The impact of immunosuppression on chronic kidney disease in people living with HIV; the D:A:D study

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summary

While HIV-related immunosuppression duration and severity both predict chronic kidney disease (CKD), the duration association is strongest. CKD risk related to low CD4 count diminishes once immune function is restored, and most strongly effects persons with low estimated CKD risk.

ABSTRACT

Background

Relations between different measures of HIV-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$\leq$200, and CD4 recovery. CKD: confirmed estimated glomerular filtration rate <60mL/min/1.73m^2.

Results

Of 33,791 persons 2,226 developed CKD. Univariably, all immunosuppression measures predicted CKD. Multivariably, the strongest predictor was %FU CD4$\leq$200 (0 vs. >25%, IRR 0.77 [0.68-0.88]) with highest effect in those at low D:A:D CKD risk (0.45 [0.24-0.80]) vs. 0.80 [0.70-0.93]).

Conclusion

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

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Introduction

It is well documented that in the modern antiretroviral treatment (ART) era people living with HIV (PLWH) are at increased risk of chronic kidney disease (CKD) compared to the general 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 more than 49,000 HIV-1-positive persons 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 is collected electronically at enrolment and every six months hereafter.

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Endpoint and immunosuppression definitions

CKD was defined as confirmed (≥3 months apart) estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73m^2 [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 *severity of immunosuppression*: baseline, nadir, current and 6-months' time-lagged current CD4 count; *duration of immunosuppression*: percentage of follow-up time (%FU) spent with CD4 count ≤200 cells/mm^3 and follow-up time spent with CD4 ≤200 cells/mm^3 (0, 0-1 and >1 years); and *CD4 count recovery*: baseline CD4 count ≤200 cells/mm^3 followed by current CD4 count >200 cells/mm^3.

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

Statistical analyses

Baseline was defined as the first eGFR after 1/1/2004 (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 1/2/2016, whichever occurred first. Follow-up was divided into series of consecutive 1-monthly 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 non-immunological factors included in the D:A:D 5-year CKD risk score including gender, age, HIV risk group, baseline eGFR, HCV status and hypertension (all measured at baseline) and exposure to nephrotoxic ART (tenofovir disoproxil fumarate,

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indinavir, unboosted atazanavir, and ritonavir boosted atazanavir and lopinavir) [3]. Akaike Information Criteria (AIC) was used to indicate which measures were better CKD predictors with a lower value indicting 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 (Statistical Analysis Software, Cary, NC, USA).

Results

During a median follow-up of 8.8 years (interquartile range, IQR, 6.1-10.7) 2,226 (6.6%) of the 33,791 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$\leq$60->30 mL/min/1.73m^2; 6.3%), while only smaller proportions developed CKD stage G4 (eGFR$\leq$30->15 mL/min/1.73m^2; 0.3%), stage G5 (eGFR$\leq$15 mL/min/1.73m^2; 0.03%) and end-stage renal disease (chronic dialysis 0.1% and renal transplantation 0.01%).

At baseline, the median age was 41 years (IQR 35-47), 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 cells/mm^3 (292-627), median nadir CD4 count 230 cells/mm^3 (108-368) and 58.4% were virologically supressed. The analysis included 633,763 eGFR measurements with a median of 18

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measurements per person (11-26) at a median rate of 2.2 measurements per year (1.7-2.9). At baseline, the median eGFR was 102 mL/min/1.73m^2 (88-118).

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 $\leq$200 cells/mm^3 (13.3 [11.4-15.1] and 13.5 [11.6-15.3] per 1000 PYFU respectively). The greatest difference in IRs were seen between nadir CD4 $\leq$50 cells/mm^3 vs. >500 cells/mm^3 (11.4 [10.3-12.4] vs. 4.9 [4.1-5.6] per 1000 PYFU).

There were 4,328 persons with baseline CD4 count $\leq$200 cells/mm^3, of whom 309 developed CKD (IR 9.5 [8.5-10.6] per 1000 PYFU). The crude CKD IR was highest in those without CD4 recovery (baseline and current CD4 count $\leq$200 cells/mm^3, 12.5 [10.4-14.6] per 1000 PYFU), and declined linearly with increased levels of current CD4 count at recovery (baseline CD4 count $\leq$200 cells/mm^3 followed by current CD4 count >500 cells/mm^3, 6.7 [4.6-8.8] per 1000 PYFU), Figure 1. Results were consistent when using a CD4 count baseline threshold of $\leq$350 cells/mm^3 rather than $\leq$200 cells/mm^3.

