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Exposure to Antiretrovirals (ARVs) and Risk of Renal Impairment among HIV-positive Persons with Normal Baseline Renal Function: the D:A:D study

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Abstract

Background. Several antiretrovirals (ARVs) are associated with chronic renal impairment, but the extent of such adverse events in HIV-positive persons with initially normal renal function is unknown.

Methods. D:A:D participants with estimated glomerular filtration rates (eGFR) >90ml/min >1/1/2004 were followed to confirmed (>3 months) eGFR<70 (possible intervention threshold), confirmed eGFR<60 (moderate chronic kidney disease, CKD) or last eGFR. Predictors and eGFR-related ARV discontinuations were identified using Poisson regression.

Results. Of 22,603 persons, 468(2.1%) experienced eGFR<70 (IR 4.78/1000 PY [95%CI 4.35-5.22]) and 131(0.6%) CKD (1.33/1000 PY [1.10-1.56]) during median 4.5 (IQR 2.7-6.1) years. Latest eGFR 60-70 caused significantly higher tenofovir (TDF) discontinuation rates (aIRR 1.72 [1.38-2.14]), but not of other ARVs, compared with eGFR≥90. Cumulative TDF (1.18 [1.12-1.25]/year) and boosted atazanavir (ATV/r, 1.19 [1.09-1.32]/year) use were independent eGFR≤70 predictors, but not significant for CKD, whilst boosted lopinavir (LPV/r) use was significant for both endpoints (1.11 [1.05-1.17]/year and 1.22 [1.16-1.28]/year). Associations were unaffected by censoring for concomitant ARV use, but diminished after ARV discontinuation.

Conclusions. TDF, ATV/r, and LPV/r use were independent predictors of chronic renal impairment in HIV-positive persons without pre-existing renal impairment. Increased TDF discontinuation rates with decreasing eGFR may have prevented further deteriorations. After discontinuation the drug estimate decreased.

Introduction

The majority of HIV-positive persons have normal renal function in terms of normal estimated glomerular filtration rate (eGFR) with a relatively low overall risk of developing chronic renal impairment [1-4]. Exposure to several antiretroviral drugs (ARVs) including tenofovir (TDF), boosted and unboosted atazanavir (ATV/r and ATV), indinavir (IDV), lopinavir/r (LPV/r) and other ritonavir-boosted protease inhibitors (other PI/r) may lead to chronic renal impairment in HIV-positive populations with varying degrees of preexisting impairment [1-4]. The extent of such adverse drug reactions in persons with normal baseline renal function is unknown, but important to elucidate given the numerous complications associated with chronic renal impairment [5]. Furthermore, the literature has not clarified the impact of clinicians discontinuing potential nephrotoxic drugs. The aim of this analysis was to assess the possible independent contribution of potentially nephrotoxic ARVs relative to established renal risk factors on the rate of progression from an initially normal renal function to chronic impairment.

Methods

The D:A:D study was established in 1999 and is a prospective cohort study including 49,734 HIV-positive persons from established cohorts in Europe, USA and Australia. Detailed information on predefined clinical events is collected real-time and centrally adjudicated. Information on treatment, laboratory values, demographics etc. is collected from the participating cohorts every 6 months. Study details have been published earlier [6]. The current analysis included persons under active follow-up in D:A:D with >3 serum creatinine measurements after 1/1/2004 (when systematic creatinine collection was first started) and a normal eGFR, defined according to the

Kidney Disease Improving Global outcomes (KIDIGO) as eGFR>90 ml/min [7]. Follow-up lasted from baseline, the first eGFR after 2004, until the development of confirmed (2 consecutive measurement >3 months apart) eGFR< 70 (eGFR<70, threshold below which we hypothesized that renal interventions may begin to occur), eGFR<60 (moderate chronic kidney disease, CKD) or last available eGFR. The Cockcroft-Gault (CG) equation [8], standardized for body surface area [9] was used to calculate eGFR [10]. The choice of CG equation was based on information restrictions on ethnicity in several participating cohorts. In case of frequent eGFR measurements a 28-day average was calculated.

Incidence rates of confirmed eGFR<70 and CKD from eGFR>90 were calculated per 1000 person years of follow-up (PYFU), and Poisson regression models were used to identify independent predictors for confirmed eGFR<70, CKD and to assess discontinuation of included ARVs according to latest eGFR. Exposure to TDF, ATV, ATV/r, LPV/r, abacavir (ABC) and other PI/r (including darunavir, tipranavir, (fos)amprenavir and other PIs when ritonavir boosted) was included a priori due to a documented or suspected relationship with renal function [1-5,11, 12]. Due to limited IDV exposures after 2004, exposure to this drug was added only to account for possible confounding. In the primary analyses, ARV exposure was assessed per additional year of exposure, as previously described [6]. Median exposure to each ARV initiated after 1/1/2004 was calculated until confirmed eGFR<70, CKD or the last eGFR for those not experiencing an event.

