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Darunavir/r Use and Incident Chronic Kidney Disease in HIV-positive Persons

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BACKGROUND

- Prior studies, including earlier studies from D:A:D, have linked cumulative exposure to several protease inhibitors (PIs) including ritonavir boosted atazanavir (ATV/r) and lopinavir (LPV/r) with excess risk of incident chronic kidney disease (CKD) [1-5].
- The association between PI use and CKD is potentially explained by the formation of crystalluria, urolithiasis and interstitial nephritis [6-10].
- In the modern combination antiretroviral treatment era only a limited number of case reports have linked darunavir (DRV/r) use with urolithiasis, and switch studies suggest DRV/r may have positive effect on eGFR trajectories as compared to other PIs [11-13].

OBJECTIVES

- To assess if cumulative use of more contemporarily used PIs, such as DRV/r and ATV/r, are associated with an increased incidence of CKD similarly to use of some older PIs.

METHODS

- D:A:D study participants with ≥3 estimated glomerular filtration rate (eGFR) measurements, and eGFR >60 ml/min/1.73m^2 prior to baseline were included in the analyses.
- The study baseline was defined as Jan 1st 2009 (year DRV/r was licensed in Europe).
- CKD was defined as confirmed (≥3 months apart) eGFR ≤60 mL/min/1.73m^2.
- Participants were followed to the earliest occurrence of CKD, last visit plus 6 months or Feb 1st 2016.
- Poisson regression was used to model associations between CKD and use of two contemporary and frequently used PI's (DRV/r and ATV/r), adjusting for demographics, other antiretroviral treatment, renal and HIV-related risk factors.
- A separate Poisson regression model assessed adjusted rates of switching away from DRV/r and ATV/r with declining eGFR levels.

RESULTS

- Of the 27,675 persons included in the analysis during 6.8 years median follow-up (interquartile range (IQR) 5.4-7.1) 1,642 developed CKD (incidence rate (IR) 9.95 [95%confidence interval (CI) 9.47-10.43]/1000 person years of follow-up (PYFU)), **Figure 1.**

FIGURE 1

Inclusion of Study Participants in Analysis

All D:A:D Participants
(N= 49,706)
↓
Baseline* eGFR >60 mL/min/1.73m^2
(N=33,427)
↓
≥ 2 eGFRs after baseline and ≥3 months follow-up
(N=27,789)
↓
With CD4 count and viral load data** at baseline
(N=27,675)
↓
CKD
(N=1,642, 5.9%)

*Baseline defined as first prospective eGFR >60 mL/min/1.73m^2 after Jan 1st 2009. ** Nearest to baseline and within 6 months before; if none available, first after and within 6 months

TABLE 1

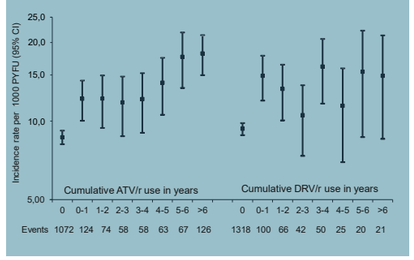
Baseline Characteristics

		All		CKD	
		N	%	N	%
All		27675	100	1642	5.9
Gender	Male	20437	73.8	1286	78.3
Race	White	12666	45.8	796	48.5
	Black African	1958	7.1	39	2.4
HIV acquisition risk	MSM	13018	47.0	816	49.7
	IDU	3229	11.7	194	11.8
HBV	Positive	1116	4.0	70	4.3
HCV	Positive	5037	18.2	322	19.6
ART	Naive	3106	11.2	68	4.1
Smoking status	Current	11127	40.2	608	37.0
Hypertension		2684	9.7	321	19.6
Prior CVD		329	1.2	59	3.6
Prior AIDS		7540	27.2	593	36.1
Diabetes		1341	4.9	205	12.5
5 yr CKD risk score	Low (≤ -1)	7931	28.7	40	2.5
	Medium (0- 4)	9855	35.6	126	7.7
	High (≥ 5)	9889	35.7	1489	90.7
HIV-VL< 400	copies/mL	22162	80.1	1476	89.9
		Median	IQR	Median	IQR
Age	Years	44	38-50	57	49-64
CD4 count	/mm^3	510	340-699	499	360-676
Nadir CD4 count	/mm^3	205	100-312	162	67-261
eGFR	mL/min./1.73m^2	101	87-117	73	66-82

