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Predictors of Advanced Chronic Kidney Disease and End-Stage Renal Disease in HIV-Positive Persons in D:A:D

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BACKGROUND

- Several antiretroviral drugs (ARVs) including tenofovir (TDF), ritonavir boosted atazanavir (ATV/r), lopinavir/r (LPV/r) and other booted protease inhibitors (other PI/r) have been associated with moderate levels of chronic kidney disease (CKD) [1-6].
- The independent contribution of these ARVs on development of more severe renal impairment such as advanced CKD and end-stage renal disease (ESRD) remains unknown.

METHODS

- The D:A:D Study is a prospective cohort-collaboration study of >49,000 HIV-positive persons from 11 cohorts in Europe, Australia, and the United States.
- Participants with ≥3 estimated glomerular filtration rate (eGFR) measurements after 1/2/2004 were followed until the first of advanced CKD (2 confirmed eGFR≤30 mL/min, ≥3 months apart), ESRD (dialysis for ≥3 months/transplantation reported on a designated event form), 6 months after last visit or 1/2/2012.
- The Cockcroft-Gault formula was used to calculate creatinine clearance (referred to as eGFR), and Kaplan-Meier estimation to investigate time from baseline to advanced CKD/ESRD.
- Poisson regression models were used to investigate ARV discontinuation rates in relation to the latest eGFR level, and to quantify the relationship between exposure to ARVs with a known nephrotoxic potential, other possible risk factors and advanced CKD/ESRD. ARV exposure was fitted categorically; never exposure/exposed, but currently off/exposed and currently on.
- Sensitivity analyses included accounting for mortality as a competing risk, time-lagging ARV exposure by 6 months (to assess recent exposure) and restricting analysis to individuals with impaired baseline eGFR (≤60 mL/min).

RESULTS

- A total of 35,192 persons were included into the analysis contributing 200,119 person-years of follow-up (PYFU), baseline characteristics in **table 1**.
- During a median follow-up of 6.2 (IQR 4.1-7.6) years, 135 (0.4%) developed advanced CKD (n=114)/ESRD (n=21), with an incidence rate of 0.67 (95%CI 0.56-0.79)/1000 PYFU.
- At five years after baseline an estimated 0.32 (95%CI 0.26-0.38) % had progressed to advanced CKD/ESRD, **figure 1**.
- The adjusted rates of switching away from the included ARVs increased significantly as eGFR declined, but especially for TDF with exponential rates, **figure 2**.
- After adjustment, those exposed but currently off TDF had similar advanced CKD/ESRD rates compared to those unexposed, while those currently on TDF had reduced rates, **table 2**

Table 1

Baseline characteristics

		All		No ADV CKD/ESRD		ADV CKD/ESRD		P-value
		N	%	N	%	N	%	
All		35,192	100.0	35,057	99.6	135	0.4	
Gender	Male	25,992	73.9	25,900	73.9	92	68.2	0.13
Ethnicity	Caucasian	16,912	48.1	16,848	48.1	64	47.4	0.91
	Unknown	15,128	43.0	15,067	43.0	61	45.2	
HIV transmission	MSM	16,129	45.8	16,081	45.9	48	35.6	<0.0001
	IDU	4,573	13.0	4,545	13.0	28	20.7	
Prior AIDS	Yes	8,006	22.8	7,949	22.7	57	42.2	<0.0001
HBV status[1]	Positive	4,353	12.4	4,333	12.4	20	14.8	0.019
HCV status[1]	Positive	4,218	12.0	4,198	12.0	20	14.8	0.010
ARV	None	10,954	31.1	10,933	31.2	21	15.6	<0.0001
	cART	23,427	66.6	23,321	66.5	106	78.5	
Smoking	current	14,241	40.5	14,183	40.5	58	43.0	0.52
Hypertension	Yes	3,230	9.2	3,191	9.1	39	28.9	<0.0001
Baseline eGFR	>30,1-≤60 ml/min	1,105	3.1	1,269	2.9	79	58.5	<0.0001
	60.1-90 ml/min	8,030	22.8	7,999	22.8	31	23.0	
	>90 ml/min	26,057	74.0	26,032	74.3	25	18.5	
Diabetes	Yes	1,347	3.80	1,314	3.8	35	24.4	<0.0001
CV event	Yes	816	2.30	803	2.3	13	7.5	<0.0001
		Median	IQR	Median	IQR	Median	IQR	
Baseline eGFR	ml/min	107	96-127	107	89-127	53	41-77	<0.0001
Age	years	41	38-48	41	35-48	52	42-63	<0.0001
CD4	count/mm³	437	289-620	436	290-620	343	203-510	<0.0001
Nadir CD4	count/mm³	210	90-347	210	90-347	94	35-177	<0.0001
Viral load	Log_{10} copies/ml	1.9	1.7-4.1	1.9	1.7-4.1	1.7	1.7-3.0	0.0053
HIV + duration	years	6.1	1.5-11.8	6.1	1.4-11.8	10.3	6.3-14.4	<0.0001

