Serious clinical events in HIV-positive persons with chronic kidney disease

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Objectives: Predictors of chronic kidney disease (CKD) amongst HIV-positive persons are well established, but insights into the prognosis after CKD including the role of modifiable risk factors are limited.

Design: Prospective cohort study.

Methods: D:A:D participants developing CKD (confirmed, >3 months apart, eGFR $\leq$ 60 ml/min per 1.73 m^2 or 25% eGFR decrease when eGFR $\leq$ 60 ml/min per 1.73 m^2) were followed to incident serious clinical events (SCE); end stage renal and liver disease (ESRL and ESLD), cardiovascular disease (CVD), AIDS-defining and non-AIDS-defining malignancies (NADM), other AIDS or death, 6 months after last visit or 1 February 2016. Poisson regression models considered associations between SCE and modifiable risk factors.

Results: During 2.7 (IQR 1.1–5.1) years median follow-up 595 persons with CKD (24.1%) developed a SCE [incidence rate 68.9/1000 PYFU (95% confidence interval 63.4–74.4)] with 8.3% (6.9–9.0) estimated to experience any SCE at 1 year. The most common SCE was death (12.7%), followed by NADM (5.8%), CVD (5.6%), other AIDS (5.0%) and ESRD (2.9%). Crude SCE ratios were significantly higher in those with vs. without CKD, strongest for ESRD [65.9 (43.8–100.9)] and death [4.8 (4.3–5.3)]. Smoking was consistently associated with all CKD-related SCE. Diabetes predicted CVD, NADM and death, whereas dyslipidaemia was only significantly associated with CVD. Poor HIV-status predicted other AIDS and death, eGFR less than 30 ml/min per 1.73 m^2 predicted CVD and death and low BMI predicted other AIDS and death.

Conclusion: In an era where many HIV-positive persons require less monitoring because of efficient antiretroviral treatment, persons with CKD carry a high burden of SCE. Several potentially modifiable risk factors play a central role for CKD-related morbidity and mortality.

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Introduction

As chronic kidney disease (CKD) has become increasingly common in the ageing community of people living with HIV (PLWH), considerable efforts have gone into uncovering potential predictors [1–4]. As such it is now commonly accepted that HIV-related factors (such as immunosuppression), co-infections, traditional renal risk factors (such as diabetes and hypertension) and drug toxicities play a central role for incident CKD in PLWH [5–10].

Meanwhile, our insights into the more general morbidity burden after acquiring CKD in PLWH and the associated modifiable risk factors are still relatively limited [8,11–15]. In a prior D:A:D analysis, we showed that up to 23% of PLWH have the potential to improve kidney function after moderate CKD (stages G3+), whereas 65% stabilized at their current estimated glomerular filtration rate (eGFR) level and 12% continued to progress over the next 36 months [16,17]. However, that analysis focused exclusively on eGFR-defined outcomes. Large population studies in the general HIV-negative population suggest that individuals with advanced and end-stage CKD (stages G4+) have a particularly poor prognosis with high morbidity and mortality [18,19]. Studies on outcomes after CKD stage G3+ are somewhat scarcer, likely because more moderate levels of CKD remain undiagnosed and are associated with lower rates of adverse outcomes than more advanced CKD stages. Large studies with long follow-up times are, therefore, required to reliably study the natural history of disease progression in this group [15,19–21].

Related to the significantly improved health of PLWH, the majority of stable PLWH on antiretroviral treatment (ART) are only seen in clinical care once or twice annually. The increasing CKD incidence in PLWH, however, makes it imperative to better understand the consequences of CKD in order to assist clinical identification of those at highest risk of severe morbidity and mortality. Identification of key factors driving CKD-related morbidity will further improve our understanding of the disease mechanistic and where to focus interventions [22].

Using the large D:A:D (Data collection on Adverse events of Anti-HIV Drugs) cohort the aim of this analysis is to investigate the disease spectrum and the prognosis after a diagnosis of CKD stage G3+ in PLWH with focus on the incidence of serious clinical events (SCE) and the role of modifiable risk factors.

Methods

Study population

The D:A:D study is a large observational cohort collaboration initiated in 1999 based on a request from the European Medicines Agency (EMA) to study adverse drug effects of ART and comorbidities in PLWH, details have been published previously [23]. From the 11 contributing cohorts in Europe, the United States and Australia, more than 49 000 HIV-1-positive persons were under prospective follow-up. Data on clinical events were reported on designated event forms and include cardiovascular disease (CVD), end-stage renal and liver disease (ESRD and ESLD), cancers and fatal cases (for details see https://www.chip.dk/Studies/DAD/Study-Documents). Events were collected in real-time during routine clinical care, centrally validated against predefined algorithms, regularly monitored and reviewed by external experts. In addition, electronic data were collected at enrolment and at every 6 months thereafter on demographics, detailed records of ART and other key HIV-variables including HIV viral load (VL), $CD4^+$ cell counts, AIDS events and viral hepatitis. In addition, CVD-related risk factors (such as familiar disposition, hypertension, diabetes, dyslipidemia and smoking) and treatment (such as antihypertensives and antiplatelets) were captured. Finally, data on selected common laboratory biomarkers (such as haemoglobin, renal and liver function markers) was systematically collected.

