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Title Predictors of eGFR Progression, Stabilisation or Improvement After Chronic Renal Impairment in HIV-positive individuals

Running title eGFR after chronic renal impairment

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Abstract

Objectives

The objectives of this analysis were to investigate predictors of progression, stabilisation or improvement in eGFR after development of chronic renal impairment (CRI) in HIV-positive individuals.

Design

Prospective observational study.

Methods

D:A:D study participants progressing to CRI defined as confirmed, ≥3 months apart, eGFR≤70 mL/min/1.73m^2 were included in the analysis. The median of all eGFRs measured 24-36 months post-CRI was compared to the median eGFR defining CRI, and changes were grouped into: improvement (>+10 mL/min/1.73m^2), stabilisation (-10 to +10 mL/min/1.73m^2) and progression (<-10 mL/min/1.73m^2). Adjusted polynomial regression models assessed odds of better eGFR outcomes after CRI, assuming eGFR improvement is better than stabilisation which in turn is better than progression.

Results

Of 2006 individuals developing CRI, 21% subsequently improved eGFR, 67% stabilised and 12% progressed. Individuals remaining on TDF or boosted atazanavir (ATV/r) 24 months post-CRI had worse eGFR outcomes compared to those unexposed (TDF: 0.47 [0.35-0.63], ATV/r: 0.63 [0.48-0.82]). Individuals off TDF for 12-24 months (0.75 [0.50-1.13]) or off ATV/r for >12 months (1.17 [0.87-1.57]) had similar eGFR outcomes as those unexposed to these ARVs. Older age, hypertension, later date of CRI and diabetes were associated with worse eGFR outcomes.

Conclusion

Current TDF and ATV/r use after a diagnosis of CRI was associated with worse eGFR outcomes. In contrast, TDF and ATV/r discontinuation lead to similar longer-term eGFR outcomes as in those unexposed suggesting these drug- associated eGFR declines may be halted or reversed after their cessation.

Key words

HIV, eGFR, chronic renal impairment, tenofovir, atazanavir, reversibility

Text

Introduction

Currently, limited knowledge exists of the longer-term outcomes of renal function after the development of chronic renal impairment (CRI) in HIV-positive persons, and the relationship with use of antiretroviral (ARV) drugs and other risk factors [1-5]. Whilst several commonly used ARVs have been associated with development of moderate levels of CRI [6-9], the possibility that ARV-associated CRI may be reversible after drug cessation, has not yet been fully investigated.

Studies of non-ARV drugs with nephrotoxic properties such as aminoglycosides and amphotericin B have shown that iatrogenic induced tubular or interstitial renal damage is reversible if the damage is recognised early, the causative drug is discontinued, low cumulative doses are administered and the patient has few other comorbidities that increase the risk of nephrotoxicity [3, 10-14]. However, in contrast to most other potentially nephrotoxic drugs, treatment with ARVs is life-long. As a consequence high cumulative doses are delivered to the kidneys with a potential for accumulating damage to the renal tissue, and risk of more permanent renal impairment. Other factors that induce chronic nephron injury leading to renal fibrosis (i.e. diabetes and hypertension) are often irreversible, despite initiation of appropriate treatment [15]. However, it is plausible that reduced renal function due to ARV-related CRI, depending on the specific effects and duration of the ARV used, may improve or stabilise, whilst CRI associated with traditional renal risk factors may be more likely to progress.

Others have investigated associations between the use (and discontinuation) of several ARVs, particularly tenofovir (TDF), and the possible reversibility of renal

function deterioration. However, the lack of a common definition of reversibility of renal function, the small number of cases, limited follow-up and a focus primarily on mild and acute renal failure have meant that these studies have provided limited insight into this question [1-4, 15-19].Reversibility of renal impairment is a difficult endpoint to define as eGFR is known to decline with advancing age [20]. Therefore, when assessing longitudinal data on renal function stretching over long follow-up periods one cannot expect to see a complete return of eGFR to levels of earlier time-periods regardless of the intervention. Likewise other comorbidities such as diabetes may be progressive in nature making resolution of any ARV-associated eGFR decline unlikely despite timely discontinuation [18]. For these reasons, assessments of reversibility of renal function should be interpreted with caution, and a focus on eGFR improvement, stabilisation or progression may be more informative.