In univariable analysis all measures of immunosuppression were significantly associated with increased CKD rates (all p<0.01), most strongly for nadir CD4 count (>500 vs. $\leq$50 cells/mm^3, IR 0.43 [0.36-0.51], AIC 40814), %FU CD4 count $\leq$200 cells/mm^3 (0% vs. >25%, IR 0.63 [0.56-0.75], AIC 40921) and latest CD4 count ($\geq$750 vs. <50 cells/mm^3, IR 0.56 [0.48-0.66], AIC 40943). After adjustment for non-immunological variables in the D:A:D CKD risk score, the strongest immunological predictor of CKD was %FU CD4 count $\leq$200

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cells/mm^3 (IR ratio, IRR 0.77 [0.68-0.88], AIC 36262) followed by nadir CD4 count ($\geq$500 vs. $\leq$50 cells/mm^3, IRR 0.77 [0.64-0.93], AIC 36304).

There was a significant (p=0.0016) interaction between %FU CD4 count $\leq$200 cells/mm^3 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 [0.24-0.80]) compared to those at highest estimated CKD risk (IRR 0.80 [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 $\leq$200 cells/mm^3 vs. 2.1 (1.6-2.7) in those with baseline CD4 >750 cells/mm^3, and a very weak correlation (r=-0.11) between number of eGFRs per year and baseline CD4 counts. Restricting the analysis to those with $\geq$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 independent immunologic predictor of incident CKD was a longer relative duration of immunosuppression. The magnitude of the observed association between immunosuppression and incident CKD is comparable to that reported for hypertension [3].

Furthermore, all measures of immunosuppression were consistently associated with

increased CKD incidence with an almost linear relation for most measures with particularly high CKD rates at CD4 counts <200 cells/mm^3 and rates levelling off at CD4 counts >500 cells/mm^3. A 2013 study from COHERE showed that immune reconstitution for AIDS events was incomplete at CD4 counts <750 cells/mm^3, but for CKD it appears this threshold is slightly lower [9]. Our data also suggest the increased risk of CKD due to immunosuppression may be at least partially reversible even after severely impaired CD4 count.

While an observational study such as D:A:D is unable to address potential mechanisms for this association our data add to previous evidence of an independent effect of immunosuppression on CKD risk over and above that of AIDS events, HIV viremia and use of nephrotoxic ART [3-5]. However, in addition, these new data suggest an association with the duration of immunosuppression. Several studies have suggested the effect of immunosuppression on CKD may be related to persistent HIV-induced inflammation and coagulation activation [10, 11]. In a combined analysis from the ESPRIT, SILCAT and SMART trials higher levels of IL6 and D-dimer predicted serious non-AIDS events, and a Danish study found soluble CD163 levels, a marker of monocyte/ macrophage activation, was strongly associated with CKD [10, 11]. In the general HIV-negative population persistent inflammation has also been linked to faster decline in renal function [12]. ART has an overall beneficial effect on CKD compared to no ART, and interruptions in ART increase levels of both renal and inflammatory biomarkers, suggesting that ART-related improvement in immune function, viremia, inflammation and coagulation activation are key renal protective measures in this population [13, 14]. In START immediate ART initiation was further associated with a slightly higher median eGFR and less proteinuria compared to deferring ART [15]. All current evidence therefore points collectively towards avoiding long-lasting and severe immunosuppression by focusing on early ART initiation and ensuring high levels of ART compliance to reduce potential immunosuppression related renal risks.

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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 i.e. 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 ageing 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 immune suppression 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 importantly we are limited by the lack of systematically collected data on

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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/mm^3. 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 more traditional renal risk factors dominated in high-risk individuals. These findings support ensuring good immune function through early ART initiation and high level of adherence also to minimise CKD risks in PLWH.