Endpoint definitions and statistical analyses

The SCE included were centrally validated CVD [myocardial infarction (MI), stroke, invasive cardiovascular procedures], ESRD, ESLD, AIDS-defining malignancies (ADM), non-AIDS defining malignancies (NADM), other AIDS events (excluding malignancies) and death from any cause.

Creatinine was collected systematically in D:A:D from 2004. We calculated creatinine clearance, used as an eGFR surrogate, as in earlier D:A:D analyses, using the Cockcroft–Gault equation [24], standardized for body surface area [25,26]. As several specific cohorts in D:A:D are prohibited from collecting ethnicity information the Cockcroft–Gault equation was used rather than an equation including ethnicity.

CKD was defined as confirmed, >3 months apart, eGFR $\leq$60 ml/min per 1.73 m^2 or a 25% decrease in eGFR level when baseline eGFR $\leq$60 ml/min per 1.73 m^2 or less [7,27]. For our main analysis of SCE after CKD, participants were followed from time of CKD diagnosis to incident SCE, 6 months after last visit or 1 February 2016, whichever occurred first. Although participants could experience several different types of incident SCE after CKD, recurrences of the same specific subtype of SCE were excluded from this analysis (e.g. someone with a prior MI could not progress to another MI but could progress to a different CVD event, such as a stroke). A separate analysis was performed for each of the SCE.

For perspectives, in a purely descriptive analysis, we followed participants from first eGFR to SCE and stratified

follow-up time according to CKD status and compared crude rates of SCE between those with/without CKD. As the baseline, study population and follow-up are defined differently in this subanalysis, SCE rates will not be directly comparable with those of the primary analysis.

Adjusted Poisson regression models considered associations between individual SCE and potential modifiable risk factors. Factors included in multivariable analysis were decided a priori based on the factors associated with CKD and each of the SCE in previous D:A:D analyses [7,11,23]. These included demographics (sex, age, ethnic origin, cohort), HIV-related factors (HIV acquisition risk, $CD4^+$ cell count, prior AIDS and viral hepatitis co-infection) and more traditional risk factors (familial disposition to CVD, hypertension, dyslipidaemia, BMI and eGFR $\leq$30 ml/min per 1.73 m^2). We further defined poor HIV-status as $CD4^+$ cell count less than 350 cells/μl or VL greater than 10000 copies/ml, good HIV-status as $CD4^+$ cell count greater than 500 cells/μl and VL less than 400 copies/ml; and intermediate status as all other combinations. We also included adjustment for any prior and time-updated specific SCE. We did not include ART in our models as we have previously shown that specific antiretrovirals, which are known to be nephrotoxic, are often actively switched once an individual's eGFR starts to decline but before they reach the threshold for CKD, meaning post-CKD analyses will be highly confounded by indication for ART and difficult to interpret [6,16]. Potential risk factors were fitted as time-updated variables when subjected to change over time (e.g. age) otherwise as time-fixed (baseline) values (e.g. ethnic origin). Interactions were considered between poor HIV-status, smoking, diabetes and low BMI. To address, which potentially modifiable risk factors have the strongest impact on the prognosis after CKD, we calculated the population attributable risk fraction (PAF) for the key identified risk factors in the multivariate model (only those with PAF >5% presented). PAF expresses the proportion of events that would not have occurred had that risk factor not been present and considers both the strengths of the associations and the incidence rate of the risk factor.

Data from the general population suggest that ESRD and death are competing outcomes in people with CKD [28]. To test for competing risk between the individual SCE after CKD we conducted a sensitivity analysis in which we removed all persons with more than one SCE during follow-up.

All statistical analyses were carried out using SAS version 9.3 (Cary, North Carolina, USA).

Results

Baseline characteristics

We included 2467 persons with CKD contributing 8636 person-years of follow-up (PYFU) in the analysis. Of these 2231 (90.4%) had CKD defined by confirmed eGFR 60 ml/min per 1.73 m^2 or less and 236 persons (9.6%) by 25% eGFR decline. Persons with CKD were predominantly white (50.6%) males (77.2%) with a median age of 60 years (interquartile range, IQR 52–67 years; Table 1). Current smoking was reported in 33.6%, whereas 16.1% had diabetes, 20.6% hypertension, 59.2% dyslipidaemia and 10.1% a low BMI (<18 kg/m^2). An eGFR of 30 ml/min per 1.73 m^2 or less was prevalent in 6.3% whereas 49.3 and 26.9% had good ($CD4^+$ cell count >500 cells/μl and VL <400 copies/ml) and poor ($CD4^+$ cell count <350 cells/μl or VL >10000 copies/ml) HIV-status, respectively. As many as 47.9% had experienced any prior SCE, most commonly an (non-malignant) AIDS event.

