

Title: Serious Clinical Events in HIV-positive Persons with Chronic Kidney Disease (CKD)

Running head: CKD disease burden in HIV-positive persons

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Funding: ‘Oversight Committee for The Evaluation of Metabolic Complications of HAART’ with representatives from academia, patient community, FDA, EMA and a consortium of AbbVie, Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck and Janssen Pharmaceuticals. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Abstract

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, $eGFR \leq 60 \text{ mL/min/1.73 m}^2$ or 25% eGFR decrease when $eGFR \leq 60$) were followed to incident serious clinical events (SCE); end stage renal (ESRD) and liver disease, cardiovascular disease (CVD), AIDS- and non-AIDS defining malignancies (NADM), other AIDS or death, 6 months after last visit or 02.01.2016. 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%CI 63.4-74.4]) with 8.3% [6.9-9.0] estimated to experience any SCE at one 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, while dyslipidaemia was only significantly associated with CVD. Poor HIV-status predicted other AIDS and death, $eGFR < 30 \text{ mL/min/1.73 m}^2$ predicted CVD and death and low BMI predicted other AIDS and death.

Conclusion: In an era where many HIV-positive persons require less monitoring due to 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.

Keywords: HIV, chronic kidney disease, CKD, renal, prognosis, modifiable risk factors, serious clinical events

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+), while 65% stabilised 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 CKD levels remain undiagnosed and are associated with lower rates of adverse outcomes than more advanced CKD. Larger studies with longer 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 six months thereafter on demographics, detailed records of ART and other key HIV-variables including HIV viral load (VL), CD4 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 anti-platelets) were captured. Finally, data on selected common laboratory biomarkers (such as hemoglobin, renal and liver function markers) was systematically collected.

Endpoint definitions and statistical analyses

The SCE included were centrally validated CVD (myocardial infarction, 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 (CG) equation^[24], standardized for body surface area^[25, 26]. As several specific cohorts in D:A:D are prohibited from collecting ethnicity information the CG equation was used rather than an equation including ethnicity.

CKD was defined as confirmed, ≥ 3 months apart, eGFR ≤ 60 mL/min/1.73m² or a 25% decrease in eGFR when baseline eGFR ≤ 60 mL/min/1.73m² [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 February 1st, 2016, whichever occurred first. While 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 to 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 renal analyses^[7, 11, 23]. These included demographics (gender, age, ethnic origin, cohort), HIV-related factors (HIV acquisition risk, CD4 count, prior AIDS and viral hepatitis co-infection) and more traditional risk factors (familial disposition to CVD, hypertension, dyslipidaemia, BMI and eGFR ≤ 30 mL/min/1.73m²). We further defined poor HIV-status as CD4 count < 350 cells/ μ L or VL > 10000 copies/mL, good HIV-status as CD4 > 500 cells/ μ L and VL < 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 2,467 persons with CKD contributing 8,636 person-years of follow-up (PYFU) in the analysis. Of these 2,231 (90.4%) had CKD defined by confirmed eGFR ≤ 60 mL/min/1.73m² & 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%, while 16.1% had diabetes, 20.6% hypertension, 59.2% dyslipidaemia and 10.1% a low BMI (< 18 Kg/m²). An eGFR ≤ 30 mL/min/1.73m² was prevalent in 6.3% while 49.3% and 26.9% had good (CD4 > 500 cells/ μ L and VL < 400) and poor (< 350 cells/ μ L 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 SCE

During a median follow-up time of 2.7 years (IQR 1.1-5.1 years) 595 (24.1%) of the 2,467 persons with CKD experienced 826 SCE (incidence rate, IR, 68.9/1,000 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 32.2/1,000 PYFU [28.6-35.8]), followed by NADM (IR 15.2/1,000 PYFU [12.7-17.7]), CVD (IR 14.6/1,000 PYFU [12.1-17.0]) and

other AIDS events (IR 13.0/1,000 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 five years, figure 1. The one- and five-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, figure 2. Besides smoking, the risk profiles differed amongst the individual SCE. Diabetes was strongly associated with an increased incidence of CVD, NADM and death, while dyslipidaemia was only significantly associated with CVD. Poor HIV-status (CD4 count <350 cells/ μ L or VL >10000 copies/mL) was significantly associated with other AIDS events and death. Having an eGFR \leq 30 mL/min/1.73m² predicted higher rates of CVD and death. Finally, a low BMI (<18 Kg/m²) was significantly associated with 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, figure 3. Had people not been current smokers between 6.1% and 11.0% 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 $eGFR \leq 30$ mL/min/1.73m² attributed to 7-13% of all deaths, and finally, between 9.9-19.3% 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 count measurements differed in the observation period before and after CKD. If anything there were slightly fewer eGFR measurements (median 2.2/year [1.8-3.0] before and 2.1/year [1.4-3.1] after CKD) and CD4 counts (median 2.6/year [2.0-3.3.] before and 2.4/year [1.6-3.0] after CKD) after CKD.