Prior studies from the Data Collection on Adverse events of Anti-HIV Drugs Study (D:A:D) have shown increased TDF discontinuation rates already at eGFR$\leq$70 mL/min/1.73m^2, thus potentially limiting the value of a confirmed eGFR$\leq$60 mL/min/1.73m^2 as a CRI threshold for addressing the question of reversibility of ARV-associated renal impairment [8]. This analysis is an extension of earlier work from D:A:D suggesting an association between use of certain ARVs and CRI, but in which follow-up was too limited to assess eGFR changes after CRI.

If switching away from ARVs associated with renal impairment results in stabilisation or even improvement in eGFR after CRI has developed, this will have major clinical implications for future risk stratification in relation to ART initiation and switches.

The aim of this analysis was therefore to investigate predictors of progression, stabilisation or improvement in eGFR after development of CRI.

Methods

The D:A:D study is a prospective cohort collaboration established in 1999 following more than 49,000 HIV-1-positive persons in Europe, Australia and the USA; details have been published previously [21]. Information on clinical events including end-stage renal disease and death is collected during routine clinical care, validated centrally and regularly monitored. Data on demographic factors, ART, laboratory values, cardiovascular risk factors and AIDS events are collected electronically at enrolment and every six months thereafter.

Participants with an eGFR>80 mL/min/1.73m^2 after 1/1/2004 (date of systematic creatinine collection) actively progressing to CRI (confirmed, $\geq$3 months apart, eGFR$\leq$70 mL/min/1.73m^2) with $\geq$2 eGFRs in the follow-up period 24-36 months after CRI were included in the analysis. Follow-up ended at the earliest of last visit plus 6 months and 1/2/2016. The requirement of a baseline eGFR>80 mL/min/1.73m^2 ensures an active eGFR decline of $\geq$10 mL/min/1.73m^2 before CRI, and aimed at preventing inclusion of individuals with longstanding CRI with limited potential for subsequent eGFR improvement. A 24-36 month follow-up period was included to allow sufficient time to establish the subsequent trajectory of renal function.

For each individual, the difference in eGFR between the median of all eGFRs measured at 24-36 months after CRI, and the median of the 2 eGFR values defining CRI were categorised as eGFR improvement (>+10 mL/min/1.73m^2)**,** stabilisation (-10 to +10 mL/min/1.73m^2) or progression (<-10 mL/min/1.73m^2), Supplementary Figure 1.

The Cockcroft-Gault (CG) equation [22], standardized for body surface area [23], was used to estimate creatinine clearance and as a surrogate for eGFR in this analysis [24]. As several specific cohorts were prohibited from collecting ethnicity information the CG was used rather than an equation including ethnicity.

Baseline was defined as the date of CRI (median date of the 2 eGFRs defining CRI), and characteristics at baseline were compared between the improvement, stabilisation and progression groups using the chi-squared test or the Wilcoxon sign rank test.

A polynomial ordinal logistic regression model was used to assess odds of better eGFR outcomes after CRI, assuming eGFR improvement is better than stabilisation which, in turn, is better than progression. The method assumes that any change in odds comparing stable to progressive eGFR is the same as the change in odds comparing improved to stable eGFR.

A multivariable model included the following non-ARV variables, selected a priori and measured at baseline; gender, age, hypertension (>150/>100 mmHg or use of antihypertensive drugs), prior cardiovascular disease; CVD (case report verified myocardial infarction, invasive cardiovascular procedure or stroke, details at www.cphiv.dk), diabetes (anti-diabetic treatment or case report verified), HCV (anti-HCV positive and HCV-RNA positive/unknown), CD4, nadir CD4, , CRI date, eGFR at CRI and eGFR slope prior to CRI. The eGFR slope was calculated as the annual eGFR change between the first eGFR>80 mL/min/1.73m^2 and the eGFR at CRI using least squares regression (using all eGFRs available). An eGFR slope of $\leq$-10

mL/min/1.73m^2 defined a faster and >-10 mL/min/1.73m^2, a slower eGFR decline prior to CRI.