Rates of serious clinical events

During a median follow-up time of 2.7 years (IQR 1.1–5.1 years), 595 (24.1%) of the 2467 persons with CKD experienced 826 SCE (incidence rate, IR, 68.9/1000 PYFU [95% confidence interval (CI) 63.4–74.4], supplementary Figure 1, http://links.lww.com/QAD/B521. The most common individual SCE was death [IR 32.2/1000 PYFU (28.6–35.8)], followed by NADM [IR 15.2/1000 PYFU (12.7–17.7)], CVD [IR 14.6/1000 PYFU (12.1–17.0)] and other AIDS events [IR 13.0/1000 PYFU (10.7–15.3)]. There were relatively few incident ESRD, ESLD and ADM events after CKD with the follow-up time available.

At one year after CKD, 8.3% (6.9–9.0) were estimated to have developed any SCE, increasing to 29.3% (26.9–31.4) at 5 years (Fig. 1). The 1-year and 5-year death rates were estimated at 4.0% (3.2–4.7%) and 15.3% (13.5–17.1%), respectively. Of the 313 deaths after CKD, the most common underlying cause was NADM (23.0%) and CVD (20.1%). Death with renal failure as the underlying cause accounted for less than 5%, Supplementary Figure 2, http://links.lww.com/QAD/B521.

Modifiable risk factors

In the following, we focus on the risk factor profiles for the four most commonly occurring SCEs after CKD; CVD, NADM, other AIDS events and death. There was inadequate power to conduct robust adjusted analyses for ESRD, ESLD and ADM after a CKD diagnosis. In four separate models, also adjusted for prior SCE, we found current smoking to be an independent risk factor for all SCE considered (Fig. 2). In addition to smoking, the risk profiles differed amongst the individual SCE. Diabetes was strongly associated with an increased incidence of CVD, NADM and death, whereas dyslipidaemia was only significantly associated with CVD. Poor HIV-status ($CD4^+$ cell count <350 cells/μl or VL >10000 copies/ml) was significantly associated with other AIDS events and death. Having an eGFR 30 ml/min per 1.73 m^2 or less predicted higher rates of CVD and death. Finally, a low BMI (<18 kg/m^2) was significantly associated with

Table 1. Baseline characteristics.

		All CKD		No SCE		Any SCE		
		N	%	*N*	%	*N*	%	*P*
Total		2467	100.0	1872	75.9	595	24.1	
Sex	Male	1904	77.2	1436	76.7	468	78.7	0.32
Race	White	1249	50.6	949	50.7	300	50.4	0.88
HIV risk	MSM	1171	47.5	908	48.5	263	44.2	0.0031
	Injecting drug use	318	12.9	222	11.9	96	16.1	
HIV status	Poor[a]	663	26.9	397	21.2	266	44.7	<0.0001
ART-naive	Yes	19	4.0	14	0.7	5	0.8	0.82
HBV status	Positive[b]	98	4.0	70	3.7	28	4.7	0.36
HCV status	Positive[c]	555	22.5	393	21.0	162	27.2	0.002
Any prior SCE	Yes	1181	47.9	844	45.1	337	56.6	<0.0001
smoking	Current	828	33.6	596	31.8	232	39.0	0.0043
Hypertension	Yes (mmHg)[d]	509	20.6	350	18.7	159	26.7	<0.0001
Diabetes	Yes[e]	398	16.1	258	13.8	140	23.5	<0.0001
eGFR	≤30 ml/min per 1.73 m^2	155	6.3	67	3.6	88	14.8	<0.0001
Dyslipidaemia	Yes[f]	1461	59.2	1055	56.4	406	68.2	<0.0001
BMI	<18 kg/m^2	249	10.1	169	9.0	80	13.4	0.0009

		Median	IQR	Median	IQR	Median	IQR	
Age	Years	60	52–67	60	52–67	60	51–68	0.92
$CD4^+$	cells/μl	516	345–723	547	380–750	388	250–610	<0.0001

ART, antiretroviral therapy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, Interquartile range; SCE, serious clinical events.
[a]$CD4^+$ cell count <350 cells/μl or VL >10000 copies/mL.
[b]Detection of hepatitis B virus (HBV) surface antigen, HBV e antigen, or HBV-DNA.
[c]Detection of anti-hepatitis C virus (HCV) and either detection or unknown status of HCV-RNA.
[d]Blood pressure >150/>100 mmHg or receipt of antihypertensive.
[e]Recording of a diagnosis of diabetes on a D:A:D study event form or receipt of antidiabetics.
[f]Total cholesterol level greater than 6.2 mmol/l, high-density lipoprotein cholesterol level >0.9 mmol/l, triglyceride level >2.3 mmol/l, or receipt of lipid-level-lowering treatment.