Non-ARV variables significant at a 5% level in univariate analysis were included in multivariate analysis. Excluded variables were tested to determine if their inclusion improved the overall model fit. We included demographic variables such as age,

gender and ethnicity, HIV-related variables such as current and nadir CD4 count, viral load (VL) and prior AIDS. Hepatitis B (positivity defined by HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive) and Hepatitis C status (positivity defined by anti-HCV and HCV-RNA positive/unknown). Also included were established renal risk factors such as hypertension; defined as blood pressure >150/>100 mmHg or use of antihypertensive drugs, diabetes; defined as initiation of anti-diabetic treatment or verification in a case report form and cardiovascular disease (CVD); defined as myocardial infarction, invasive cardiovascular procedure or stroke verified in a case report form (more information is available at www.cphiv.dk).

Various sensitivity analyses were performed. Data on ethnicity was not available for a number of cohorts and an analysis was performed only in those of known ethnicity. Analyses were also repeated in persons with current virologic suppression (<400 copies/ml). In addition, ARV exposure was assessed categorically (never exposed, exposed < 1, 1-2, 2-3, >3 years). Follow-up for the ARVs significant in multivariate analysis were censored for follow-up for concomitant exposure to each of the other ARVs included in the analysis (e.g. follow-up on ATV exposure was censored for any TDF exposure and vice versa). Additional censoring was made for any ARV exposure prior to baseline by excluding all treatment- experienced persons. Another sensitivity analysis included only the baseline values of all covariates to address possible time-related confounding. Finally, confirmed eGFR>90 at baseline was used rather than a single measurement.

Analyses to investigate possible interactions were performed between ARVs significant in multivariate analysis for confirmed eGFR<70 and age, HCV, HBV, prior AIDS and current CD4 count. For a conservative approach and to account for multiple testing, we used a p-value of 0.01 to assess statistical significance. Possible selection bias and the generalizability of our findings was assessed by comparing patients included and excluded from analysis using logistic regression. Channeling bias for ABC was assessed by censoring follow-up for those initiating ABC at eGFR<90.

All statistical analyses were carried out using SAS version 9.2 (Statistical Analysis Software, Cary, NC, USA).

Results

Of 49,734 persons enrolled in D:A:D, 80% (n=39,629) had creatinine data available. Of these, 83% (n= 32,805) had >3 eGFR measurements and 57% or 22,603 persons had both >3 eGFR measurements and baseline eGFR> 90. Excluded individuals were more likely to be of African descent, HCV or HBV positive, smokers or having experienced AIDS, CVD, hypertension and IDU as mode of transmission. Among the 22,603 included individuals, there were 283,040 eGFR measurements available with a median of 12 (interquartile range, IQR, 7-16) per person a median time of 3.7 (IQR 2.8-5.7) months apart. Included persons were predominantly white, males, infected though MSM (men having sex with men) and with a median age of 39 (IQR 33-44) years, (Table 1).

Sustained and progressive decline

468 persons (2.1%) progressed from eGFR>90 to confirmed eGFR≤70 (incidence rate (IR) 4.78/1000 PYFU [95% confidence interval 4.35-5.22]) and 131 (0.6%) to CKD (1.33/1000 PYFU [1.10-1.56]) during a median follow-up of 4.5 years (IQR 2.7-6.1).

Those reaching confirmed eGFR≤70 therefore experienced an absolute eGFR decline of >20 ml/min during follow-up.

ARV switches and eGFR

Assessment of discontinuation rates in relation to latest eGFR showed, after adjustment, that persons with current eGFR 60-70 had significantly higher discontinuation rates (adjusted incidence rate ratio, aIRR, 1.72 [1.38-2.14]) of TDF, but not of other ARVs, compared to persons with current eGFR>90, (Figure 1).

The nucleosides most commonly initiated after TDF discontinuation depended on eGFR level; at lower eGFR significantly higher proportions initiated ABC (eGFR<60: 55%, eGFR 60-70: 32%, vs. eGFR>90:11%) and lamivudine (3TC eGFR<60: 62%, eGFR 60-70: 46%, vs. eGFR>90). In contrast at eGFR>90 most (re)initiated TDF (78%) and emtricitabine (64%), p<0.0001 for all comparisons.

ARV exposure

At baseline, 21% were on TDF, 15% on LPV/r, 14% on ABC and 5% on any ATV regimen. Among those progressing to confirmed eGFR<70, the longest median exposure was to ABC (1.7, IQR 0.2-3.9, years) and LPV/r (1.5, IQR 0.2-3.4, years) while ATV/r had one of the shortest median exposures (0.2, IQR 0-1.7, years).

Cumulative exposure to the investigated ARVs was similar among those developing confirmed eGFR<70, CKD or neither of the endpoints.