The model was further adjusted for use of ARVs with a reported association with renal impairment: TDF; atazanavir with (ATV/r) or without (ATV) ritonavir; lopinavir (LPV/r); other boosted protease inhibitors (PI/r); and abacavir (ABC) [6-9, 25-27]. Indinavir use after 2004 was limited and was only included to adjust for potential unmeasured confounding. In all analyses ARV drug use was fitted at time of CRI diagnosis plus 24 months to allow for assessment of drug switches at and around the time of CRI, Supplementary Figure 1. ARV use was further categorised as never exposed, currently on and currently off for ATV, and as never exposed, currently on, and currently off (≤12 months, 12-24 months and >24 months) for TDF, and never exposed, currently on, and currently off (≤12 months, >12 months) for all other ARVs. These categories were mutually exclusive and chosen to allow sufficient numbers within each category for meaningful analysis. Those currently off an individual ARV <12-24 months will, by definition, have discontinued use between the CRI diagnosis and the time of CRI plus 24 months, while those off the ARV >24 months, by definition, will have discontinued use before development of CRI.

All statistical analyses were carried out using SAS version 9.3 (Cary, NC, USA).

Results

A total of 33,151 persons had an eGFR>80 mL/min/1.73m^2 and ≥3 eGFR measurements after 1/1/2004, Figure 1. Of these, 4,456 (13.4%) progressed to CRI during prospective follow-up, and 2,006 persons had ≥2 eGFR measurements 24-36 months after CRI.

Those included in analyses were predominantly white (49.4%) male (76.2%), having acquired HIV homosexually (51.2%). The CD4 count closest to baseline (time of CRI) was 520 cells/mm^3 and median eGFR 65 mL/min/1.73m^2. A total of 93.8% were on cART, 16.8% had hypertension, 6.3% diabetes for >5 years and 9.2% previous CVD. Baseline characteristics in Table 1.

Persons with CRI excluded from the analysis due to lack of eGFR measurements in the follow-up period (n=832) or inadequate length of follow-up (n=1618, of whom 144 persons died) were generally older, had a later baseline date, were less likely to be on ART, and have a lower baseline eGFR. Prior exposure to ARVs was similar in those excluded to those included (data not shown). Among the 144 persons dying in in the follow-up period after CRI the most common individual causes of death were non-AIDS defining malignancies (40, 27.8%), AIDS defining illness (19; 13.2%), chronic viral hepatitis (17; 11.8%) and unknown causes (16; 11.1%). Only 2 individuals (1.4%) died of renal related causes.

During follow-up after CRI, 20.7% of included individuals experienced improvement in eGFR, 67.0% stabilisation and 12.3% progression.

After adjustment, individuals remaining on TDF at the time of CRI plus 24 months follow-up had lower odds of better eGFR outcomes (adjusted odds ratio, aOR, 0.47 [95% confidence interval, 0.35-0.63]) compared to individuals who had never started TDF, Figure 2. Likewise individuals who had been off TDF<12 months at CRI plus 24 months had lower odds of better eGFR outcomes (0.26 [0.17-0.40]). In contrast, individuals off TDF for 12-24 months (0.75 [0.50-1.13]) or >24 months (0.89 [0.61-

1.31]) had similar odds of better outcomes compared to individuals never exposed to TDF. Similar trends were seen for ATV/r except the odds of better eGFR outcomes returned to the levels of those who had never started ATV/r <12 months of ATV/r discontinuation, Figure 3. Data for unboosted ATV was limited and showed similar results to those seen for LPV/r (although not statistically significant), Figure 3. In contrast, there was no clear association between use of, or time since discontinuation of ABC and other PI/r and outcomes after CRI, Figure 3.
The results were consistent after follow-up for each of the ARVs was censored for any follow-up with concomitant use of the other included ARVs (i.e. follow- up on ATV/r use was censored for any TDF use, data not shown).