Rates of SCE according to CKD status

Having established that PLWH 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 PLWH contributing 272,424 PYFU without CKD and 2,460 persons with CKD contributing 7,328 PYFU. During a median follow-up of 8.8 (IQR 5.8-

10.8) years for those without CKD 18.5% (n=6,300) 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 rate 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]), figure 4.

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 five years of their CKD diagnosis. The most common SCE was death with a five-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 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 CKD

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<30 mL/min/1.73m². 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 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 and colleagues also found an essential role of diabetes in CKD prognosis, and concluded that while CKD stage G3 prevalence is similar in Norway and the US, rates of progression to ESRD are 2.5 times higher in the US, 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 CKD incidence and 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].

CKD prognostics and the SCE 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 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 (i.e. ESLD), it seems there is an additional added impact of the CKD diagnosis itself 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 pathologic 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]}.

While 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 eGFR ≤ 60 mL/min/1.73m² 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 due to both a relatively short follow-up, limited study size and using a single measurement of renal impairment likely reflecting a different underlying pathology. 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 and colleagues also suggest 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 to HIV-negative individuals with CKD^[15].

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 three 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 didn't find strong evidence of such competing risks but could be due to 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 IR 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 collect 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 due to 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 five years. Our data further suggest the modifiable risk factors smoking, dyslipidaemia, poor HIV-status, diabetes and low BMI in addition to $eGFR < 30 \text{ mL/min/1.73m}^2$ 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.

Table 1. Baseline Characteristics

a. CD4 count <350 cells/ μ L 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 >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

Funding

The D:A:D study was supported by the Highly Active Antiretroviral Therapy Oversight Committee (HAART-OC), a collaborative committee with representation from academic institutions, the European Agency for the Evaluation of Medicinal Products, the United States Food and Drug Administration, the patient community, and pharmaceutical companies with licensed anti-HIV drugs in the European Union: AbbVie, Bristol-Myers Squibb, Gilead Sciences Inc., ViiV Healthcare, Merck & Co Inc. and Janssen Pharmaceuticals. Supported also by a grant [grant number DNRF126] from the Danish National Research Foundation (CHIP & PERSIMUNE); by a grant from the Dutch Ministry of Health, Welfare and Sport through the Center for Infectious Disease Control of the National Institute for Public Health and the Environment to Sticking HIV Monitoring (ATHENA); by a grant from the Agence nationale de recherches sur le sida et les hépatites virales [ANRS, Action Coordonnée no.7, Cohortes] to the Aquitaine Cohort; The Australian HIV Observational Database (AHOD) is funded as part of the Asia Pacific HIV Observational Database, a program of The Foundation for AIDS Research, amfAR, and is supported in part by a grant from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) [grant

number U01-AI069907] and by unconditional grants from Merck Sharp & Dohme; Gilead Sciences; Bristol-Myers Squibb; Boehringer Ingelheim; Janssen-Cilag; ViiV Healthcare. The Kirby Institute is funded by The Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, The University of New South Wales; by grants from the Fondo de Investigación Sanitaria [grant number FIS 99/0887] and Fundación para la Investigación y la Prevención del SIDA en Españã [grant number FIPSE 3171/00], to the Barcelona Antiretroviral Surveillance Study (BASS); by the National Institute of Allergy and Infectious Diseases, National Institutes of Health [grants number 5U01AI042170-10 , 5U01AI046362-03], to the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA); by primary funding provided by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n° 260694 and unrestricted grants by Bristol-Myers Squibb, Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC, (the participation of centres from Switzerland is supported by The Swiss National Science Foundation (Grant 108787)) to the EuroSIDA study; by unrestricted educational grants of AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, Janssen Pharmaceuticals to the Italian Cohort Naive to Antiretrovirals (The ICONA Foundation); and by a grant from the Swiss National Science Foundation (grant #148522) to the Swiss HIV Cohort Study (SHCS). The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Role of authors

L. Ryom had full access to all the data in the study and takes responsibility for the integrity of the data and analysis. L. Ryom, A. Mocroft and J. Lundgren proposed and developed the research question, and A. Mocroft performed the statistical analyses. M. Law, O. Kirk, W. El-Sadr, A. Phillips, R. Weber, E. Fontas, A. d' Arminio Monforte, P. Reiss, S. de Wit, F. Bonnet, C.I. Hatleberg and C. Sabin contributed with ideas around study design and interpretation of data. L. Ryom wrote the first draft of the manuscript. All authors have seen and contributed to the final version of the manuscript.