In multivariate analysis cumulative TDF (aIRR 1.18 [1.12-1.25] per year) and ATV/r (aIRR 1.19 [1.09-1.32] per year), but not unboosted ATV, exposure were independently associated with increased rates of progression to confirmed eGFR≤70, without reaching statistical significance for CKD (aIRR 1.08 [0.97-1.21] and 1.14 [0.93-1.39] per year, respectively). Cumulative LPV/r exposure was significantly associated with both endpoints (aIRR 1.11 [1.05-1.17] and 1.22 [1.16-1.28] per year, respectively), (Figure 2). Censoring for concomitant exposure to each of the other ARVs studied resulted in highly consistent estimates for confirmed eGFR≤70 (TDF aIRR 1.23 [1.10-1.38], LPV/r aIRR 1.11 [0.95-1.29] and ATV/r aIRR 1.58 [1.13-2.20] per year). These results were also unaffected by excluding persons on any ARVs prior to baseline; TDF aIRR 1.18 [0.97-1.44], LPV/r 1.22 [0.99-1.51] and ATV 1.40 [1.05-1.86]. Restricting follow-up to those with current virologic suppression or requiring confirmed values of eGFR >90 at baseline did not alter our results (data not shown).

When ARV exposure was fitted in categories depending on duration, those currently on TDF, ATV/r and LPV/r experienced increased rates of confirmed eGFR≤70 from eGFR>90 with increasing lengths of exposure, whereas ≥12 months after drug discontinuation the incidence rates decreased towards one, (Figure 3).

Channeling bias

Inconsistent trends were seen for ABC exposure and the renal outcomes (Figure 2, 3). We performed a number of exploratory analyses and found that lower eGFR was

associated with higher ABC initiation rates. Right censoring follow-up for initiating ABC at eGFR<90 did not, however, decrease the CKD effect estimates in adjusted models compared to the primary analysis (right censored CKD aIRR 1.18 [1.03-1.21] vs. primary CKD aIRR 1.08 [1.00-1.17] per year). As ABC and 3TC were the ARVs most commonly initiated at low eGFR, we repeated our primary models with 3TC and observed a marginally increased rate of both endpoints (data not shown).

Other renal predictors

In adjusted models, other significant predictors of confirmed eGFR<70 included age (aIRR 2.60 [2.31-2.93], per 10 years older), female gender (aIRR 1.57 [1.23-2.00]), diabetes (aIRR 1.52 [1.05-2.21]), IDU as mode of transmission (aIRR 1.53, vs. MSM, [1.07-2.19]), prior AIDS (aIRR 1.39 [1.13-1.70]) and current CD4 count (aIRR 0.75 [0.69-0.82], per doubling), with similar findings for CKD, (Figure 4). Hypertension (aIRR 0.93 [0.65-1.32]) and HBV (aIRR 0.89 [0.59-1.34]) were not associated with either endpoint, while a higher baseline eGFR and later calendar year were significantly associated with a lower confirmed eGFR<70 rate only. Sensitivity analyses which adjusted for all non-ARV variables at baseline, rather than as time-updated variables, did not alter our findings.

There were no significant interactions between ARV use and age, HCV, HBV, AIDS or CD4 count (all p> 0.01), indicating that the relationship between cumulative ARV exposure and confirmed eGFR<70 was similar for younger and older patients, in those with or without Hepatitis B, C or a prior AIDS diagnosis, and also according to level of immunosuppression.

Discussion

In this analysis we investigated progression from normal renal function to two different levels of chronic renal impairment. Given the relatively short length of follow-up (< 5 years) these declines were substantial compared to the expected age-related decline of 1 ml/min/year [13, 14].

Such rapid deterioration of renal function is currently attracting much attention [3, 15] as a more dynamic measurement of renal impairment and work is underway to further standardise this term [16].

The primary findings of this analysis were that ongoing exposure to TDF, ATV/r and LPV/r were each associated with an adverse chronic effect on renal function in persons without pre-existing renal impairment. In contrast to other recent studies, this study further showed an independent effect of these ARVs rather than an effect only when co-administered with each other [4, 17, 18].

ATV may, similar to several other PIs, cause urolithiasis and crystaluria, but cases of interstitial nephritis have also been described [19-23]. In recent years evidence has emerged that ATV may also be associated with chronic impairment and other renal outcomes with and without co-administration of TDF [1, 4, 17, 20, 24-26]. We identified ATV/r, but not unboosted ATV use, as a predictor of chronic renal impairment independently of TDF use and pre-existing impairment. Importantly only 25% of the ATV-treated persons received unboosted ATV, which may have reduced our power to demonstrate an effect of this drug without ritonavir. A recent study with similar follow-up also found an association between ATV use and rapid decline in

renal function, but no association with CKD. It was unclear, however, whether ATV use was boosted or unboosted [3].