Older persons had significantly lower odds of better eGFR outcomes (0.58 [0.52-0.65] per 10 years), but there was no suggestion of a given age at which odds of better outcomes started to decrease, Figure 4, Other predictors of worse eGFR outcomes were diabetes >5 years (0.47 [0.32-0.71], hypertension (0.73 [0.56-0.95]) and a later date of CRI (0.93 [0,89-0.97). HIV viremia and HCV positivity did not significantly impact on eGFR outcomes. While there was no interaction between hypertension, diabetes and ARV use (all p>0.05), a significant interaction between TDF, age and eGFR outcomes (p=0.0009) was observed, suggesting that the higher odds of better outcomes associated with discontinuing TDF were decreased for individuals >50 compared to those <50 years.

A large number of sensitivity analyses were carried out to test the robustness of the ARV drug associations with eGFR outcomes including looking at outcomes at time of CRI, at 12-24 months after CRI or at >36 months after CRI .Results were further

unchanged by adjustment for calendar time. Further stratification of exposure to ARVs was also investigated, but the confidence intervals became too wide to draw clinically relevant conclusions.

Additional sensitivity analyses tested if the proportional odds assumption was reasonable (i.e. that changes in odds comparing eGFR improvement to stabilisation was similar to changes comparing eGFR stabilisation to progression).Results were tested using a nominal logistic regression model, which showed highly consistent results (data not shown). Consistent results were also seen using only two eGFR outcomes; improvement/stabilisation versus progression (data not shown).

Use of confirmed eGFR$\leq$60 mL/min/1.73m^2 as an alternative CRI definition (with progression from an initial eGFR>70 mL/min/1.73m^2) did not significantly alter the proportions in the eGFR improvement, stabilisation or progression groups, Figure 1. The predictors of better eGFR outcomes were likewise largely similar to the primary analysis with the exception of women having better odds of improvement than men (1.59 [1.15-2.20]) and being currently on TDF at time of CKD plus 24 months, which was no longer significantly associated with a worse eGFR outcome (0.77 [0.50-1.19]) as compared to TDF unexposed. Those off TDF for <12 months had similar odds of a better eGFR outcome (0.88 [0.52-1.50]), while those off 12-24 months had higher odds (1.96 [1.20-3.20]) compared to TDF unexposed.

Finally, a CRI resolution endpoint was investigated; a return to confirmed eGFR>70 mL/min/1.73m^2 at 24-36 months after CRI. Of the 2,006 persons included 470 (23.4% [21.5-25.3]) experienced CRI resolution, and younger age and earlier date of CRI diagnosis were significant predictors (data not shown). The relation between TDF use and discontinuation and resolution confirmed the findings of the primary

analysis (currently on TDF at CRI plus 24 months 0.43 [0.31-0.60], off ≤12 months 0.32 [0.19-0.53], off 12-24 months 0.98 [0.63-1.56] and off >24 months 0.90 [0.59-1.39]), all compared to TDF unexposed). The relation with the other nephrotoxic ARVs did not reach statistical significance, but showed similar findings to those shown in Figure 3 (data not shown).

Discussion

This is the first study to investigate longer-term confirmed eGFR outcomes after progression to CRI in HIV-positive persons. Our results suggest that continued use of TDF and ATV/r after a CRI diagnosis is associated with worse renal outcomes, and that discontinuation of these drugs may in time halt or improve eGFR in particular in individuals younger than 50 years. These analyses extend previous work from D:A:D demonstrating the association between use of TDF, ATV/r and LPV/r and progression to CRI from an initial normal eGFR [8].

ARV use and discontinuation as predictors of eGFR outcomes

The observation that current use of primarily TDF and ATV/r after CRI, are associated with worse eGFR outcomes after CRI are consistent with previous, primarily observational, studies linking use of these ARVs with a CRI diagnosis [6-9]. The associations with LPV/r and ATV were less clear, possibly due to lack of power, but trended towards a worse eGFR outcome, after stopping these ARVs. In contrast, there was no suggestion of an association between eGFR outcomes and use of ABC or other PI/r. These results suggest that TDF- and ATV/r-associated eGFR declines may not represent irreversible renal tissue damage and timely discontinuation may independently be beneficial for HIV-positives with declining eGFR. The observation that eGFR outcomes were similar in those off ATV/r <12 months and those never

exposed to ATV/r, but that this first occurred at >12 months after stopping TDF may suggest different underlying biological mechanisms of ARV-related renal impairment. As such ATV/r crystaluria/interstitial nephritis may be easier to resolve than TDF-related tubulopathy, but additional mechanistic studies are warranted.

