Use of contemporary protease inhibitors and risk of incident chronic kidney disease in HIV-positive persons; the D:A:D Study

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summary

After more than six years median follow-up in D:A:D cumulative darunavir/ritonavir use was not significantly associated with a gradually increasing CKD incidence. In contrast, a 40% increased CKD incidence after four years atazanavir/ritonavir use, compared to never used, was confirmed.

Abstract

Background It is unclear if use of contemporary protease inhibitors (PIs) pose a similar chronic kidney disease (CKD) risk as older PIs.

Methods D:A:D participants were followed to CKD, last visit or 2016. Adjusted Poisson regression assessed associations between CKD and boosted atazanavir (ATV/r) and darunavir (DRV/r).

Results CKD incidence (10.0/1000 PYFU [95%CI 9.5-10.4]) increased gradually with increasing exposure to ATV/r, but less clearly for DRV/r. After adjustment, only exposure to ATV/r (1.4 [1.2-1.6]), but not DRV/r (1.0 [0.8-1.3]) remained significantly associated with CKD.

Conclusion While DRV/r use was not significantly associated with CKD an increasing incidence with longer ATV/r use was confirmed.

Key words: CKD, HIV, darunavir, atazanavir, protease inhibitors, adverse drug effect, nephrotoxicity

Introduction

Prior studies, including analyses of the D:A:D (Data collection on Adverse events of Anti-HIV Drugs) study, have shown an association between longer cumulative exposure to several HIV protease inhibitors (PIs) including indinavir (IDV), ritonavir boosted atazanavir (ATV/r) and lopinavir (LPV/r) and excess risk of incident chronic kidney disease (CKD) [1, 2]. The association between PI/r use and CKD may be explained by the increased propensity of these drugs to cause crystalluria, urolithiasis and interstitial nephritis [3-5]. Ritonavir boosted darunavir (DRV/r) was widely implemented as part of routine clinical care for HIV in Europe from 2009 onward, with steadily increasing use due to its efficacy and high genetic barrier to resistance. In contrast to several of the older PIs, only a very limited number of case reports have linked use of DRV/r with development of urolithiasis [6-8]. A recent switch study from the UK further suggested DRV/r use may even exert a positive effect on eGFR trajectories as compared to other PIs [7].

CKD is increasingly common amongst people living with HIV (PLWH) with a wide spectrum of potential risk factors and is associated with considerable morbidity and mortality. Improved insights into both primary and secondary preventive measures are therefore urgently required [9].

The aim of this analysis was to assess whether cumulative use of more contemporary PIs including DRV/r, are associated with an increased incidence of CKD to a similar extent as some of the older PIs.

Methods

The D:A:D study is a large cohort collaboration established in 1999 with more than 49,000 HIV-1-positive persons under prospective follow-up in Europe, Australia and the USA; details have been published previously [10]. Data on demographics, CD4 count, HIV-RNA and other laboratory measurements, antiretroviral treatment (ART), cardiovascular risk factors and AIDS events are collected electronically at the time of enrolment and every six months thereafter. In addition, clinical events including end-stage renal

disease, myocardial infarction, stroke, invasive cardiovascular procedures and death are reported during routine clinical care, validated centrally and regularly monitored. All participating cohorts followed local national guidelines/regulations regarding patient consent and/or ethical review.

CKD was defined as confirmed (≥3 months apart) estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m^2 [11, 12]. The Cockcroft-Gault (CG) equation, standardized for body surface area, was, as in prior D:A:D renal analyses, used to estimate creatinine clearance, and used as a surrogate for eGFR in this analysis [13]. As several participating cohorts are prohibited by law from collecting information on ethnicity the CG was used rather than an equation including ethnicity. Further, the CG equation has the advantage of weight adjustment which is relevant in a population with lipohypertrophy and lipoatrophy.

