching away from TDF as eGFR declines and before CKD. It is important to note that the CKD events in this study represented large and clinically important changes in eGFR. All subjects started with eGFR>90ml/min/1.73m^2, those who developed CKD lost one third or more of eGFR during follow up and had >5ml/min/1.73m^2 decline in eGFR, the threshold for "rapid progression" of CKD[27].

There are several limitations which should be noted. This is an observational study and unmeasured confounding cannot be ruled out and causality between antiretrovials and CKD cannot be proven. Due to limitations on collection of data regarding race in some European cohorts, we were limited to use the Cockcroft-Gault equation for creatinine clearance for estimating eGFR. Previous research has suggested that Cockcroft Gault is similar to the CKD-EPI formula for predicting CKD in cohort studies [28]. The D:A:D study has no information on proteinuria, and we were not able to adjust for this as a risk factor for CKD, however studies adjusting for proteinuria have shown similar findings to ours[12]. We were also not able to adjust for concomitant medication, such as NSAIDs. Participants in D:A:D contributing data to this study were Europe and Australia, and while availability and access to antiretrovirals and serum creatinine measurements in different cohorts can be assumed to be similar after 1/1/2004, differences will remain between cohorts in patient management. We adjusted for cohort to account for some of these differences, but unmeasured confounding may remain. We used a single measurement to categorise persons as having a normal eGFR at baseline, but our results were consistent if we used a confirmed eGFR > 90 mL/min/1.73m^2 at baseline as an inclusion criterion, with significantly less power. We have demonstrated an increased incidence of CKD over 6 years of exposure, but even longer follow-up is required to determine whether that increase will plateau with longer exposure to the antiretrovirals.

To conclude, the incidence of CKD in HIV-positive persons increases continuously with duration of exposure to specific antiretrovirals, with no evidence that CKD was limited to the first few months of starting antiretrovirals and no plateau in the increasing incidence after a median follow-up of over 6 years. Our results were consistent across a range of sensitivity analyses and when using CRI as an alternative endpoint. TDF, ATV/r and LPV/r are among the most widely used antiretrovirals used to treat HIV worldwide. The D:A:D study has previously published a risk-score for CKD[29] which is available online at http://hivpv.org/Home/Tools/ChronicKidneyDiseaseTool.aspx . This online tool enables individuals to determine the risk of CKD and risk and benefits of potentially nephrotoxic antiretroviralsshould be weighed against the long term risk of CKD with extended exposure to antiretrovirals.

Role of authors

Amanda Mocroft had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Amanda Mocroft, Jens D Lundgren and Lene Ryom proposed and developed the research question, and developed the statistical analyses. Michael Ross, Christoph A Fux, Peter Reiss, Olivier Moranne, Philippe Morlat, Antonella d'Arminio Monforte, and Ole Kirk contributed with ideas around study design and interpretation of data. Amanda Mocroft wrote the first draft of the manuscript. All authors have seen and contributed to the final version of the manuscript.

Conflicts of Interest

Amanda Mocroft has received honoraria, speaker fees, travel support or honoraria from Gilead, Pfizer, Merck, BMS, BI and Wragge LLC. Antonella d'Arminio Monforte reports personal fees from Abbvie, grants and personal fees from Bms, grants and personal fees from Gielad, personal fees from Janssen, personal fees from MSD, personal fees from ViiV, outside the submitted work. . Olivier Moranne has received honoraria, speaker fees, travel support or honoraria from Gilead. Philippe Morlat reports personal fees and non-financial support from ViiV health care, personal fees and non-financial support from Gilead , personal fees from Janssen, personal fees and non-financial support from BMS, personal fees from MSD, outside the submitted work. .