Conflicts of Interests

L. Ryom, J.D. Lundgren, 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, and Gilead Sciences. M. Law has received research grants from Boehringer Ingelheim, Bristol Myer Squibb, Gilead, GlaxoSmithKline, Janssen-Cilag Pty Ltd, Merck Sharp & Dohme, Pfizer and Roche. 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. R. Weber. 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'Arminio Monforte has past board membership at Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Merck. F. Bonnet has received personal fees and nonfinancial support from Gilead, ViiV Healthcare, Janssen, and MSD, and grants from Gilead and Janssen. 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. A. Phillips received personal fees from Gilead Sciences, Abbvie, GlaxoSmithKline Vaccines and grants from Bristol-Myers Squibb. C. Sabin received personal fees from Gilead Sciences, Bristol-Myers Squibb, Janssen Pharmaceuticals, Abbott Pharmaceuticals, and ViiV Healthcare

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.

Acknowledgements

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ACCEPTED

References

1. Gupta SK, Mamlin BW, Johnson CS, Dollins MD, Topf JM, Dube MP. **Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients.** *Clinical nephrology* 2004; 61(1):1-6.
2. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. **Premature age-related comorbidities among HIV-infected persons compared with the general population.** *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011; 53(11):1120-1126.
3. Fernando SK, Finkelstein FO, Moore BA, Weissman S. **Prevalence of chronic kidney disease in an urban HIV infected population.** *The American journal of the medical sciences* 2008; 335(2):89-94.
4. Jose S, Hamzah L, Jones R, Williams D, Winston A, Burns F, et al. **Chronic Kidney Disease Risk in African and Caribbean Populations With HIV.** *The Journal of infectious diseases* 2018; 218(11):1767-1772.
5. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. **Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients.** *AIDS* 2010; 24(11):1667-1678.
6. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. **Association Between Antiretroviral Exposure and Renal Impairment Among HIV-Positive Persons With Normal Baseline Renal Function: the D:A:D Study.** *The Journal of infectious diseases* 2013; 207(9):1359-1369.
7. Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, et al. **Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study.** *PLoS medicine* 2015; 12(3):e1001809.

8. Jotwani V, Li Y, Grunfeld C, Choi AI, Shlipak MG. **Risk Factors for ESRD in HIV-Infected Individuals: Traditional and HIV-Related Factors.** *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2011.
9. Scherzer R, Gandhi M, Estrella MM, Tien PC, Deeks SG, Grunfeld C, et al. **A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans.** *AIDS* 2014; 28(9):1289-1295.
10. Kalayjian RC, Lau B, Mechekeano RN, Crane HM, Rodriguez B, Salata RA, et al. **Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care.** *AIDS* 2012; 26(15):1907-1915.
11. Ryom L, Lundgren JD, Ross M, Kirk O, Law M, Morlat P, et al. **Renal Impairment and Cardiovascular Disease in HIV-Positive Individuals: The D:A:D Study.** *The Journal of infectious diseases* 2016; 214(8):1212-1220.
12. Campbell LJ, Desai M, Hegazi A, Ibrahim F, Melikian N, Hay P, et al. **Renal impairment is associated with coronary heart disease in HIV-positive men.** *HIV clinical trials* 2012; 13(6):343-349.
13. Ibrahim F, Hamzah L, Jones R, Nitsch D, Sabin C, Post FA. **Baseline Kidney Function as Predictor of Mortality and Kidney Disease Progression in HIV-Positive Patients.** *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2012; 60(4):539-547.
14. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. **Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons.** *Circulation* 2010; 121(5):651-658.
15. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. **The impact of HIV on chronic kidney disease outcomes.** *Kidney international* 2007; 72(11):1380-1387.

16. Ryom L, Mocroft A, Kirk O, Reiss P, Ross M, Smith C, et al. **Predictors of estimated glomerular filtration rate progression, stabilization or improvement after chronic renal impairment in HIV-positive individuals.** *AIDS* 2017; 31(9):1261-1270.