Study participants with at least three eGFR measurements (one at or before baseline and two after), minimum 3 months follow-up, baseline eGFR >60 mL/min/1.73m^2 and data on CD4 count and HIV viral load (VL) at baseline were included in the analyses. The study baseline was defined as January 1st, 2009 reflecting the broader licensing of DRV/r in Europe. Participants were followed to the earliest occurrence of CKD, last visit plus six months or February 1st, 2016.

Poisson regression was used to model the association between CKD and cumulative use of the presently most commonly used PIs DRV/r and ATV/r, while adjusting for demographics (i.e. gender, age and cohort), other ART that may impact renal function (i.e. tenofovir disoproxil fumarate, TDF), traditional renal risk factors (i.e. hypertension, diabetes, baseline eGFR and cardiovascular disease) and HIV-related risk factors (i.e. CD4 count, viral hepatitis co-infection and prior AIDS). Based on earlier D:A:D renal analyses the association between CKD and longer ATV/r use is expected to be gradual and could therefore be reasonably fitted as a continuous variable. However, since such a relation may not exist for DRV/r in this analysis ART exposure was fitted categorically [11]. Variables not changing over time were fitted as time-fixed (baseline) values, whereas variables that changed during follow-up i.e. use of ART and CD4 count, were fitted as time-

updated values. A separate Poisson regression model assessed adjusted associations of switching away from DRV/r and ATV/r with declining eGFR levels.

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

Results

Of the 36,283 persons in D:A:D with prospective follow-up after January 1st 2009, 8,494 persons were excluded from the analysis due to having a baseline eGFR $\leq$60 mL/min/1.73m^2, fewer than two eGFR measurements after baseline or less than three months follow-up. An additional 114 persons were excluded due to missing baseline CD4 and/or VL data. Compared to the 27,675 persons included in the analysis those excluded were less likely to be on ART and have undetectable VL, and more likely to have lower CD4 counts, be older, Caucasian and HCV positive.

The median age at baseline was 44 (IQR 38-50) years, median eGFR 101 (IQR 87-117) mL/min/1.73m^2 and median CD4 count 510 (IQR 340-699) cells/mm^3, 80.1% had VL <400 copies/mL and 28.7%, 35.6% and 35.7% were at low, medium and high 5-year CKD risk as estimated by the D:A:D CKD risk score [12]. Most participants were male (73.8%), of white origin (45.8%) and men-having sex with men (47.0%). Of the total follow-up time (164,983 PYFU) 14.4% and 25.0% was accrued after DRV/r and ATV/r initiation respectively (Supplementary Table 1).

A total of 1,642 persons (5.9%) developed CKD (incidence rate, IR, 10.0 [95% confidence interval, CI, 9.5-10.4] per 1,000 person years of follow-up (PYFU)) during 6.8 years median follow-up (interquartile range (IQR) 5.4-7.1). The crude IR of CKD in persons unexposed to DRV/r was 9.3 per 1,000 PYFU [8.8-9.8] and in persons unexposed to ATV/r 8.7 per 1,000 PYFU [8.1-9.2]. There was a consistently increasing IR of CKD with increasing exposure to ATV/r, and while there was some increase in CKD IR with increasing exposure to DRV/r the IR was more variable, Figure 1.

After adjustment for potential confounding factors, only cumulative exposure to ATV/r (adjusted IR ratio, aIRR 1.4 [1.2-1.6] after >4 years use vs. never exposed), but not DRV/r (1.0 [0.8-1.3] after >4 years use vs. never exposed) remained significantly associated with increased incidence of CKD, Figure 2. These associations remained similar when restricting the analysis to individuals with baseline eGFR>90 mL/min/1.73m^2 (data not shown).