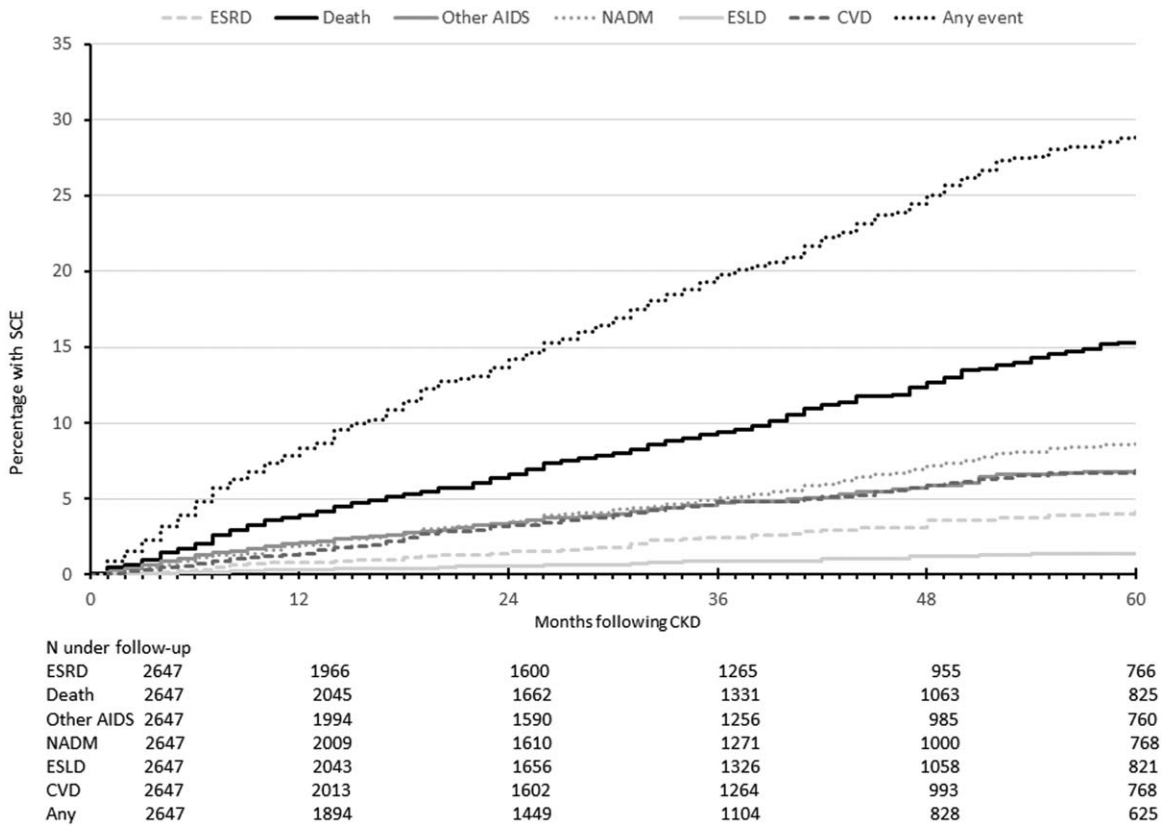

Fig. 1. Kaplan–Meier estimation of cumulative incidence of serious clinical events in the 5 years after chronic kidney disease. Each individual type of SCE was treated as a separate analysis of time to SCE. CKD, chronic kidney disease; SCE, serious clinical events.