LPV/r is mainly metabolized in the liver, but approximately 10% is excreted in urine and may therefore also cause urolithiasis [27]. Prior evidence that LPV/r causes CKD is limited [1] and primarily described when co-administered with TDF [17, 28, 29]. Our findings suggested an independent association of LPV/r with both renal endpoints from normal eGFR.

In our analysis the effect of the other PI/r group was not significant in adjusted analysis. A recent study has found use of darunavir to be associated with asymptomatic crystalluria and may therefore be similar to other PIs in terms of influencing renal function [30]. Use of darunavir is however currently limited in this study, which may explain why no association was observed. In the prescribing information for tipranavir and fos(amprenavir) renal damage, possibly due to urolithiasis, is mentioned [11, 12], but little is known about the nephrotoxic potential of these newer PIs. Because of their infrequent use we are unable to comment specifically on the effects of tipranavir and fos(amprenavir), and the presence of other PI's than tipranavir and fos(amprenavir) in the other PI/r group may have diluted any possible effects of these two ARVs.

In addition to mechanistic studies supporting a nephrotoxic potential of TDF [31-33] numerous other studies have investigated TDF nephrotoxicity including case-reports [25, 34, 35], cohort studies [1, 2, 36-38] and randomised controlled trials [39-43]. Most recently a large US study found an independent TDF association with 3 renal outcomes (proteinuria, CKD and rapid eGFR decline) in treatment naive persons [3].

Of note, follow-up in this study ended in 2007 and hence focused on TDF use fairly early after its introduction, where it was used predominantly in persons with acquired drug resistance. Our study extends these findings to a more contemporary cohort of HIV-positive persons where TDF is used earlier in the course of treating HIV. Several randomized trials have also investigated adverse renal events of TDF among individuals with an initially normal renal function [39-43]. Many of these were, however, of insufficient size and follow-up to detect such rare events as chronic renal impairment as done in this analysis. Furthermore, the risk of developing renal impairment in the populations included in these trials is likely reduced, as persons with co-morbidities rendering them at risk of renal impairment – often seen in the general HIV-population – are typically excluded from these trials [39, 40].

Our analysis revealed a provider driven switch away from TDF in persons experiencing renal function decline while on this drug. As the nephrotoxic potential of TDF has been vigorously discussed [39, 40, 44], these proactive switches away from TDF are reassuring.

We found an excess risk from LPV/r use for both renal endpoints, whereas use of TDF and ATV/r was significantly associated only with confirmed eGFR<70 (although consistent non-significant trends were seen also for CKD). The proactive switch away from TDF in persons with deteriorating renal function may have limited our ability to fully address the potential association between TDF use and CKD from eGFR>90, since other parts of our analyses suggested that the TDF effect decreased after discontinuation. In relation to ATV/r, the drug was introduced much later into clinical care than LPV/r and the duration of follow-up therefore substantially shorter. This may have limited our ability to assess the full extent to which ATV/r may

influence renal function. Once additional follow-up has accrued in the D:A:D study, we will re-assess the association between ATV/r and CKD incidence.

The fact that the association between all three drugs and confirmed eGFR<70 was markedly decreased after their discontinuation, does suggest that the effect depends on ongoing exposure and that these associations were not just due to chance or confounding by indication. Importantly these observed declines in incidence rate ratio after the potential nephrotoxic drugs were discontinued (for whatever reason) does not answer the question of reversibility of renal function, but rather suggests that the rate of experiencing the renal impairment endpoint was reduced after stopping the drug for persons that have not already developed this endpoint. A study with the specific aim of assessing the reversibility of declining renal function among persons experiencing chronic renal impairment while on antiretroviral therapy is currently being designed. In this analysis we were unable to address reversibility of renal function as such analyses require longer follow-up after these still relatively rare renal events occurring from initially normal renal function.
In the meantime this analysis highlights the need for a continued and ongoing monitoring of renal function among HIV-positive persons and an increased awareness of such likely drug associations.

Initiating ABC and 3TC was common at eGFR<70, which may possibly explain the observed small and borderline significant association with both renal endpoints. We did however not find evidence of channeling bias for ABC after censoring for initiation with impaired eGFR. To our knowledge only one other study [2] has reported an association between CKD and ABC. Single cases of ABC related Fanconi syndrome [45] and hypersensitivity related interstitial nephritis [46] have

been described. However, due to the small effect size, the inconsistent trends in our analysis, and the tendency to start ABC at lower eGFR, we urge caution in interpreting this finding. Further investigation for a possible biological mechanism is required.

Our analyses also identified and confirmed a variety of other renal risk factors than ARVs, which were the main focus. Importantly, the study focused on the development of renal impairment in HIV-positive persons with an initially normal renal function, currently the largest group seen in clinical practice. As a consequence patients with prevalent comorbidities influencing renal function were excluded because renal impairment (i.e. eGFR < 90) had already developed. This likely affects our ability to identify other potential risk factors, such as hypertension and race, in this analysis.