It is, of some concern, that the potential to improve/stabilise eGFR seems less strong in individuals >50 years, and focus should hence be put on older individual on TDF with declining eGFR. Using confirmed eGFR≤60 mL/min/1.73m^2 to define CRI did not reach statistical significance for current TDF use, but showed similar trends of increasing odds of better eGFR outcomes with time since TDF discontinuation as in the primary analysis. These findings must be interpreted with some caution, as they are affected by the common nephrotoxic ARV switches in this eGFR range [8]. The eGFR outcomes after ATV/r discontinuation in this exploratory analysis were similar to those observed in the primary analysis, with higher odds of better renal outcomes after discontinuation, although not reaching statistically significance and limited by reduced power and shorter follow-up periods.

Among the other studies investigating associations between TDF discontinuation and renal function, Jose and colleagues likewise showed an overall eGFR improvement using median piecewise slope evaluation after switching away from TDF [5]. Two safety studies and a small US study found improvement/resolution of all TDF-associated renal impairment cases after TDF discontinuation, but suffered from several methodological challenges [16, 17, 19]. Other studies have found that only certain individuals discontinuing TDF reached their pre-exposure eGFR levels suggesting incomplete recovery [1, 4, 6, 18], but the progressive age-related eGFR decline is difficult to account for in these analyses. For ATV, a 2007 FDA study found that all individuals with ATV-related urolithiasis regained renal function after

stone removal and ATV discontinuation [28], which was supported by the EuroSIDA study [6]. Other PI-related urolithiasis are relatively rare, although asymptomatic crystalluria may be more prevalent and have, to date, not been assessed in safety trials.

From this and other studies it seems increasingly compelling that a better renal outcome is possible after discontinuation of TDF and ATV/r, and possibly other nephrotoxic ARVs, after CRI. We were unable to identify a threshold below which eGFR improvement or stabilisation was no longer possible despite drug discontinuation. It is unknown if such a threshold exists, but it represents an essential question to address in the future to enhance identification of when ARVs with nephrotoxic potential need to be discontinued to avoid irreversible damage [5].

Non-ARV predictors of eGFR outcomes

Age, was as expected, consistently one of the factors most strongly associated with a worse eGFR outcome after CRI in this analysis, and is not modifiable. As also expected, hypertension and longer term diabetes were associated with worse eGFR outcomes, underlining the importance of optimising blood pressure levels, glycemic control, limiting diabetic-related proteinuria. Interestingly a diagnosis of CRI in later years was also independently associated with a worse outcome, highlighting the need for a more proactive screening and management to prevent CRI.

We found no association between a fast or slowly declining eGFR slope prior to CRI and eGFR outcomes, contrasting a smaller study where a slowly declining eGFR led to worse renal outcomes [1, 31]. No HIV-related factors were associated with better eGFR outcomes despite other studies, including earlier D:A:D studies, have seen a strong association between eGFR, and current CD4 cell count [8, 32, 33]. This may

be due, in part, to the majority of the persons included in this study having well controlled HIV and high CD4 counts.

Our results suggest that eGFR improvement after CRI is relatively common, with one in five individuals experiencing significant eGFR improvement, and 23% experiencing complete resolution of CRI. Likewise, most HIV-positive individuals progressing to CRI subsequently stabilised eGFR at moderate levels of renal impairment rather than continued to decline. These observations offer reassurance for HIV-positive persons and their health care providers as it seems that at least some of the excess renal risk among HIV positive persons can be modified with appropriate management [32, 33]. Future studies are however needed to assess which renal interventions are the most effective for HIV-positive individuals, and at which level of renal impairment they should be initiated.