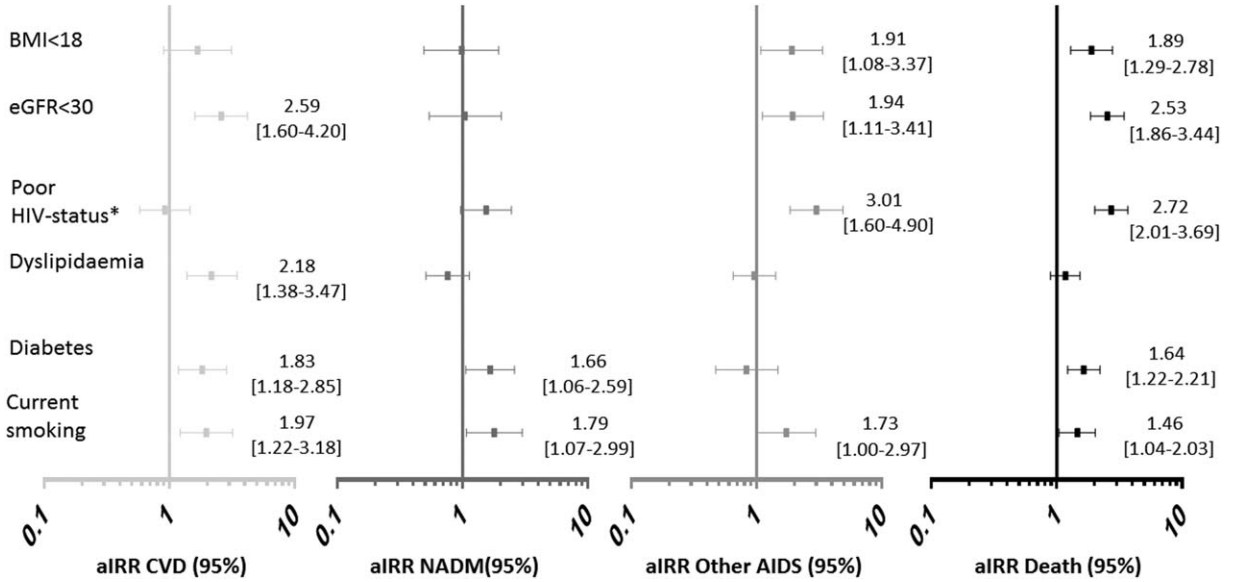

Fig. 2. Adjusted analysis of risk factor profiles of serious clinical events after chronic kidney disease. aIRR; adjusted incidence rate ratio. Adjusted for age, sex, ethnicity (those with missing ethnicity were handled as an unknown category), HIV risk acquisition, baseline date, smoking status, diabetes, hypertension, dyslipidaemia, eGFR, BMI, HBV and HCV status, *HIV status (poor $CD4^+$ cell count < 350/VL > 10000; good $CD4^+$ cell count > 500/VL < 400; intermediate all other combinations), $CD4^+$ cell count, previous events (pre-baseline) and time-updated ESLD, ESRD, NADM, ADM other AIDS and CVD (where they were not the endpoint under consideration). ADM, AIDS-defining malignancies; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESLD, end-stage liver disease; ESRD, end-stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NADM, non-AIDS-defining malignancies; SCE, serious clinical events.

higher rates of other AIDS and death. We did not find evidence of an interaction between poor HIV-status, current smoking, low BMI and diabetes for CVD, NADM, other AIDS events or death (all $P > 0.1$). Neither hypertension nor high BMI reached statistical significance for any of the CKD-related SCE.

The corresponding PAFs for key factors associated with each of the SCE were calculated (Fig. 3). Had people not been current smokers between 6.1 and 11% of the individual SCEs after CKD may not have occurred. Likewise, a diagnosis of diabetes contributed between 6.4 and 11.5% of all CVD and death events after CKD. A striking 34.9% of deaths and 13.5% of other AIDS events in persons with CKD may have been avoided with optimal HIV-status. An eGFR less than 30 ml/min per 1.73 m^2 or less attributed to 7–13% of all deaths, and finally, between 9.9 and 19.3% of deaths and CVD could potentially have been avoided by reducing dyslipidaemia.

Subanalyses

Our findings were consistent after removal of those with competing events (data not shown), suggesting in this population of PLWH with more moderate levels of CKD and with the relatively short median follow-up, competing risks did not play a major role.

To address the possibility of surveillance bias after CKD, we tested if the median number of eGFR and $CD4^+$ cell count measurements differed in the observation period before and after CKD. If anything there were slightly fewer eGFR measurements and $CD4^+$ cell counts after CKD (median 2.6 eGFR/year (2.0–3.3) before and 2.4 eGFR/year (1.6–3.0) after CKD and median 2.2 $CD4^+$ cell counts/year (1.8–3.0) before and 2.1 $CD4^+$ cell counts/year (1.4–3.1) after CKD).

Rates of serious clinical events according to chronic kidney disease status

Having established that people living with both HIV and CKD have a high burden of SCE and which individual factors contribute to each of these, we wished to put these observations into a broader perspective by comparing rates of SCE in PLWH with and without CKD. In this descriptive analysis, we included 34 116 persons contributing 272 424 PYFU without CKD and 2460 persons contributing 7328 PYFU with CKD. During a median follow-up of 8.8 (IQR 5.8–10.8) years for those without CKD 18.5% ($n = 6300$) experienced any SCE [IR 23.0/1000 PYFU (22.4–23.6)]. In comparison, those with CKD were followed for a median of 2.1 (IQR 0.4–4.9) years, during which 18.9% had any incident SCE [IR 63.7/1000 PYFU (57.9–69.5)]. When comparing the crude IR ratios for individual SCE types amongst PLWH with and without CKD, except for ADM, the SCE IR ratios were considerably higher in those with CKD [all SCE 2.7 (2.5–3.4)], but strongest for ESRD [65.9 (43.8–100.9)] and death [4.8 (4.3–5.4)] (Fig. 4).