Age is a traditional risk factor [25, 47, 48] and, despite being adjusted for in the eGFR equation itself, remained among the strongest predictors in this analysis, as were diabetes [37] and CD4 count [1, 37]. Prior AIDS events also represented an expected predictor [1] that may include infections and antimicrobial treatment harmful to the kidneys. Interestingly, nadir CD4 was not a predictor after accounting for other HIV-related factors and further investigations should examine the role of prior immune suppression on renal function in the modern cART era. Several illicit drugs have nephrotoxic potential and are associated with infections, which may explain the observed association. Neither prior CVD nor hypertension reached statistical significance, possibly due to the exclusion of a high proportion with impaired renal function at baseline, inclusion of well-treated patients with hypertension and missing hypertension values. HCV infection was associated with

confirmed eGFR<70 and CKD in unadjusted analyses, but only with CKD in adjusted analyses. However, both adjusted estimates were >1 suggesting a possible relation which may be mediated both directly by a HCV glomerulonephritis and indirectly by hepatorenal syndrome and factors associated with IDU. In the literature there are conflicting reports on this association [49, 50].

African ancestry was not associated with chronic renal impairment in our analysis, but our power to detect such an association was low (<10% with African ancestry and >40% without ethnicity information*).* Sensitivity analyses including only persons with known ethnicity showed entirely consistent results.

Women generally have lower eGFR than males, but after accounting for this in the eGFR equation, female gender was still associated with impaired renal function among persons with initially normal eGFR. Women however only constituted 27% of included persons which limits our ability to fully investigate the influence of gender.

Limitations

Data on proteinuria, other urinary markers, serum phosphate, biopsies and family history of renal disease were not available within the study. Other potentially nephrotoxic non-ARV drugs may represent unmeasured confounding. The assessment of possible selection bias showed that persons with traditional and HIV-related risk factors were more likely to be excluded due to pre-existing renal impairment and inadequate renal data. As a consequence the presented estimates of chronic renal impairment may be underestimated.

We were unable to use the CKD-EPI/MDRD equation to calculate eGFR due to restrictions on ethnicity information. Further imputation of ethnicity was not possible as this information was not missing at random. Finally the conclusions should be

viewed in light of eGFR being a surrogate marker of renal function and the inability of any observational study to draw definitive conclusions on causality.

Conclusion

In HIV-positive persons with normal eGFR, use of TDF, ATV/r and LPV/r were independently associated with adverse chronic renal impairment as were established renal- and HIV-related factors. The TDF discontinuation rates were increased in persons with decreasing eGFR and may have prevented further deterioration to CKD. The incidence of chronic renal impairment associated with these ARV's decreased after their discontinuation.

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A detailed list of the members of the 11 cohorts is to be found as online supplemental information

Conflicts of interests

L. Ryom, S.W. Worm, J.D. Lundgren, D.A. Kamara and M. Ross no conflicts of interest. A. Mocroft has received consultancy fees/honoraria/speaker fees from BMS, Pfizer, Merck, BI, and Gilead Sciences. O. Kirk had prior board membership at ViiV Healthcare, received payment for lectures and/or for development of educational presentations from Abbott, Gilead Sciences and Tibotec. Travel/accommodations/meeting expenses from Abbott, BMS, Gilead Sciences, Merck and ViiV Healthcare. P. Reiss has served as a scientific advisor to Bristol-

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Footnote page

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Table 1. Characteristics at baseline[1]

[1] Baseline defined as date of first eGFR after 01/01/2004 during prospective follow-up

[2]HBV positive: HBs Ag or HBe Ag or DNA positive/anti-HBe positive

[3]HCV positive: HCV antibody positive & RNA positive/unknown

[4] Cumulative defined as per year of additional exposure

[5] Median exposures measured in years

Figure 1. ARV discontinuation rates & eGFR levels

Models adjusted for baseline eGFR (per 5 ml/min higher), age (per 10 years), gender, ethnicity (Caucasian, of African origin, unknown), HIV mode of transmission (MSM, heterosexual, intravenous drug use (IDU), unknown or other), CD4 nadir, enrolment cohort, baseline date. Prior AIDS, HCV (defined by anti-HCV and HCV-RNA positive/unknown) +, HBV (defined by HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive) +, smoking status +, hypertension +, diabetes +, CVD +, CD4 (per doubling) +. Viral load (per log 10 increase) +, and cumulative exposure (per year) + to ATV, ATV/r, LPV/r, TDF, ABC, IDV and other PI/r. + included as time-updated variables.

