The Impact of Immunosuppression on Chronic Kidney Disease in People Living With Human Immunodeficiency Virus: The D:A:D Study

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Background. Relations between different measures of human immunodeficiency virus–related immunosuppression and chronic kidney disease (CKD) remain unknown.

Methods. Immunosuppression measures included baseline, current, time-lagged and nadir CD4, years and percentage of follow-up (%FU) with CD4 ≤200 cells/μL, and CD4 recovery. CKD was defined as confirmed estimated glomerular filtration rate <60 mL/minute/1.73 m².

Results. Of 33 791 persons, 2226 developed CKD. Univarially, all immunosuppression measures predicted CKD. Multivariably, the strongest predictor was %FU CD4 ≤200 cells/μL (0 vs >25%; incidence rate ratio [IRR], 0.77 [95% confidence interval [CI], .68-.88]), with highest effect in those at low D:A:D CKD risk (IRR, 0.45 [95% CI, .24-.80]) vs 0.80 [95% CI, .70-.93]).

Conclusions. Longer immunosuppression duration most strongly predicts CKD and affects persons at low CKD risk more. Key words. CKD, chronic kidney disease; eGFR; renal; HIV; immunosuppression; CD4.

It is well documented that in the era of modern antiretroviral treatment (ART), people living with human immunodeficiency virus (PLWH) are at increased risk of chronic kidney disease (CKD) compared to the general human immunodeficiency virus (HIV)–negative population [1, 2]. The risk profile for CKD in PLWH is complex with multiple possible aetiologies including HIV itself, systemic inflammation, nephrotoxic ART, viral hepatitis, diabetes, and hypertension [3–5]. Several studies have further showed that immunosuppression, expressed as a low CD4 count, is an independent predictor of CKD [3–5]. Likewise, in the Strategic Timing of AntiRetroviral Treatment (START) trial, the prevalence of CKD in PLWH with preserved immune function was relatively low [6]. Data on the exact nature of the relation between immunosuppression and CKD is, however, limited. The aim of this study was therefore to investigate the association between different measures of impaired immune function including duration and severity of immunosuppression and incident CKD in a large heterogeneous cohort.

METHODS

Study Population

The Data Collection on Adverse Events of Anti-HIV Drugs Study (D:A:D) is a prospective cohort collaboration with >49 000 people living with HIV type 1 in Europe, the United States, and Australia; details have been published previously [7]. Clinical events are collected in real time and data on demographics, ART, AIDS events, laboratory test results, viral hepatitis, and cardiovascular risk factors are collected electronically at enrollment and every 6 months hereafter.

Endpoint and Immunosuppression Definitions

CKD was defined as confirmed (≥3 months apart) estimated glomerular filtration rate (eGFR) ≤60 mL/minute/1.73 m² [8]. The Cockcroft–Gault equation was, as in earlier D:A:D renal analyses, used as an eGFR surrogate as several of the participating cohorts are prohibited from collecting data on ethnic origin.

The immune function measurements considered included (1) severity of immunosuppression: baseline, nadir, current, and 6-month time-lagged current CD4 count; (2) duration of immunosuppression: percentage of follow-up time (%FU) spent with CD4 count ≤200 cells/μL and follow-up time spent with CD4 ≤200 cells/μL (0, 0–1, and >1 years); and (3) CD4...
count recovery: baseline CD4 count ≤200 cells/μL followed by current CD4 count >200 cells/μL.

By time-lagging the CD4 count, we aim at limiting risks of reverse causality.

Statistical Analyses
Baseline was defined as the first eGFR after 1 January 2004 (date of systematic creatinine collection initiation). Study participants without CKD and with ≥3 prospective eGFR measurements were followed until the earliest of CKD, last eGFR plus 6 months, or 1 February 2016, whichever occurred first. Follow-up was divided into series of consecutive 1-month periods and the immunological status at the start of each follow-up period was established.