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Figure 1 Crude Incidence Rate of CKD per 1000 PYFU By Measures of Immunosuppression

Figure 2 CKD Incidence Rate Ratio and Percentage of Follow-up Time with CD4 Count $\leq$200 cells/mm^3 Stratified by the D:A:D CKD Risk Score

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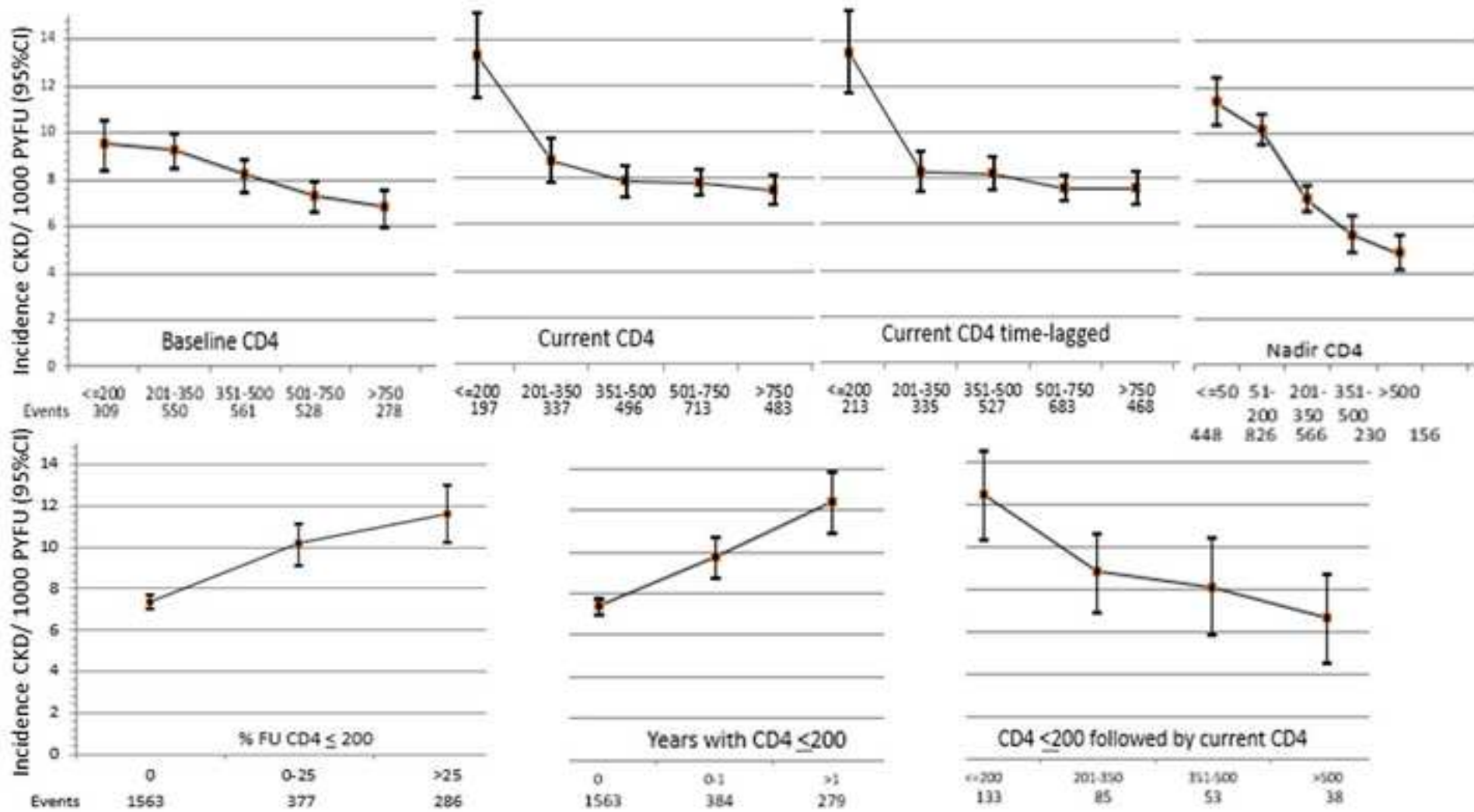**External endpoint reviewers**: A Sjøl (CVD), P Meidahl (oncology), JS Iversen (nephrology)