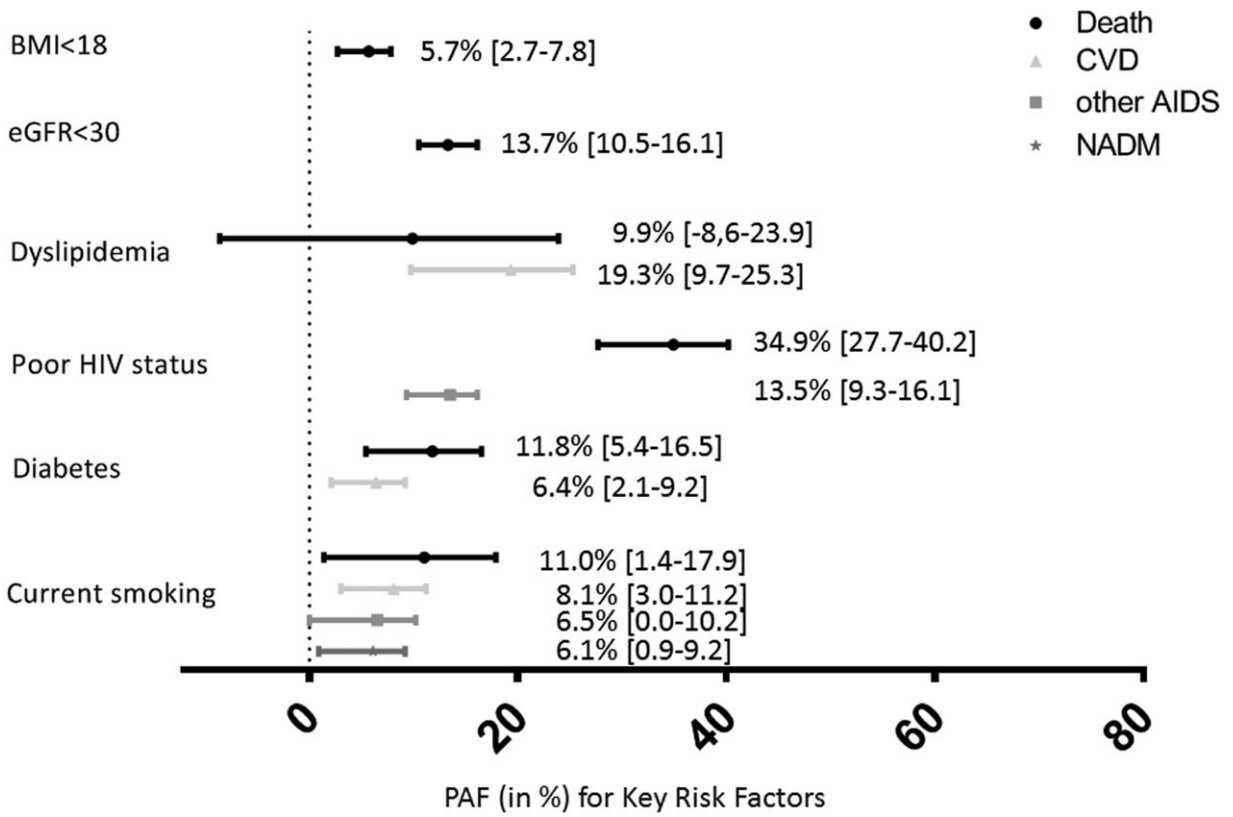

Fig. 3. Population attributable fraction of risk factors for individual serious clinical events after chronic kidney disease. The population attributable fraction (PAF, only shown for those >5%) for each of the individual key risk factors associated with each of the individual SCE. SCE, serious clinical events.

Discussion

In this analysis of a large heterogenous cohort we found that individuals living with both HIV and moderate CKD have a high burden of SCE, with almost one in three experiencing a SCE within 5 years of their CKD diagnosis. The most common SCE was death with a 5-year CKD-related mortality rate exceeding 15%. The rates of SCE were further almost three times higher in those with CKD vs. without CKD. Several potentially

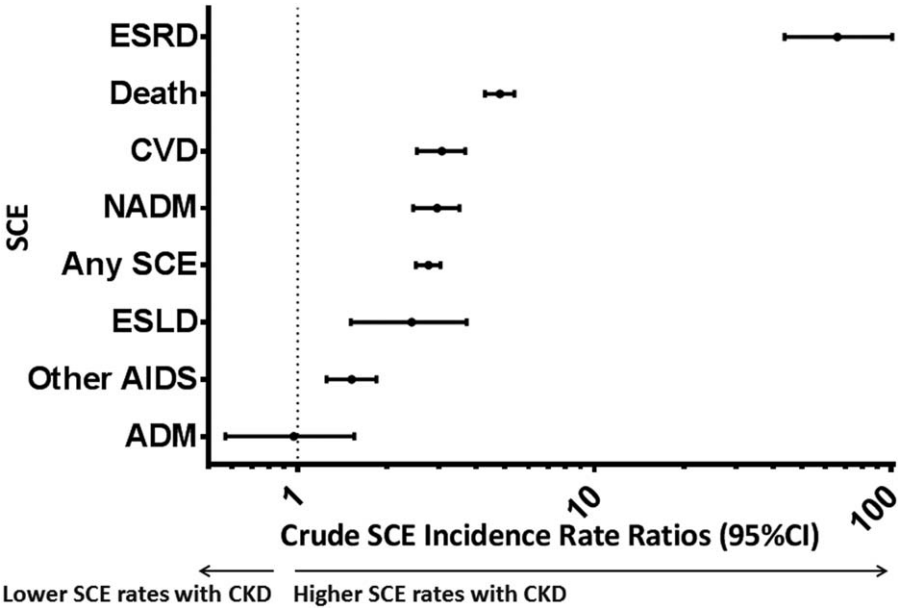

Fig. 4. Crude serious clinical event incidence rate ratios in people living with HIV with and without chronic kidney disease.

modifiable risk factors strongly predicted post-CKD SCE. Our findings suggest more intensified monitoring and interventions targeted towards these modifiable risk factors in those with CKD is warranted.