Table 1 Study population : Characteristics at baseline

		All		Develop CKD		No CKD	
		N	%	N	%	N	%
All		23905	100	23620	98.8	285	1.2
Gender	Male	17378	72.7	17175	72.7	203	71.2
	Female	6527	27.3	6445	27.3	82	28.8
Race	White	10939	45.8	10778	45.6	161	56.5
	Black	1980	8.3	1970	8.3	10	3.5
	Other	543	2.3	539	2.3	4	1.4
	Unknown	10443	43.7	10333	43.8	110	38.6
Risk	Homosexual	20710	44.8	10604	44.9	106	37.2
	IDU	3074	12.9	2992	12.7	82	28.8
	Heterosexual	8681	36.3	8600	36.4	81	28.4
	Other	1440	6.0	1424	6.0	16	5.6
Hepatitis B	Negative	21054	88.1	20803	88.1	251	88.41
	Positive	1102	4.6	1088	4.6	14	4.9
	Unknown	1749	7.3	1729	7.3	20	7.0
Hepatitis C	Negative	17201	72.0	17050	72.2	151	53.0
	Positive	4340	18.2	4234	17.9	106	37.2
	Unknown	2364	9.9	2336	9.9	28	9.8
Antiretrovirals	Naïve	6354	26.6	6320	26.8	34	11.9
	Ever started cART	17151	71.8	16903	71.6	248	87.0
Smoking	Current	10138	42.4	9996	42.3	142	49.8
Status	Previous	4247	17.8	4183	17.7	64	22.5
	Never	6625	27.7	6566	27.8	59	20.7
	Unknown	2895	12.1	2875	12.2	20	7.0
BMI	<18	666	2.8	641	2.7	25	8.8
	18 – 26	16576	69.3	16369	69.3	207	72.6
	26 – 30	3867	16.2	3833	16.2	34	11.9
	>30	1493	6.3	1479	6.3	15	4.9
	Unknown	1303	5.4	1298	5.5	5	1.7
Family	No	15327	64.1	15134	64.1	193	67.7
History	Yes	1737	7.3	1710	7.2	27	9.5
CVD	Unknown	6841	28.6	6776	28.7	65	22.8
Hypertension		1846	7.7	1802	7.6	44	15.4
Prior CVD		113	0.5	109	0.5	4	1.4
AIDS		5305	22.2	5204	22.0	101	35.4
Recent AIDS	In last 12 mths	1069	4.5	1051	4.5	18	6.3
Diabetes		737	3.1	707	3.0	30	10.5
Anaemia[1]		6047	32.5	5935	32.3	112	46.3
VL < 400		13410	56.1	13225	56.0	185	64.9
		Median	IQR	Median	IQR	Median	IQR
Age	Years	39	33 – 45	39	33 – 44	47	42 – 54
CD4	/mm^3	441	294 – 628	441	294 – 629	414	259 – 585
Nadir CD4	/mm^3	240	120 – 380	240	120 – 380	161	63 – 279
Baseline	month/year	7/05	6/04 – 3/07	7/05	6/04 – 4/07	7/04	3/04 – 9/05
eGFR	mL/min/1.73m^2	110	100 – 125	110	100 – 125	102	95 – 113

Baseline : first eGFR measured during prospective follow-up in D:A:D after 1/1/2004. IQR; interquartile range. [1]Baseline haemoglobin known for18,601 (77.8%) overall, 242 (84.9%) in those who develop CKD and 18,359 in those who do not (77.8%). CVD; cardiovascular disease

Table 2 Incidence rates of CKD and CRI associated with increasing exposure to antiretrovirals

