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 boosted 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 23 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 (diagnosis for ≥3 months/transplantation reported on a designated event form), 6 months after last visit or 1/2/2012.

The Cockroft-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.

Poison 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 exposed/exposed, but currently off/exposed and currently on.

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.

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 ATV/r, LPV/r and other boosted 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.

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.

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.

REFERENCES

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