1 Pos: HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive 2 Pos: anti-HCVand HCV-RNA positive/unknown

Figure 1

Kaplan-Meier progression to Advanced CKD/ESRD

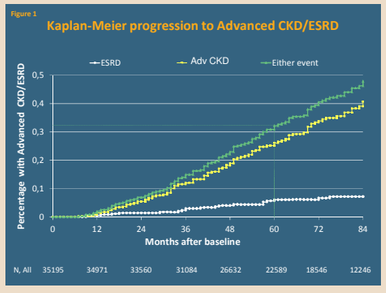
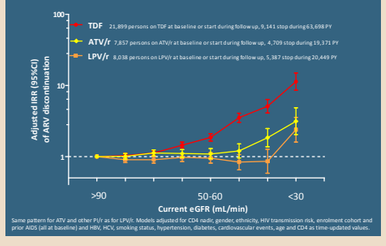


Figure 2

ARV discontinuation according to current eGFR level



Same pattern for ATV and other PI/r as for LPV/r. Models adjusted for CD4 nadir, gender, ethnicity, HIV transmission risk, enrolment cohort and prior AIDS (all at baseline) and HBV, HCV, smoking status, hypertension, diabetes, cardiovascular events, age and CD4 as time-updated values.

- No consistent and statistically significant associations were seen with the other included ARVs and advanced CKD/ESRD. All ARV associations were robust after time-lagging ARV exposure, stratifying by baseline eGFR≤60 mL/min and allowing for competing risks. The ATV/r association did become significant for those with eGFR≤60 mL/min, but the confidence intervals were overlapping with that of our primary analysis and an interaction analysis between ATV/r use and eGFR> vs ≤60 mL/min was not significant.
- Other factors associated with advanced CKD/ESRD were diabetes (3.29, 95%CI 2.18-4.98), hypertension (2.48, 95%CI 1.70-3.62), lower baseline eGFR (2.05, 95% CI 1.86-2.26, per 10 mL/min), never vs. current smoking (0.56, 95%CI 0.34-0.93) and higher current CD4 count (0.73, 95%CI 0.64-0.84, per doubling), **figure 3**.
- The advanced CKD/ESRD incidence rate in those with baseline eGFR>60 mL/min and no diabetes, hypertension or smoking was 0.16 (95%CI 0.09-0.26)/1000 PYFU.

LIMITATIONS

- Receipt of non-ARV nephrotoxic drugs, proteinuria and a family history of renal disease may represent unmeasured confounding.
- Exclusion due to no follow-up after 2004 and inadequate number of eGFR measurements may have introduced selection bias.
- Restrictions on ethnicity information for a high proportion of persons prohibited us from using the MDRD/CKD-EPI formulas and to determine effects of ethnicity on advanced CKD/ESRD.