A total of 3,580 persons discontinued ATV/r use during follow-up (IR 183.6/1000 PYFU [177.8-189.4]). At eGFR >90 mL/min/1.73m^2 discontinuation rates of ATV/r were 181.9/1000 PYFU [174.1-189.6] gradually increasing at declining eGFR levels to 318.2/1000 PYFU [255.2-381.2] at eGFR<60 mL/min/1.73m^2. The aIRR of discontinuing ATV/r use during follow-up was 80% higher at current eGFR ≤60 mL/min/1.73m^2 compared to current eGFR >90 mL/min/1.73m^2 (1.8 [1.4–2.1]). For DRV/r 2,084 persons discontinued use during follow-up (IR 111.6/1000 PYFU [106.8-116.4]) with rates of 113.3/1000 PYFU [106.8-119.5] at eGFR >90 mL/min/1.73m^2 and 138.4/1000 PYFU [95.5-181.3] at eGFR ≤60 mL/min/1.73m^2. In contrast to ATV/r, discontinuation of DRV/r use was largely unaffected by the declining eGFR levels (1.2 [0.9-1.7] for eGFR ≤60 mL/min/1.73m^2 vs eGFR >90 mL/min/1.73m^2). The ATV/r discontinuations also increased in those at high estimated risk of CKD, from 58% of these ATV/r discontinuations in 2009 to 65% in 2015 (p=0.0033).

Discussion

This is the first study to systematically investigate associations between longer cumulative use of the contemporary PIs DRV/r and ATV/r and incident CKD. While prior studies have linked use of the older PIs IDV and LPV/r and the more contemporary ATV/r with CKD at increased rates between 11-20% per additional year of use, controversies have existed about DRV/r and about a possible PI class effect on CKD risk [7, 11, 12]. With more than six years median follow-up we were unable to find a statistically significant, gradual or equally strong association compared to several other PIs between more extended use of DRV/r and CKD. In contrast, the year on year risk previously observed between longer ATV/r use and CKD

remained with a 40% increased incidence of CKD after four years use compared to no use in fully adjusted analyses, including adjusting for concomitant TDF use. The strength of the ATV/r associated CKD risk has decreased over time (initially reported to be up to 20% per additional year of use), likely explained by the increased general awareness of the nephrotoxic potential of ATV/r use and the subsequent high rates of switching away from ATV/r in PLWH with high predicted CKD risks and/or declining eGFR levels [1, 7, 12]. In contrast, rates of DRV/r discontinuations were unrelated to eGFR levels, and the lack of an association with CKD is therefore unlikely to be explained by channeling [11].

The D:A:D study does not collect information on drug dosages and we are therefore unable to address if CKD risks may differ according to DRV/r dosage, although our findings were unchanged by adjusting for factors associated with increased dosing (i.e. low CD4 count, viremia and prior AIDS events) and the 2009 study baseline reflects a wider use of DRV/r with a mixture of dosing regimens. While a cross-sectional study found that both contemporary PIs ATV/r and DRV/r may precipitate as crystals in urine in a small proportion of PLWH and therefore have a similar theoretical potential for inducing urolithiasis, both a UK and a Japanese study found that individuals on ATV/r had significantly higher rates of urolithiasis than those on DRV/r with adjusted rates between 3.8 and 21.5 respectively [6, 8, 14]. For the first time using CKD, a more rigorously defined clinical endpoint, in a large cohort setting, our findings support previous study findings using eGFR slopes and rates of urolithiasis formation in suggesting there is no uniform or equally strong nephrotoxic effect of all contemporarily used PIs [7, 8]. Instead, there seems to be a gradually increasing risk of CKD related to use of specific PIs such as ATV/r, even after adjustment for other potentially nephrotoxic ARVs. This finding has direct clinical implications when considering ART drug choices for the increasing group of PLWH at increased risk of renal disease or with prevalent CKD.