Figure 2. ARV exposure (per year) & incidence rate ratios of confirmed eGFR<70 & CKD from eGFR>90

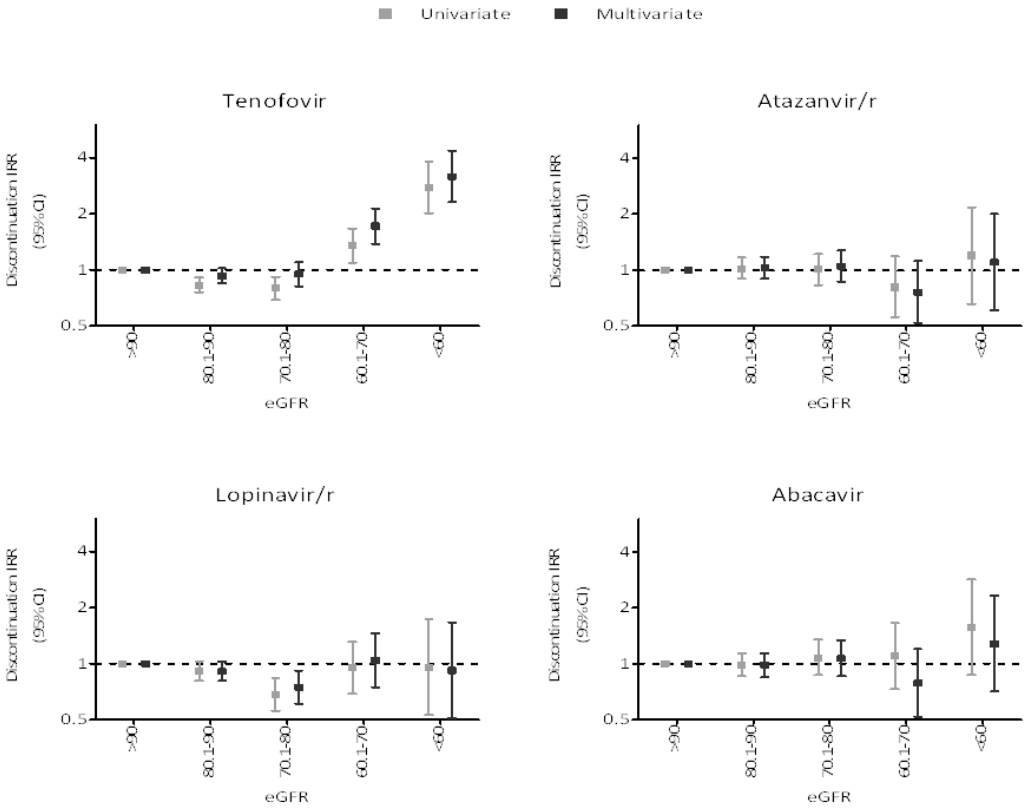
Models adjusted for baseline eGFR (per 5 ml/min higher), age (per 10 years), gender, ethnicity (Caucasian, of African origin, unknown), HIV mode of transmission (MSM, heterosexual, intravenous drug use (IDU), unknown or other), CD4 nadir, enrolment cohort, baseline date. Prior AIDS, HCV (defined by anti-HCV and HCV-RNA positive/unknown) +, HBV (defined by HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive) +, smoking status +, hypertension +, diabetes +, CVD +, CD4 (per doubling) +, Viral load (per log 10 increase) +, and cumulative exposure (per year) + to ATV, ATV/r, LPV/r, TDF, ABC, IDV and other PI/r. + included as time-updated variables.

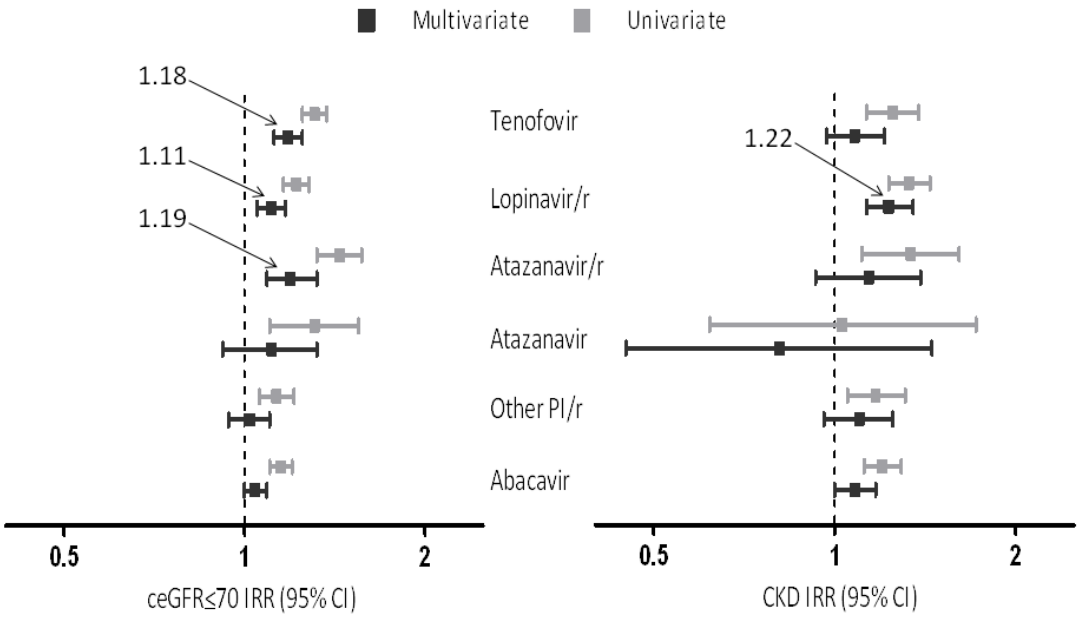
Figure 3. ARV exposure & rates of confirmed eGFR<70 from eGFR>90, adjusted analysis