Role of modifiable risk factors in the prognosis following chronic kidney disease

The rates of prior SCE were high in those with CKD with over half having experienced an event at baseline, most commonly an (non-malignant) AIDS event, suggesting a possible contribution to the development of CKD. Our data also suggest the SCE rates are already increased relatively shortly after the CKD diagnosis. These findings raise the question about the underlying mechanistics driving SCE after CKD. With this study, many of the modifiable risk factors previously shown to predict CKD incidence in PLWH, such as diabetes and HIV status are now shown to also play an important role for driving CKD-related morbidity [7,9]. Each CKD-related SCE had a distinct risk factor profile, as also shown for CVD, ESRD and mortality among HIV-indeterminant persons with CKD stage G4 in the CRIC study [18]. For NADM after CKD, smoking and diabetes were the main modifiable predictors, both of which also predicted CVD together with dyslipidaemia and eGFR less than 30 ml/min per 1.73 m^2. For fatal cases (where NADM and CVD accounted for 43% of the underlying causes), all modifiable factors included, apart from dyslipidaemia, were independently associated with higher incidence rates, likely reflecting the more heterogenous pathways leading to death. As many of 35% of all deaths and 14% of other AIDS events after CKD were directly attributed to having a poor HIV-status. The higher rates of prior other AIDS events in those with CKD and the strong association with poor HIV-status underlines the importance of avoiding late presentation of HIV, ensuring fast initiation of effective ART and high levels for compliance to ensure a better renal prognosis [29,30]. The percentage of CVD events and death attributable to diabetes was 6 and 11%, respectively. In the general population, Hallan *et al*. also found an essential role of diabetes in CKD prognosis, and concluded that while CKD stage G3 prevalence is similar in Norway and the United States, rates of progression to ESRD are 2.5 times higher in the United States, and closely related to the higher proportion of diabetics [20]. With a continued increasing diabetes prevalence in ageing PLWH, this trend may lead to major adverse health outcomes over time [31]. Smoking was the only modifiable risk factor uniformly related with increased incidence of all SCE, and a potential to have prevented up to 11% of deaths had the person not been a current smoker. A recent large meta-analysis in the general population also found that among individuals with CKD stage G4+ diabetes and low eGFR predicted both CVD and mortality, while smoking only predicted mortality [32]. The high proportion of smoking PLWH and the complex interplay between HIV and smoking in inducing inflammation and immune exhaustion may, however, possibly explain the wider SCE association in PLWH than in the general population [33]. If we succeed in intervening effectively against these modifiable risks, both the CKD incidence and the CKD-related prognosis in PLWH are likely to be improved. Such targeted interventions for CVD-related modifiable risk factors including dyslipidaemia, hypertension and smoking have proven effective in reducing CKD-related CVD risks in the general population [34].

Chronic kidney disease prognostics and the serious clinical events spectrum

The high rates of CKD-related SCE observed may also reflect CKD as a marker of a general health deterioration. Interestingly, however, the monitoring frequency (estimated by median number of eGFR and $CD4^+$ cell count measurements) did not increase after a CKD diagnosis in this population. Therefore, while we are unable to fully exclude the possibility of reverse causality for some of the SCE after CKD (i.e. ESLD), it seems there is an additional added impact of the CKD diagnosis itself, which is also supported by the fact that SCE rates remained high even after accounting for those who had experienced a prior SCE. The high SCE rates in those with vs. without CKD also suggest that CKD itself may induce a worse prognosis, perhaps by activating additional pathogenic pathways and reflecting the inability of the kidneys to remove waste products and maintain electrolyte and hormonal balance, the increased levels of inflammation and the compromised immune function [35]. The underlying cause of CKD stage G3+ is unknown, and believed to be multifactorial, in up to 20% of all cases in the general German population [21]. For PLWH, where there are even more potential CKD risk factors and a wide spectrum of renal manifestations, it is indeed possible that CKD-related SCE are also driven by activating several different pathways concomitantly [36]. As such, the combination of HIV status, ongoing risk factors, such as smoking, and CKD may induce a state of 'triple trouble' for increased inflammation, coagulation activation, oxidative stress, accelerated atherosclerosis and ultimately increased risks of a broad spectrum of adverse health outcomes [21,35,37,38].

Although several studies have investigated predictors for and progression to ESRD, CVD or mortality, few have investigated the natural history of CKD-associated morbidity burden in PLWH more broadly [11,14,39–42]. A 2014 study from EuroSIDA found an association between current eGFR level, proportion of follow-up time spent with an eGFR of 60 ml/min per 1.73 m^2 or less and both AIDS and non-AIDS events, but lacked the power to look in more detail at individual SCE and the CKD diagnosis more formally [39]. The study did, however, also show that time-lagging outcomes did not change the observations, suggesting the associations are not simply explained by reverse causality. A Kenyan study also associated moderately impaired renal function with