As our analysis was limited by the 6.8 years median follow-up time, and as DRV/r may precipitate in urine, albeit relatively rarely, it is not possible to exclude the possibility that there is an association between DRV/r and CKD, but that this only emerges with very extended drug use. However, our data did not indicate a year on year increase in risk. Within D:A:D there is only very limited follow-up among participants receiving cobicistat and so an analysis of the impact of using an alternative PI boosting agent on CKD incidence was not possible, but nevertheless relevant. Likewise, the D:A:D study does not systematically collect data on proteinuria or genetic predisposition to CKD which may have modified the effects observed between PI use and CKD. The observations presented in this analysis are therefore conservative estimates.

Conclusions

In this large heterogeneous cohort of PLWH more extended use of DRV/r was not significantly associated with a gradually increasing incidence of CKD even after a median follow-up of more than six years. Discontinuation of DRV/r use was, in contrast to ATV/r, unrelated to declining eGFR levels. A gradually increasing CKD risk with longer use of ATV/r was confirmed with a 40% increased CKD incidence after four years of use when compared to those never exposed to ATV/r.

Figure 1. Crude Incidence Rates of CKD per 1000 PYFU Stratified by Cumulative Use of ATV/r and DRV/r

Figure 2. Multivariate Relationship Between CKD and Cumulative Exposure to ATV/r and DRV/r

Multivariate models were adjusted for gender, race, HIV exposure group, enrolment cohort, prior cardiovascular disease (CVD), age, CD4 nadir, baseline date and eGFR (all fixed at baseline), HIV-VL, current CD4, prior AIDS, HBV, HCV, diabetes, hypertension, dyslipidemia, smoking status, BMI, family history of CVD, CVD, cancer, cumulative exposure to tenofovir, atazanavir (unboosted), lopinavir, abacavir, tipranavir, other PI/r (all time-updated).

Footnote page

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For a complete list of the members of the 11 participating cohorts, please see Appendix 1

Conflicts of Interests

L. Ryom, J.D. Lundgren, M. Ross, E. Fontas, W. EL-Sadr, S. De Wit and CI Hatleberg have reported no conflicts of interest. A. Mocroft has received consultancy fees/honoraria/speaker fees from BMS, Pfizer, Merck, BI, and Gilead Sciences. P. Reiss has served as a scientific advisor to Bristol-Myers Squibb, Gilead Sciences, Grupo Ferrer, GlaxoSmithKline, Janssen Pharmaceuticals, Merck & Co, Inc, and ViiV Healthcare. He has served on data and safety monitoring boards and endpoint adjudication committees for Janssen Pharmaceuticals and his institution has received honoraria for speaking engagements at scientific conferences from Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline. He has received research support from Gilead Sciences, ViiV Healthcare, Merck & Co, Inc, Janssen Pharmaceuticals, Bristol-Myers Squibb, Abbott, and Boehringer Ingelheim Pharmaceuticals. O. Kirk had prior/present board membership at