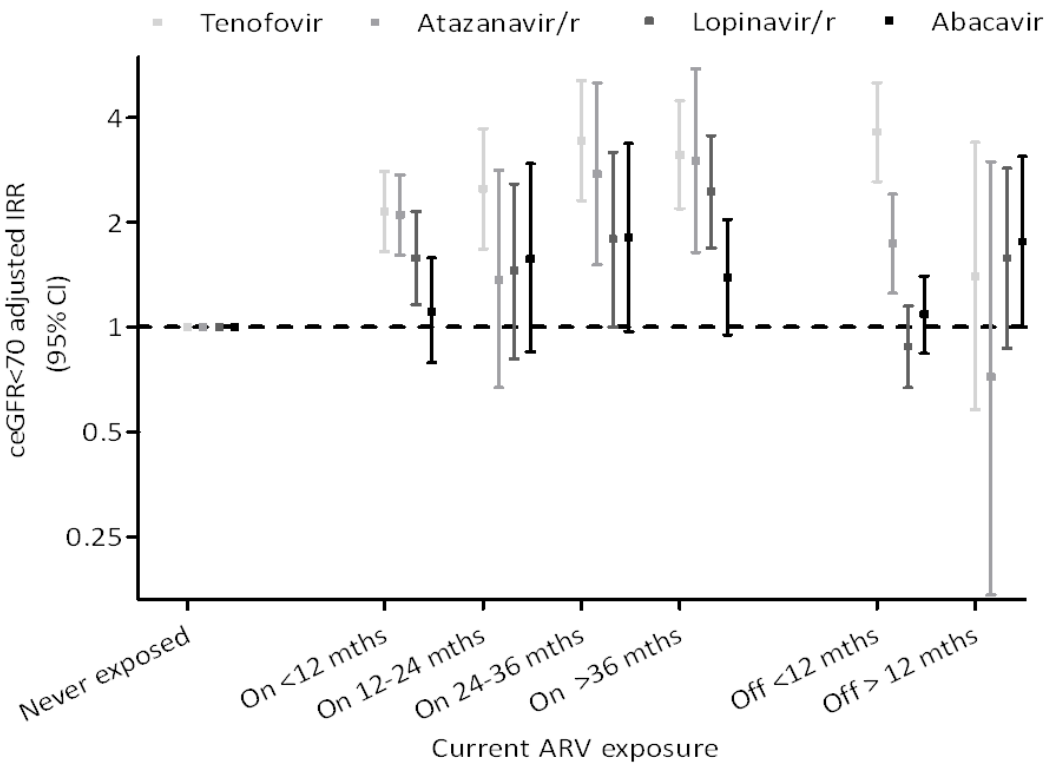
Models adjusted for baseline eGFR (per 5 ml/min higher), age (per 10 years), gender, ethnicity (Caucasian, of African origin, unknown), HIV mode of transmission (MSM, heterosexual, intravenous drug use (IDU), unknown or other), CD4 nadir, enrolment cohort, baseline date. Prior AIDS, HCV (defined by anti-HCV and HCV-RNA positive/unknown) +, HBV (defined by HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive) +, smoking status +, hypertension +, diabetes +, CVD +, CD4 (per doubling) +. Viral load (per log 10 increase) +, and cumulative exposure (per year) + to ATV, ATV/r, LPV/r, TDF, ABC, IDV and other PI/r. + included as time-updated variables.