Poisson regression was, in separate models, used to assess the relationship between incident CKD and each measure of immunosuppression. In multivariable models, we accounted for nonimmunological factors included in the D:A:D 5-year CKD risk score including gender, age, HIV risk group, baseline eGFR, hepatitis C virus status, and hypertension (all measured at baseline) and exposure to nephrotoxic ART (tenofovir disoproxil fumarate, indinavir, unboosted atazanavir, and ritonavir-boosted atazanavir and lopinavir) [3]. Akaike information criterion (AIC) was used to indicate which measures were better CKD predictors, with a lower value indicating a better-fitted model.

The strongest immunosuppression predictors of CKD were tested for interactions with the D:A:D CKD risk score, demographics, ART, and HIV-related factors [3].

All statistical analyses were carried out using SAS version 9.4 software (SAS Institute).

RESULTS
During a median follow-up of 8.8 (interquartile range [IQR], 6.1–10.7) years, 2226 of the 33 791 (6.6%) persons included in the analysis developed CKD (incidence rate [IR], 8.1 [95% confidence interval {CI}, 7.8–8.5] per 1000 person-years of follow-up [PYFU]). The majority developed CKD stage G3 (eGFR ≤60 to >30 mL/minute/1.73 m²; 6.3%), whereas only smaller proportions developed CKD stage G4 (eGFR ≤30 to >15 mL/minute/1.73 m²; 0.3%), stage G5 (eGFR ≤15 mL/minute/1.73 m²; 0.03%), and end-stage renal disease (chronic dialysis 0.1% and renal transplantation 0.01%).

At baseline, the median age was 41 (IQR, 35–47) years; 47.6% of the study population were of white origin, and 73.9% were male (Supplementary Table 1). Hypertension was present in 8.5%, diabetes in 3.8%, and prior AIDS in 24.3%. The median CD4 count was 440 (292–627) cells/μL, the median nadir CD4 count was 230 (108–368) cells/μL, and 58.4% were virologically suppressed. The analysis included 633 763 eGFR measurements with a median of 18 measurements per person (IQR, 11–26) at a median rate of 2.2 measurements per year (IQR, 1.7–2.9). At baseline, the median eGFR was 102 (IQR, 98–118) mL/minute/1.73 m².

The crude IR of CKD varied for the different immunodeficiency measures considered, but all showed approximated...
linear relations with declining CD4 counts (Figure 1). The highest crude IRs were seen for current and 6 months time-lagged current CD4 count ≤200 cells/μL (IR, 13.3 [95% CI, 11.4–15.1] and 13.5 [95% CI, 11.6–15.3] per 1000 PYFU, respectively). The greatest difference in IRs were seen between nadir CD4 ≤50 cells/μL vs >500 cells/μL (11.4 [95% CI, 10.3–12.4] vs 4.9 [95% CI, 4.1–5.6] per 1000 PYFU).

There were 4328 persons with baseline CD4 count ≤200 cells/μL, of whom 309 developed CKD (IR, 9.5 [95% CI, 8.5–10.6] per 1000 PYFU). The crude CKD IR was highest in those without CD4 recovery (baseline and current CD4 count ≤200 cells/μL; IR, 12.5 [95% CI, 10.4–14.6] per 1000 PYFU), and declined linearly with increased levels of current CD4 count at recovery (baseline CD4 count ≤200 cells/μL followed by current CD4 count >500 cells/μL; IR, 6.7 [95% CI, 4.6–8.8] per 1000 PYFU), Figure 1. Results were consistent when using a CD4 count baseline threshold of ≤350 cells/μL rather than ≤200 cells/μL.

In univariable analysis, all measures of immunosuppression were significantly associated with increased CKD rates (all P < .01), most strongly for nadir CD4 count (>500 vs ≤50 cells/μL; IR, 0.43 [95% CI, 0.36–0.51]; AIC = 40 814), %FU CD4 count ≤200 cells/μL (0% vs >25%; IR, 0.63 [95% CI, 0.56–0.75]; AIC = 40 921), and latest CD4 count (≥750 vs <50 cells/μL; IR, 0.56 [95% CI, 0.48–0.66]; AIC = 40 943). After adjustment for nonimmunological variables in the D:A:D CKD risk score, the strongest immunological predictor of CKD was %FU CD4 count ≤200 cells/μL (incidence rate ratio [IRR], 0.77 [95% CI, .68–.88]; AIC = 36 262) followed by nadir CD4 count (≥500 vs ≤50 cells/μL; IRR, 0.77 [95% CI, 0.64–0.93]; AIC = 36 304).

