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

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BACKGROUND

Tenofovir (TDF), atazanavir (ATV) and other ARVs have been associated with renal impairment (ref. 1-5), but the extent of such adverse drugs reactions in HIV+ persons with normal baseline renal function is unknown.

METHODS

D:A:D is a prospective cohort of 49,734 HIV+ persons from participating cohorts in Europe, USA and Australia. As of 2004 individuals in D:A:D with normal renal function defined as Cockcroft-Gault-estimated glomerular filtration rates (eGFR)>90 ml/min/1.73m^2 were followed to confirmed (≥3 months apart) eGFR≤70 (ceGFR≤70; threshold below which protective ARV switches may occur), confirmed eGFR≤60 (CKD) or last eGFR. Discontinuation rates of individual ARVs according to latest eGFR were assessed. Poisson regression models, adjusting for renal and HIV-related risk factors, were used to assess association with ceGFR≤70 and CKD.

RESULTS

Of 22,603 persons included with a normal baseline renal function 468 (2.1%) progressed to ceGFR≤70 (incidence rate (IR) 4.78/1000 PY [95%CI 4.35-5.22]) and 131 (0.6%) to CKD (1.33/1000 PY [1.10-1.56]) during a median follow-up (FU) of 4.5 years (IQR 2.7-6.1). This eGFR decline of at least 20 ml/min (from eGFR>90 to ≤70) during 4.5 years equals an annual decline of at least 4-5 ml/min. Baseline characteristics of included persons are shown in **Table 1**.

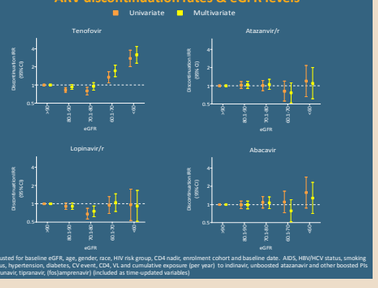
Persons with eGFR levels between 60 and 70 had significantly higher rates of discontinuing TDF (adjusted IR ratio (aIRR) 1.72 [1.38-2.14]), but not of other ARVs tested, compared to persons with eGFR>90, **Figure 2**.

Cumulative TDF (aIRR 1.18 [1.12-1.25] per year) and ATV/r (1.19 [1.09-1.32]) use were independently associated with increased rates of ceGFR≤70 from eGFR>90, but not with CKD, whereas lopinavir/r (LPV/r) use was associated with both endpoints (1.11 [1.05-1.17] and 1.22 [1.16-1.28] respectively), **Figure 3**. Inconsistent trends were seen with abacavir use.

Table 1 — **Baseline Characteristics**

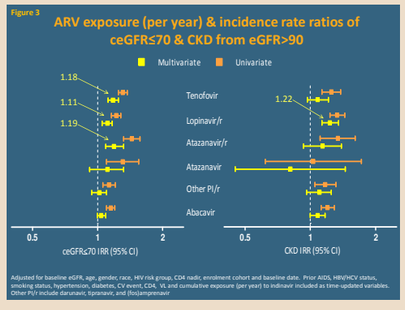
	N, all included (%) [IQR]	N, ceGFR≤70 (%) [IQR]	N, CKD (%) [IQR]
All	22603 (100)	468 (2)	131 (0.6)
Gender Male	16438 (73)	340 (73)	89 (68)
Race White Unkown	10573 (47) 9714 (43)	309 (66) 129 (28)	88 (67) 37 (28)
Median Age (years)	39 [33-44]	46 [41-52]	46 [40-51]
HIV Risk Homosex.	10006 (44)	176 (38)	39 (30)
Prior AIDS	4553 (20)	154 (33)	48 (37)
cART exposed	14263 (63)	346 (74)	94 (72)
CD4 (count/mm^3)	440 [290-624]	380 [217-568]	380 [221-585]
HIV-RNA (log10copies/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 (HBs Ag or HBc Ag or DNA pos./anti-HBc pos.)	2773 (12)	64 (14)	17 (13)
HCV (seropos. & RNA pos. /unkown)	2765 (12)	93 (20)	37 (28)
Hypertension	1761 (8)	53 (11)	20 (15)
Diabetes	664 (3)	43 (9)	14 (11)
Prior CV event	336 (2)	17 (4)	6 (5)

Figure 2 — **ARV discontinuation rates & eGFR levels**



Adjusted for baseline eGFR, age, gender, race, HIV risk group, CD4 nadir, enrolment cohort and baseline date. AIDS, HBV/HCV status, smoking status, hypertension, diabetes, CV event, CD4, VL and cumulative exposure (per year) to indinavir, unboosted atazanavir and other boosted PIs (darunavir, tipranavir, fos)amprenavir) (included as time-updated variables)