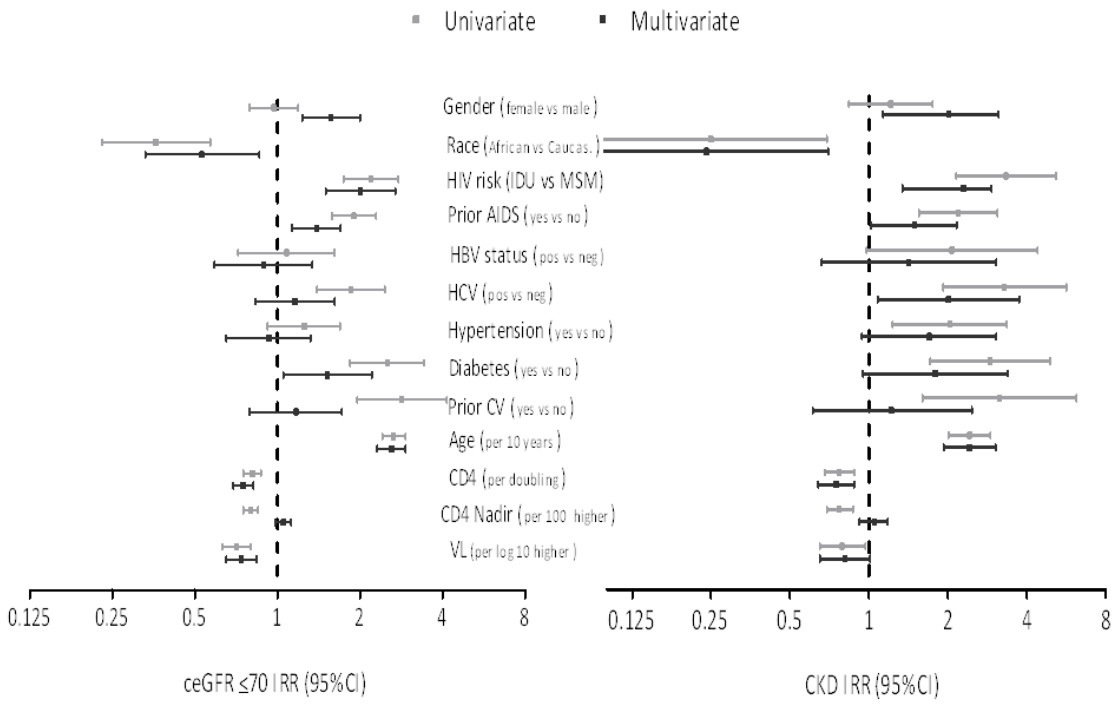
Figure 4. Other predictors of confirmed eGFR<70 & CKD from eGFR>90

Models adjusted for baseline eGFR (per 5 ml/min higher), age (per 10 years), gender, ethnicity (Caucasian, of African origin, unknown), HIV mode of transmission (MSM, heterosexual, intravenous drug use (IDU), unknown or other), CD4 nadir, enrolment cohort, baseline date. Prior AIDS, HCV (defined by anti-HCV and HCV-RNA positive/unknown) +, HBV (defined by HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive) +, smoking status +, hypertension +, diabetes +, CVD +, CD4 (per doubling) +. Viral load (per log 10 increase) +, and cumulative exposure (per year) + to ATV, ATV/r, LPV/r, TDF, ABC, IDV and other PI/r. + included as time-updated variables.









	N, all included (%) [IQR]	N, eGFR≤70 (%) [IQR]	N, CKD (%) [IQR]
All	22603 (100)	468 (2)	131 (0.6)
Gender (Male)	16438 (73)	340 (73)	89 (68)
Ethnicity			
-Caucasian	10573 (47)	309 (66)	88 (67)
- Unknown	9714 (43)	129 (28)	37 (28)
- African	1806 (8)	20 (4)	4 (3)
Median Age (years)	39 [33-44]	46 [41-52]	46 [40-51]
HIV-transmission			
- MSM	10006 (44)	176 (38)	39 (30)
- IDU	3058 (14)	121 (26)	41 (31)
- Heterosexual	8095 (36)	150 (32)	42 (32)
Prior AIDS	4553 (20)	154 (33)	48 (37)
CD4 (count/mm^3)	440 [290-624]	380 [217-568]	380 [221-585]
HIV-RNA (log_{10}copies/ml)	2.1 [1.7-4.2]	1.8 [1.7-4.0]	2.3 [1.7-4.0]
Years HIV+	5.2 [1.2-11.1]	10.0 [5.3-14.9]	10.8 [4.5-15.5]
HBV[2]	2773 (12)	64 (14)	17 (13)
HCV[3]	2765 (12)	93 (20)	37 (28)
Hypertension	176 (8)	53 (11)	20 (15)
Diabetes	664 (3)	43 (9)	14 (11)
Prior CV event	336 (2)	17 (4)	6 (5)
Smoking	9548 (42)	239 (51)	71 (54)
cART exposed	14263 (63)	346 (74)	94 (72)

	N, all included	Use of Antiretrovirals Cumulative Exposure[4] (PYFU)	Median Exposure[5] [IQR]
TDF	5366	2015	0 [0-0.4]
LPV/r	4963	3358	0.1 [0-1.0]
ABC	4937	5613	0.3 [0-1.9]
ATV/r	1055	296	0 [0-0.2]
ATV	352	192	0.1 [0-0.6]
Other PI/r	2216	3669	1.1 [0.3-2.5]
IND	4567	9135	1.5 [0.6-3.0]