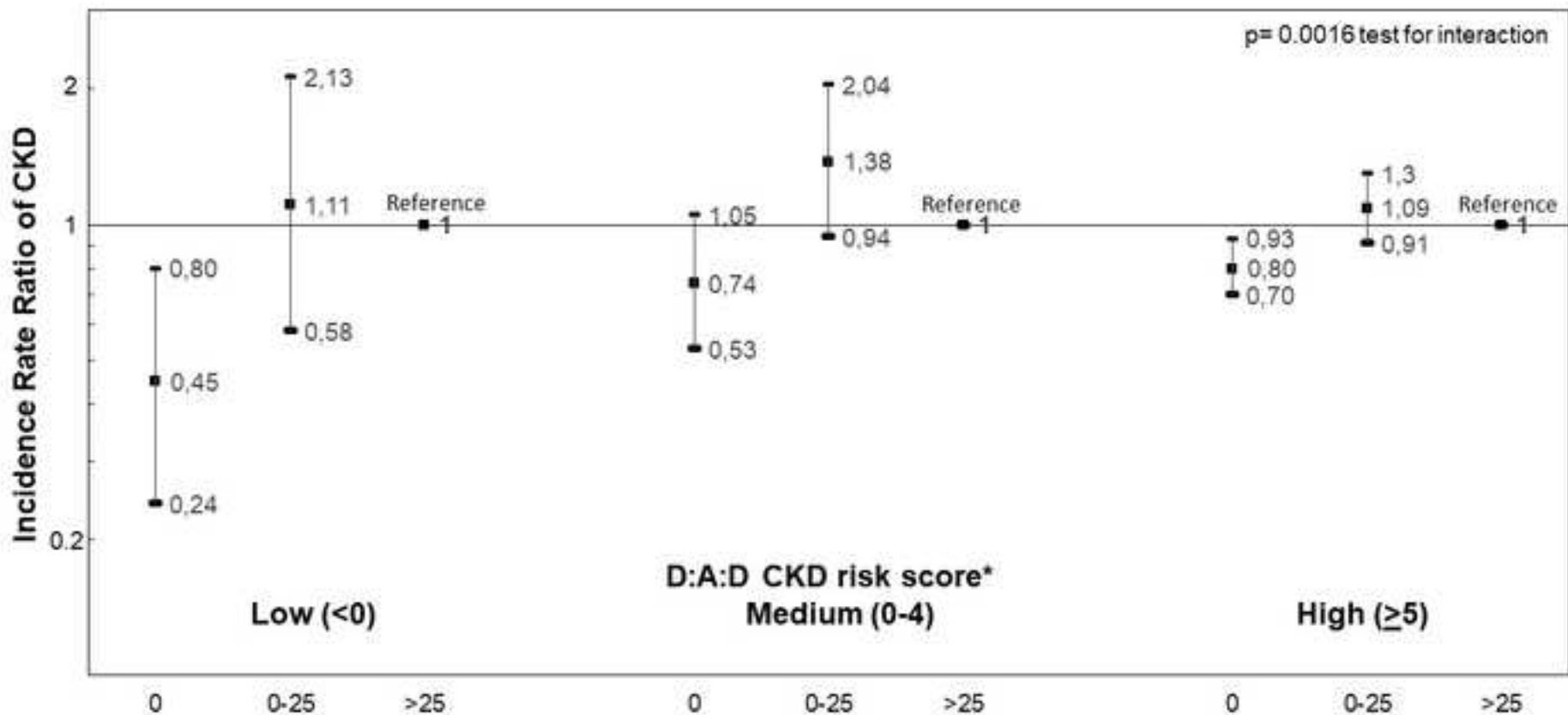For a complete list of the members of the 11 participating cohorts, please see Appendix 1.

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Conflicts of Interests

L. Ryom, J.D. Lundgren, M. Ross, E. Fontas, W. EL-Sadr, S. De Wit and CI Hatleberg have reported no conflicts of interest. A. Mocroft has received consultancy fees/honoraria/speaker fees from BMS, Pfizer, Merck, BI, Gilead Sciences and Eiland and Bonin. P. Reiss has served as a scientific advisor to Bristol-Myers Squibb, Gilead Sciences, Grupo Ferrer, GlaxoSmithKline, Janssen Pharmaceuticals, Merck & Co, Inc, and ViiV Healthcare. He has served on data and safety monitoring boards and endpoint adjudication committees for Janssen Pharmaceuticals and his institution has received honoraria for speaking engagements at scientific conferences from Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline. He has received research support from Gilead Sciences, ViiV Healthcare, Merck & Co, Inc, Janssen Pharmaceuticals, Bristol-Myers Squibb, Abbott, and Boehringer Ingelheim Pharmaceuticals. O. Kirk had prior/present board membership at ViiV Healthcare, Gilead Sciences and Merck, received payment for lectures and/or for development of educational presentations from Abbott, Gilead Sciences and Tibotec and had travel/accommodations/meeting expenses paid by Abbott, BMS, Gilead Sciences, Merck and ViiV Healthcare. M. Law has received research grants from Boehringer Ingelheim, Bristol Myer Squibb, Gilead, GlaxoSmithKline, Janssen-Cilag Pty Ltd, Merck Sharp &

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