	Model		Tenofovir IRR (95% CI) p-value	Atazanavir/r IRR (95% CI) p-value	Lopinavir/r IRR (95% CI) p-value	Other PI/r IRR (95% CI) p-value	Abacavir IRR (95% CI) p-value
CKD							
Including all follow-up and events (Fig. 3)	(a)	Univariate / year	*1.23 (1.18 – 1.27)* *<0.0001*	*1.30 (1.24 – 1.37)* *<0.0001*	*1.17 (1.12 – 1.22)* *<0.0001*	*1.11 (1.07 – 1.16)* *<0.0001*	*1.09 (1.05 – 1.13)* *<0.0001*
		Multivariate / year	*1.14 (1.10 – 1.19)* *<0.0001*	*1.20 (1.13 – 1.26)* *<0.0001*	*1.11 (1.06 – 1.16)* *<0.0001*	*1.02 (0.97 – 1.08)* *0.37*	*1.03 (0.99 – 1.08)* *0.053*
		Multivariate/5 years	***1.94 (1.57 – 2.39)***	***2.44 (1.86 – 3.21)***	***1.66 (1.32 – 2.09_***		
Censoring at start TDF	(b)	Multivariate / year		1.22 (1.05 – 1.41) 0.0076	1.13 (1.02 – 1.25) 0.018		
		Multivariate/5 years		2.71 (1.30 – 5.64)	1.84 (1.11 – 3.03)		
Excluding those never started ARV	(c)	Multivariate / year	1.09 (1.04 – 1.15) 0.0009	1.13 (1.04 – 1.23) 0.0054	1.07 (1.00 – 1.14) 0.041	1.02 (0.96 – 1.09) 0.52	0.98 (0.93 – 1.03) 0.36
		Multivariate/5 years	1.55 (1.20 – 2.02)	1.85 (1.20 – 2.84)	1.40 (1.01 – 1.93)		
Currently on ARV, excluding those never started ARV	(d)	Multivariate / year	1.13 (1.06 – 1.21) 0.0002				
		Multivariate/5 years	1.87 (1.34 – 2.61)				
CRI							
Including all follow-up and events	(a)	Univariate / year	1.24 (1.22 – 1.27) <0.0001	1.27 (1.23 – 1.30) <0.0001	1.12 (1.09 – 1.15) <0.0001	1.10 (1.07 – 1.13) <0.0001	1.06 (1.04 – 1.08) <0.0001
		Multivariate / year	1.18 (1.15 – 1.22) <0.0001	1.14 (1.10 – 1.17) <0.0001	1.06 (1.03 – 1.09) <0.0001	1.02 (0.99 – 1.05) 0.14	1.02 (0.99 – 1.05) 0.056
		Multivariate/5 years	***2.27 (2.02 – 2.54)***	***1.91 (1.63 – 2.23)***	***1.32 (1.15 – 1.52)***		

CKD; chronic kidney disease : confirmed (> 3 months apart) eGFR < 60 mL/min/1.73m^2. CRI; chronic renal impairment : confirmed (> 3 months apart) eGFR < 70 mL/min/1.73m^2. IRR; incidence rate ratio. CI; confidence interval.

Multivariate models were adjusted for gender race, HIV exposure group, D:A:D enrolment cohort, D:A:D participating cohort, prior CVD, age, CD4 nadir, GFR at baseline, baseline date and hepatitis B/C, AIDS diagnosis within the past 12 months, smoking status, BMI, family history of CVD, CD4, viral load, anaemia, diabetes, hypertension and cART (on/off) as time updated variables. Models were additionally adjusted for cumulative exposure to indinavir. A separate category was included for missing data where data was missing. Each multivariate model is additionally adjusted for cumulative exposure to all other potentially nephrotoxic antiretrovirals which are the not the focus of the model. For example, for tenofovir, the model is additionally adjusted for exposure to atazanavir, atazanavir/r, lopinavir/r, other boosted protease inhibitor regimens not already adjusted for and abacavir.

Model (a); main analysis, including all events and person years of follow-up in all eligible patients. Model (b); as model (a) but right censoring when persons start tenofovir. Model (c) considers the cumulative effect of antiretrovirals excluding persons who had never started the antiretroviral of interest; a separate model is run for each antiretroviral. For example, for tenofovir, persons are left censored at starting tenofovir; person-years of follow-up and events occurring before starting tenofovir are excluded. Model (d) extends model (c) and considers the cumulative effect of antiretrovirals excluding persons who had never started the antiretroviral of interest and only among persons who are currently taking the drug; a separate model is run for each antiretroviral. For example, for tenofovir, persons are left censored at starting tenofovir and right censored at stopping tenofovir; person-years of follow-up and events occurring before starting tenofovir are excluded as are person-years of follow-up and events occurring whilst off tenofovir.

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