There was a significant (P = .0016) interaction between %FU CD4 count ≤200 cells/μL and the D:A:D CKD risk score. The impact of duration of immunosuppression was stronger for those at lowest estimated CKD risk (IRR, 0.45 [95% CI, 0.24–0.80]) compared to those at highest estimated CKD risk (IRR, 0.80 [95% CI, 0.70–0.93]), Figure 2. We did not observe any statistically significant interaction between immunosuppression and ethnicity, age, ART status, or use of nephrotoxic antiretrovirals.

To assess potential surveillance bias, we calculated the frequency of eGFR measurements according to CD4 count strata. We found only small differences with a median of 2.5 (IQR, 1.8–3.5) eGFRs per year in those with baseline CD4 ≤200 cells/μL vs 2.1 (IQR, 1.6–2.7) in those with baseline CD4 >750 cells/μL, and a very weak correlation (r = −0.11) between number of eGFRs per year and baseline CD4 counts. Restricting the analysis to those with ≥2 eGFRs per year was consistent, albeit with lower statistical power (data not shown).

**DISCUSSION**

While prior studies have focused on the severity of HIV-related immunosuppression as a risk factor for CKD, in this analysis we also investigated the impact of duration of immunosuppression and CD4 count recovery [3–5]. We found that the strongest
We further described an intriguing dynamic suggesting that immunosuppression is associated with the greatest relative increase in CKD rates in persons at low estimated baseline risk of CKD, that is, those without comorbid conditions such as diabetes, hypertension, or advanced age. It is worth noting, however, the low underlying rates of CKD in those at low estimated CKD risk. In an era where multimorbidity is increasingly common in the aging population of PLWH it is crucial for clinicians to better understand which key factors to focus on depending on the individual risk profile to limited clinical outcomes such as CKD [3].

The association between CKD and immunosuppression could be biased by an increased monitoring frequency in those with low CD4 counts. While the frequency of measurement of CD4 count and eGFR were slightly increased at lower CD4 counts, the difference was small and the correlation between the number of annual eGFR measurements and current CD4 count was weak, arguing against surveillance bias as a major contributor to the observed association.

Despite the large size and extensive follow-up in D:A:D, the relatively high median and nadir CD4 count after the 2004 baseline may explain the slightly stronger association with duration of severe immunosuppression than with severity of immunosuppression.

In clinical practice, severity of immunosuppression may be an easier variable to use for risk stratification than duration of immunosuppression [3]. CD4 nadir, in adjusted analysis, displayed only marginally inferior model fit compared to duration of immunosuppression and could therefore be used as an alternative. We are unable to exclude residual confounding due to failure to fully adjust for unknown, unmeasured, or incompletely assessed confounders. Most important, we are limited by the lack of systematically collected data on proteinuria, genetic predispositions to CKD, use of nephrotoxic treatments other than ART, CD8 count, substance abuse, and a relatively low proportion of individuals with Black African ethnicity.

**CONCLUSIONS**

The strongest association between incident CKD and immunosuppression was observed for the relative duration of severe immunosuppression. Risk of CKD was low when CD4 counts increased above 500 cells/μL. The impact of immunosuppression was of greatest relative importance in persons at low estimated CKD risk, and less important at higher estimated CKD risk levels, suggesting that more traditional renal risk factors dominated in high-risk individuals. These findings support ensuring good immune function through early ART initiation and a high level of adherence to minimize CKD risks in PLWH.

**Supplementary Data**

Supplementary materials are available at The Journal of Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and
are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

**Author contributions.** All authors have seen and approved the content of the manuscript and have contributed significantly to this work.


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