Limitations

There are some limitations to acknowledge in this analysis. We cannot exclude the possibility of selection bias as those excluded from the analysis were more likely to have several common renal risk factors, and as a result, we may have underestimated the proportion of individuals progressing to CRI. Further a relatively large number of individuals were excluded due to insufficient number of eGFR measurements or follow-up after the CRI diagnosis, although only two of those excluded were known to have died of renal related causes. As a consequence the proportion of individuals with eGFR improvement or stabilisation after CRI may be overestimated. Exposure to tenofovir alafenamide and cobicistat in D:A:D is to date extremely limited and is unlikely to affect our findings. The integrase inhibitor

dolutegravir inhibits renal creatinine secretion with artefactual eGFR declines, but this is unlikely to explain our findings as all individuals in this analysis had an eGFR decline >10 mL/min/1.73m^2. Finally, unmeasured confounding cannot be ruled out due to the lack of urinary markers, biopsy findings, family history and the use of other nephrotoxic non-ARV drugs. Our main conclusions were however tested in a number of sensitivity analyses with consistent results, including modifying the CRI and eGFR outcomes; fitting ARV exposure at different time-points and after censoring follow-up time for concomitantly used ARVs.

Conclusions

Even after progression to a diagnosis of CRI, subsequent longer-term improvements in renal function are relatively common among HIV-positive persons, with the majority stabilising and only few persons experiencing continued decline in eGFR over time. Older age, hypertension, longer-term diabetes, later date of CRI diagnosis and use of TDF and ATV/r were associated with lower odds of better eGFR outcomes after CRI. Persons who stopped TDF and ATV/r had similar eGFR outcomes compared to those who had never started these ARVs, suggesting that ARV-associated eGFR decline may be halted or reversed with timely drug cessation.

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Conflicts of interest

L. Ryom, J.D. Lundgren and M. Ross have 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/present board membership at ViiV Healthcare, Gilead Sciences and Merck, received payment for lectures and/or for development of educational presentations from Abbott, Gilead Sciences and Tibotec and had travel/accommodations/meeting expenses paid by Abbott, BMS, Gilead Sciences,

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Figure 1. Flowchart of inclusion into the primary and sensitivity analyses

Table 1. Characteristics at time of CRI[1]

1. CRI = baseline; date of confirmation eGFR measurement, 2 Improvement in eGFR defined as (>+10 mL/min/1.73m^2), stabilisation (-10 to +10 mL/min/1.73m^2) and progression (<-10 mL/min/1.73m^2). 3. men having sex with men, 4. Defined as the annual eGFR change between the first eGFR>80 mL/min/1.73m^2 and the eGFR at CRI; ≤-10 mL/min/1.73m^2 defined a faster and >-10 mL/min/1.73m^2 a slower eGFR decline

Figure 2.

Adjusted Odds Ratios of Better eGFR Outcomes After Chronic Renal Impairment according to Use of TDF

Adjusted for gender, age, nadir CD4, baseline CD4 count, CRI date, eGFR at CRI, eGFR slope prior to CRI, HCV status, diabetes, hypertension, prior cardiovascular disease and use of TDF, ATV/r, ATV, LPV/r, other PI/r, IDV and ABC at CRI plus 24 months.

Figure 3.

Adjusted Odds Ratios of Better eGFR Outcomes After Chronic Renal Impairment According to Use of Other ARVs

Adjusted for gender, age, nadir CD4, baseline CD4 count, CRI date, eGFR at CRI, eGFR slope prior to CRI, HCV status, diabetes, hypertension, prior cardiovascular disease and use of TDF, ATV/r, ATV, LPV/r, other PI/r, IDV and ABC at CRI plus 24 months.

Figure 4.

Associations Between Non-ARV Factors

and Better Renal Outcomes after Chronic Renal Impairment

Adjusted for gender, age, nadir CD4, baseline CD4 count, CRI date, eGFR at CRI, eGFR slope prior to CRI, HCV status, diabetes, hypertension, prior cardiovascular disease and use of TDF, ATV/r, ATV, LPV/r, other PI/r, IDV and ABC at CRI plus 24 months.

Supplementary Figure 1.

Methods