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Figure 1

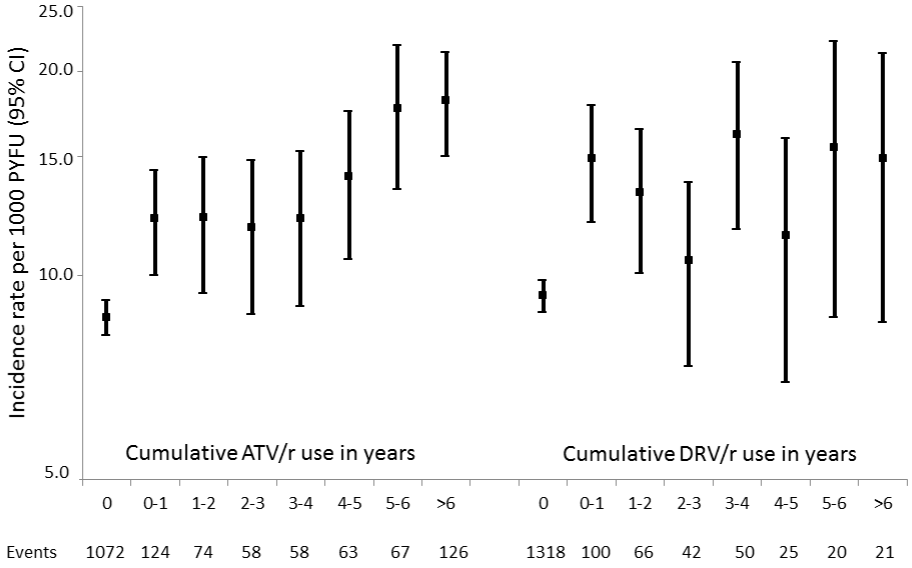
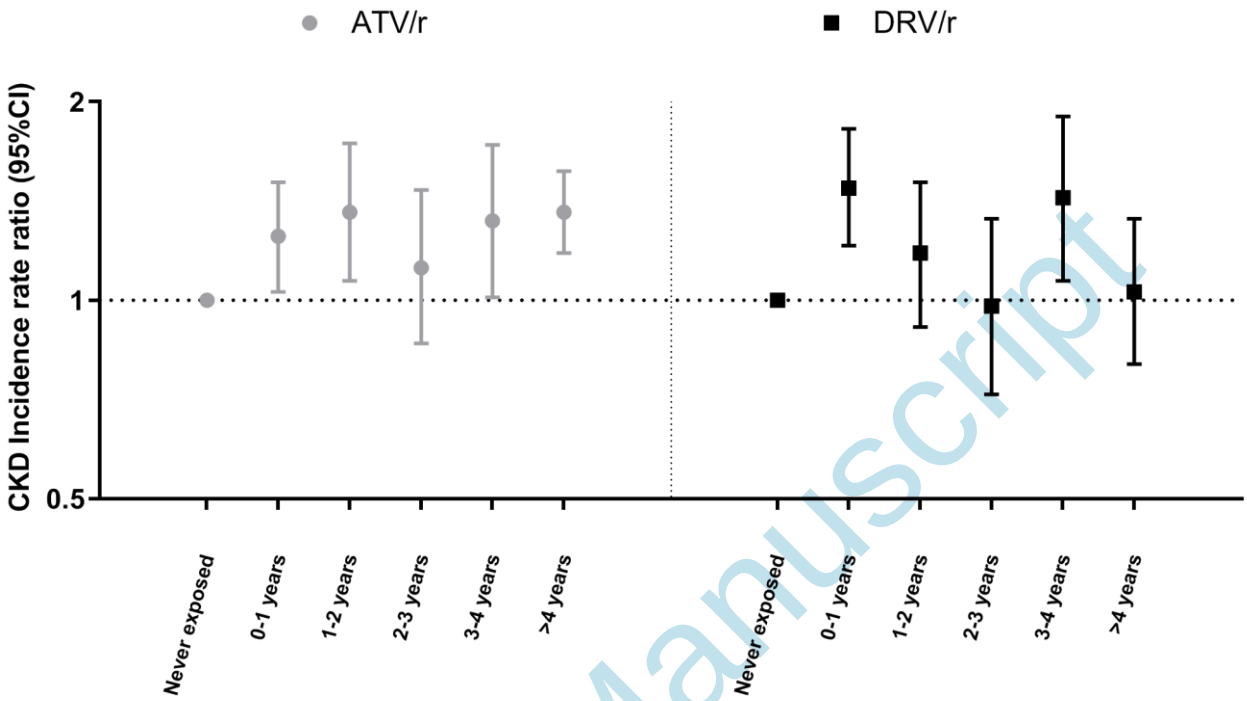


Figure 2



Appendix 1

D:A:D Study Acknowledgements

The current members of the 11 Cohorts are as follows:

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CLINICAL CENTRES ** denotes site coordinating physician*

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Nice HIV Cohort (France):

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SHCS (Swiss HIV Cohort Study, Switzerland):

The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals,15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

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