faster progression to AIDS, but did not find an association with mortality [42], possibly because of both a relatively short follow-up, limited study size and using a single measurement of renal impairment likely reflecting a different underlying mechanism. In the Canadian general population rates of CVD, mortality and ESRD all increased with CKD stage, although at considerably lower rates than those found in our analysis amongst PLWH [19]. US national sample data from Choi *et al.* [15] also suggest that HIV status plays an individual role for the CKD-related disease burden in that PLWH with CKD stage G3+ had significantly higher mortality rates compared with HIV-negative individuals with CKD. For cancers, data on the association between CKD and malignancies in PLWH is limited, albeit well described in the general population. The relation is considered multifactorial with close relation to shared underlying risk factors for CKD and malignancies, accumulation of toxins, oxidative stress and infections as discussed above [37,39,43]. Progression from CKD stage G3+ to ESRD is often a gradual process and reflected in the relatively low number of ESRD events ($n = 72$) in our analysis with less than 3 years median follow-up time after CKD. Earlier studies further suggest that age modifies the most likely CKD-related outcomes in a way where older individuals are more likely to die rather than develop ESRD [44]. In this analysis, we did not find strong evidence of such competing risks but could be because of the relatively high median age of those with CKD and the limited follow-up time. The close relation between CKD stage G3+ and ESRD was, however, evident with a 65 times higher ESRD incidence in those with vs. without CKD.

Limitations

The most important limitation to acknowledge is the relatively short follow-up after CKD allowing us only to conclude about the intermediate-term post-CKD prognosis, although still adequately long to show gradually increasing rates of all SCE. As the D:A:D study does not collected proteinuria, we are unable to address any effect modification hereof and consequently, our SCE rates are conservative [19]. Due to national regulations data on ethnicity were missing for a high proportion of participants (46% without difference between those with and without SCE, $P = 0.88$), without the possibility to perform imputations as these data were not missing randomly. Calculating PAFs based on the effect sizes in multivariate analysis are intrinsically limited by not taking into account any potential correlations of these factors [45]. Finally, we are unable to rule out effects of unmeasured confounders, such as genetic predispositions to CKD, use of NSAID and levels of phosphate, calcium, vitamin D and parathyroid hormone.

Conclusion

In an era where many PLWH require less monitoring because of effective and well tolerated ART, those living with even moderate levels of CKD have a high morbidity and mortality burden with almost one in three developing a SCE within just 5 years. Our data further suggest the modifiable risk factors smoking, dyslipidaemia, poor HIV-status, diabetes and low BMI in addition to eGFR less than 30 ml/min per 1.73 m^2 play a central role for CKD-related morbidity, and highlight the need of increased monitoring, targeted interventions and focus on preventive measures for those living with both HIV and CKD.

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Ethical approval: All participating cohorts followed local national guidelines/regulations regarding patient consent and/or ethical review. In particular, of the countries represented by the participating cohorts, only Switzerland and Australia require specific ethical approval for D:A:D in addition to that required for their national cohorts (Swiss HIV Cohort Study and AHOD), France, Italy and Belgium do not require specific ethical approval over-and-above that required for the individual cohorts (Nice/Aquitaine, Brussels St. Pierre and ICONA, respectively), and the Netherlands do not require any specific ethical approval as data is provided as part of HIV care (ATHENA). For the EuroSIDA study (which includes the data from the BASS and Swedish cohorts), which contains participants from across many European countries, each participating site has a contractual obligation to ensure that data collection and sharing is done in accordance with national legislation; each site principal investigator either maintains appropriate documentation from an ethical committee (if required by law) or has a documented written statement to say that this is not required.

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Role of authors: L.R. had full access to all the data in the study and takes responsibility for the integrity of the data and analysis. L.R., A.M. and J.L. proposed and developed the research question and A.M. performed the statistical analyses. M.L., O.K., W.E.-S., A.P., R.W., E.F., A.d.A.M., P.R., S.d.W., F.B., C.I.H., and C.S. contributed with ideas around study design and interpretation of data. L.R. wrote the first draft of the manuscript. All authors have seen and contributed to the final version of the manuscript.

Conflicts of interest

L.R., J.D.L., E.F., W.E.S., S.D.W. and C.I.H. have reported no conflicts of interest. A.M. has received consultancy fees/honoraria/speaker fees from BMS, Pfizer, Merck, BI, and Gilead Sciences. M.L. has received research grants from Boehringer Ingelheim, Bristol Myer Squibb, Gilead, GlaxoSmithKline, Janssen-Cilag Pty Ltd, Merck Sharp & Dohme, Pfizer and Roche. O.K. 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. R.W. received travel grants from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dome, Pfizer, Roche, TRB Chemedica and Tibotec, the clinic has received unrestricted educational grants from GlaxoSmithKline, ViiV and Gilead Sciences. A.d'.M. has past board membership at Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Merck. F.B. has received personal fees and nonfinancial support from Gilead, ViiV Healthcare, Janssen, and MSD, and grants from Gilead and Janssen. P.R. 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. A.P. received personal fees from Gilead Sciences, Abbvie, GlaxoSmithKline Vaccines and grants from Bristol-Myers Squibb. C.S. received personal fees from Gilead Sciences, Bristol-Myers Squibb, Janssen Pharmaceuticals, Abbott Pharmaceuticals and ViiV Healthcare.

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