Baseline: first eGFR >60ml/min/1.73m²after Jan 1st 2009, CVD, cardiovascular disease, MSM: men that have sex with men. HBV positive: HBS-Ag, HBe-Ag or HBV-DNA positive. HCV-Positive: seropositive and HCV-RNA positive or HCV-RNA unknown/not tested

FIGURE 2

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



- Median age at baseline was 44 (IQR 38-50) years, median CD4 count was 510 (IQR 340-699) cells/mm^3, 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, **Table 1**.
- 14.4% and 25.0% of the follow-up time (164,983 PYFU) was after starting DRV/r and ATV/r respectively.
- The crude CKD IR in persons unexposed to DRV/r was 9.33/1000 PYFU [95%CI 8.82-9.83] and in persons unexposed to ATV/r 8.66/1000PYFU [95%CI 8.14-9.18] and increased with increasing duration of exposure for both drugs, although more gradually for ATV/r, **Figure 2.**
- After adjustment for potential confounders, only exposure to ATV/r (adjusted IR ratio (aIRR) 1.36 [1.18-1.57), but not DRV/r 1.03 [0.80-1.33]) remained significantly associated with CKD after >4 years exposure, **Figure 3.**
- The adjusted rate of discontinuing ATV/r use was 75% higher at current eGFR ≤60 mL/min/1.73m^2 compared to eGFR >90 mL/min/1.73m^2 (aIRR 1.75 [1.43–2.14]), whereas discontinuation of DRV/r use was largely unaffected by current eGFR levels (aIRR 1.22 [0.89-1.68]), **Figure 4.** The rates of ATV/r discontinuations increased during follow-up in individuals at high estimated CKD risk (58% of the discontinuations in 2009 vs. 65% in 2015).

LIMITATIONS

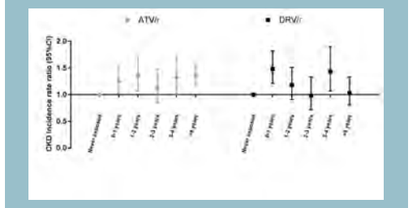
- This analysis was limited by the 6.8 years median follow-up data on DRV/r, the lack of data on proteinuria and drug dosages, and by a relatively low proportion of persons of African origin.
- There remains limited follow-up data on cobicistat in D:A:D to analyse the impact of this alternative PI boosting agent.

CONCLUSIONS

- In this large heterogeneous cohort of HIV-positive persons, discontinuation of DRV/r use was unrelated to eGFR levels, and with more than six years median follow-up, more extended use of DRV/r was not significantly associated with excess risk of CKD.
- The previously reported association between increasing risk of CKD with more extended use of ATV/r remained with 36% higher rates after four years exposure, although this signal has weakened in more recent years. The latter is likely due to increased awareness of the drug's nephrotoxic potential with high discontinuation rates at lower eGFR levels prior to development of CKD and for persons with high estimated CKD risk.

FIGURE 3

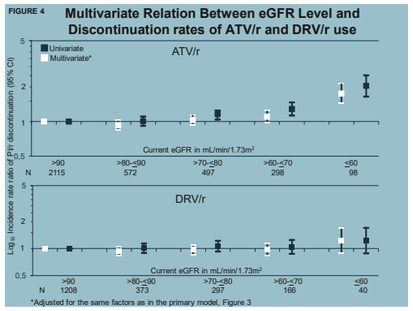
Multivariate Relationship Between CKD and Cumulative Exposure to ATV/r and DRV/r



Multivariate models were adjusted for gender, race, HIV exposure group, enrolment cohort, prior cardiovascular disease (CVD), age, CD4 nadir, baseline date (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).

FIGURE 4

Multivariate Relation Between eGFR Level and Discontinuation rates of ATV/r and DRV/r use



*Adjusted for the same factors as in the primary model, Figure 3

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