CONCLUSIONS

- This is the largest prospective study with long term follow-up to address the clinical impact of suspected nephrotoxic ARVs on development of severe chronic renal impairment.
- Neither current nor recent use of these ARVs was associated with advanced CKD/ESRD. interventions in the form of ARV switches likely play a central role for the lack of an observed ARV association.
- TDF discontinuation rates increased with decreasing eGFR levels, leaving a highly selected group still on TDF at lower advanced CKD/ESRD risk.
- Our findings do not, however, exclude the possibility that such ARV relations may exist in populations without access to regular eGFR screening.
- It also cannot be excluded that such issues may arise with more prolonged use of these ARVs in an older HIV-positive population at higher underlying risk of renal impairment.
- The strongest identified predictors of advanced CKD/ESRD were traditional renal risk factors and current CD4 count.

Table 2

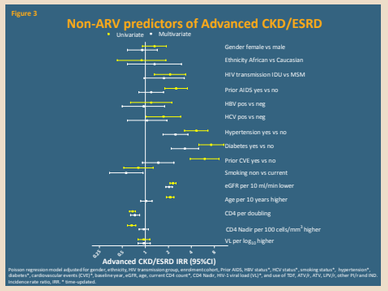
Adjusted incidence rate ratio (IRR) of Advanced CKD/ERSD and ARV use

		All patients	eGFR≤60 at baseline	Lagged analysis*
		IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
TDF	Never started	1.00	1.00	1.00
	Started, Off	1.00 (0.66 – 1.51)	0.80 (0.52 – 1.24)	1.13 (0.84 – 1.45)
	Started, On	0.23 (0.13 – 0.41)	0.27 (0.12 – 0.58)	0.40 (0.20 – 0.80)
LPV/r	Never started	1.00	1.00	1.00
	Started, Off	1.07 (0.69 – 1.67)	0.89 (0.47 – 1.69)	1.10 (0.58 – 2.08)
	Started, On	1.26 (0.79 – 2.01)	1.21 (0.65 – 2.26)	0.99 (0.52 – 1.88)
ATV	Never started	1.00	1.00	1.00
	Started, Off	1.50 (0.74 – 3.03)	1.29 (0.44 – 3.80)	1.08 (0.31 – 3.74)
	Started, On	1.85 (0.92 – 3.71)	1.35 (0.53 – 3.45)	1.45 (0.57 – 3.68)
ATV/r	Never started	1.00	1.00	1.00
	Started, Off	1.52 (0.91 – 2.54)	2.31 (1.12 – 4.18)	1.72 (0.77 – 3.83)
	Started, On	1.52 (0.92 – 2.51)	2.11 (1.08 – 4.09)	1.79 (0.91 – 3.53)
Other PI/r	Never started	1.00	1.00	1.00
	Started, Off	1.40 (0.90 – 2.16)	1.73 (0.95 – 3.15)	1.60 (0.87 – 2.96)
	Started, On	1.51 (0.54 – 4.21)	1.21 (0.28 – 5.25)	1.06 (0.24 – 4.58)

Poisson regression model adjusted for CD4 nadir, gender, race, HIV transmission group, enrolment cohort, prior AIDS, baseline eGFR, ARV use, HBV, HCV, smoking status, hypertension, diabetes, CVE, age and current CD4 count.
*Lagged analyses uses ARV treatment at current time minus 6 months.

Figure 3

Non-ARV predictors of Advanced CKD/ESRD



Poisson regression model adjusted for gender, ethnicity, HIV transmission group, enrolment cohort, Prior AIDS, HBV status*, HCV status*, smoking status*, hypertension*, diabetes*, cardiovascular events (CVE)*, baseline year, eGFR, age, current CD4 count*, CD4 Nadir, HIV-1 viral load (VL)*, and use of TDF, ATV/r, ATV, LPV/r, other PI/r and (NI) Nucleoside rate ratio, IRR, * time-updated

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