17.

http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.

KDIGO clinical practice guidelines. In; 2012.

18. Grams ME, Yang W, Rebholz CM, Wang X, Porter AC, Inker LA, et al. **Risks of Adverse Events in Advanced CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study.** *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2017; 70(3):337-346.

19. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, et al. **Relation between kidney function, proteinuria, and adverse outcomes.** *JAMA : the journal of the American Medical Association* 2010; 303(5):423-429.

20. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. **International comparison of the relationship of chronic kidney disease prevalence and ESRD risk.** *Journal of the American Society of Nephrology : JASN* 2006; 17(8):2275-2284.

21. Titze S, Schmid M, Kottgen A, Busch M, Floege J, Wanner C, et al. **Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney Disease (GCKD) cohort.** *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2015; 30(3):441-451.

22. EACS. **Guidelines version 9.1.** 2018.

23. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, et al. **Combination antiretroviral therapy and the risk of myocardial infarction.** *The New England journal of medicine* 2003; 349(21):1993-2003.

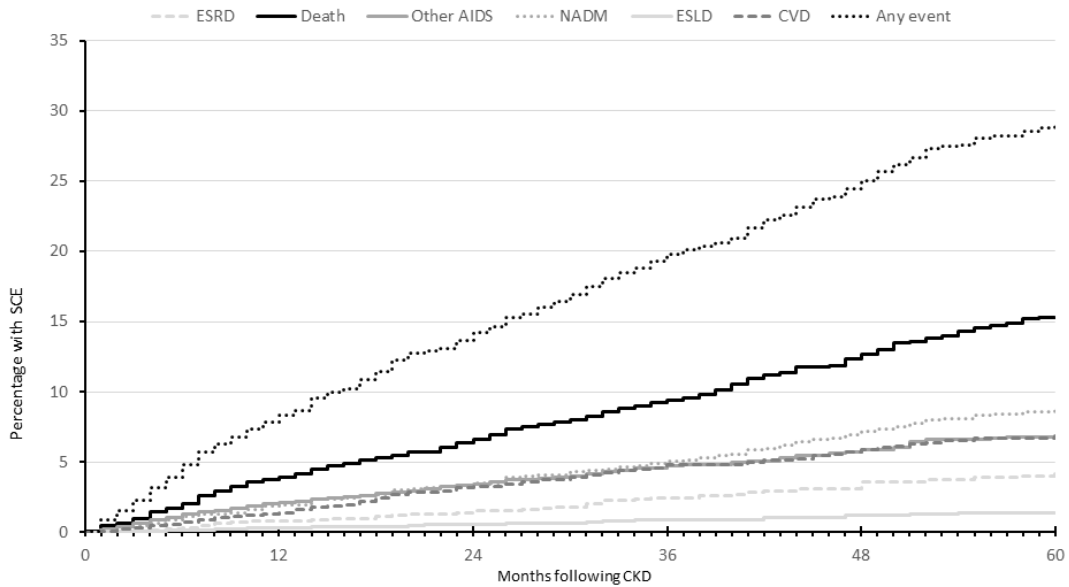
24. Cockcroft DW, Gault MH. **Prediction of creatinine clearance from serum creatinine.** *Nephron* 1976; 16(1):31-41.
25. Mosteller RD. **Simplified calculation of body-surface area.** *The New England journal of medicine* 1987; 317(17):1098.
26. Vrouenraets SM, Fux CA, Wit FW, Garcia EF, Brinkman K, Hoek FJ, et al. **A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function.** *Clinical nephrology* 2012; 77(4):311-320.
27. Mocroft A, Neuhaus J, Peters L, Ryom L, Bickel M, Grint D, et al. **Hepatitis B and C co-infection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults.** *PloS one* 2012; 7(7):e40245.
28. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al. **Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality.** *JAMA : the journal of the American Medical Association* 2014; 311(24):2518-2531.
29. Group ISS, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. **Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection.** *The New England journal of medicine* 2015; 373(9):795-807.
30. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. **CD4+ count-guided interruption of antiretroviral treatment.** *The New England journal of medicine* 2006; 355(22):2283-2296.
31. Duncan AD, Goff LM, Peters BS. **Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study.** *PloS one* 2018; 13(3):e0194199.
32. Evans M, Grams ME, Sang Y, Astor BC, Blankestijn PJ, Brunskill NJ, et al. **Risk Factors for Prognosis in Patients With Severely Decreased GFR.** *Kidney Int Rep* 2018; 3(3):625-637.