Figure 3 — **ARV exposure (per year) & incidence rate ratios of ceGFR≤70 & CKD from eGFR>90**



Adjusted for baseline eGFR, age, gender, race, HIV risk group, CD4 nadir, enrolment cohort and baseline date. Prior AIDS, HBV/HCV status, smoking status, hypertension, diabetes, CV event, CD4, VL and cumulative exposure (per year) to indinavir included as time-updated variables. Other PI/r include darunavir, tipranavir, and (fos)amprenavir

Analyses censoring for concomitant use of each of the ARVs were highly consistent. Results were also robust after adjustment for prior ARV exposures.

Fitting ARVs according to current or prior use, those currently on TDF, ATV/r and LPV/r experienced increased rates of ceGFR≤70 from eGFR>90 with increased lengths of exposure, whereas ≥12 months after drug discontinuation the rates approached normal levels, **Figure 4**.

Other predictors of ceGFR≤70 from eGFR>90 in adjusted models included age (aIRR 2.60 [2.31-2.93] per 10 years older), diabetes (1.52 [1.05-2.21]), current CD4 count (0.75 [0.69-0.82] per doubling) and prior AIDS (1.39 [1.13-1.70]), all included as time-updated variables, **Figure 5**. Adjustment for variables at baseline did not alter the results. There were no significant interactions between ARV use (per year) and main predictors.

LIMITATIONS

Neither information on proteinuria nor familiar disposition to kidney disease is available within the study, and ethnicity information is restricted in some cohorts. Exposure to other potential nephrotoxic non-ARV drugs was not included. 4.5 years median FU may have been too limited to explore a drastic eGFR decline from levels >90 to CKD.

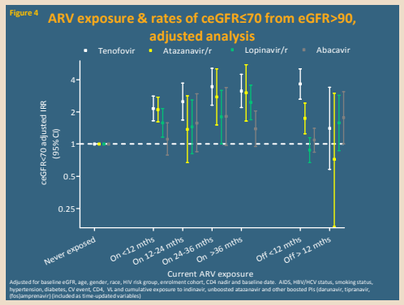
CONCLUSIONS

In HIV+ persons with normal baseline renal function, cumulative use of TDF, ATV/r and LPV/r were each associated with a fast eGFR decline, as were more traditional renal risk factors and HIV-related factors in adjusted models.

The rates of ARV associated deteriorations in renal function from normal function were low over the 4.5 years of FU available, but may represent significant issues for lifelong use should the rates remain constant or even increase with age. For instance after 5 years of TDF use the incidence rate of progression to ceGFR≤70 from levels >90 will be twice as high in TDF exposed compared to unexposed persons.

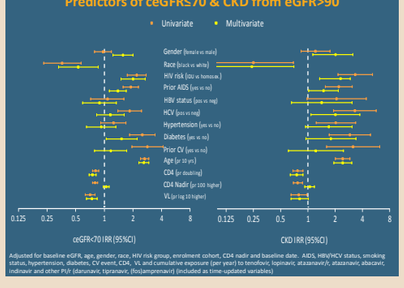
Increased discontinuation rates of TDF, but not of other ARVs in persons with decreasing eGFR suggest that drug switches are occurring more commonly for certain ARVs in relation to declining eGFR, and the switches may have prevented further deterioration to CKD. Closer monitoring of renal function may be appropriate for persons also on ATV/r and LPV/r.

Figure 4 — **ARV exposure & rates of ceGFR≤70 from eGFR>90, adjusted analysis**



Adjusted for baseline eGFR, age, gender, race, HIV risk group, enrolment cohort, CD4 nadir, enrolment date. AIDS, HIV/HCV status, smoking status, hypertension, diabetes, CV event, CD4, VL and cumulative exposure to indinavir, unboosted atazanavir and other boosted PIs (darunavir, tipranavir, (fos)amprenavir) (included as time-updated variables)

Figure 5 — **Predictors of ceGFR≤70 & CKD from eGFR>90**



Adjusted for baseline eGFR, age, gender, race, HIV risk group, enrolment cohort, CD4 nadir and baseline date. AIDS, HBV/HCV status, smoking status, hypertension, diabetes, CV event, CD4, VL and cumulative exposure (per year) to tenofovir, lopinavir, atazanavir/r, atazanavir, abacavir, indinavir and other PI/r (darunavir, tipranavir, (fos)amprenavir) (included as time-updated variables)

Acknowledgements

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Download poster at: www.cphiv.dk

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