33. Valiathan R, Miguez MJ, Patel B, Arheart KL, Asthana D. **Tobacco smoking increases immune activation and impairs T-cell function in HIV infected patients on antiretrovirals: a cross-sectional pilot study.** *PloS one* 2014; 9(5):e97698.
34. Al Hamarneh YN, Tsuyuki RT, Jones CA, Manns B, Tonelli M, Scott-Douglass N, et al. **Effectiveness of Pharmacist Interventions on Cardiovascular Risk in Patients With CKD: A Subgroup Analysis of the Randomized Controlled RxEACH Trial.** *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2018; 71(1):42-51.
35. Cohen G, Horl WH. **Immune dysfunction in uremia;an update.** *Toxins* 2012; 4(11):962-990.
36. Berliner AR, Fine DM, Lucas GM, Rahman MH, Racusen LC, Scheel PJ, et al. **Observations on a cohort of HIV-infected patients undergoing native renal biopsy.** *American journal of nephrology* 2008; 28(3):478-486.
37. Lowrance WT, Ordonez J, Udaltsova N, Russo P, Go AS. **CKD and the risk of incident cancer.** *Journal of the American Society of Nephrology : JASN* 2014; 25(10):2327-2334.
38. Grund B, Baker JV, Deeks SG, Wolfson J, Wentworth D, Cozzi-Lepri A, et al. **Relevance of Interleukin-6 and D-Dimer for Serious Non-AIDS Morbidity and Death among HIV-Positive Adults on Suppressive Antiretroviral Therapy.** *PloS one* 2016; 11(5):e0155100.
39. Mocroft A, Ryom L, Begovac J, Monforte AD, Vassilenko A, Gatell J, et al. **Deteriorating renal function and clinical outcomes in HIV-positive persons.** *AIDS* 2014; 28(5):727-737.
40. Lucas GM, Lau B, Atta MG, Fine DM, Keruly J, Moore RD. **Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races.** *The Journal of infectious diseases* 2008; 197(11):1548-1557.

41. Ryom L, Mocroft A, Kirk O, Ross M, Reiss P, Fux CA, et al. **Predictors of advanced chronic kidney disease and end-stage renal disease in HIV-positive persons.** *AIDS* 2014; 28(2):187-199.
42. Gupta SK, Ong'or WO, Shen C, Musick B, Goldman M, Wools-Kaloustian K. **Reduced renal function is associated with progression to AIDS but not with overall mortality in HIV-infected Kenyan adults not initially requiring combination antiretroviral therapy.** *Journal of the International AIDS Society* 2011; 14:31.
43. Stengel B. **Chronic kidney disease and cancer: a troubling connection.** *Journal of nephrology* 2010; 23(3):253-262.
44. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. **Age affects outcomes in chronic kidney disease.** *Journal of the American Society of Nephrology* : *JASN* 2007; 18(10):2758-2765.
45. Rockhill B, Newman B, Weinberg C. **Use and misuse of population attributable fractions.** *Am J Public Health* 1998; 88(1):15-19.

Figure 1. Kaplan Meier Estimation of Cumulative incidence of SCE in the Five years After CKD

Each individual type of SCE was treated as a separate analysis of time to SCE.



N under follow-up	12	24	36	48	60	
ESRD	2647	1966	1600	1265	955	766
Death	2647	2045	1662	1331	1063	825
Other AIDS	2647	1994	1590	1256	985	760
NADM	2647	2009	1610	1271	1000	768
ESLD	2647	2043	1656	1326	1058	821
CVD	2647	2013	1602	1264	993	768
Any	2647	1894	1449	1104	828	625

ACCV

Figure 2. Adjusted Analysis of Risk Factor Profiles of SCE After CKD

aIRR; adjusted incidence rate ratio. Adjusted for age, gender, ethnicity (those with missing ethnicity were handled as an unknown category), HIV acquisition, baseline date, smoking status, diabetes, hypertension, dyslipidaemia, eGFR, BMI, HBV and HCV status, *HIV status (poor CD4<350/VL>10000; good CD4>500/VL<400; Intermediate all other combinations), CD4 count, previous events (pre-baseline) and time-updated ESLD, ESRD, NADM, ADM other AIDS and CVD (where they were not the endpoint under consideration).

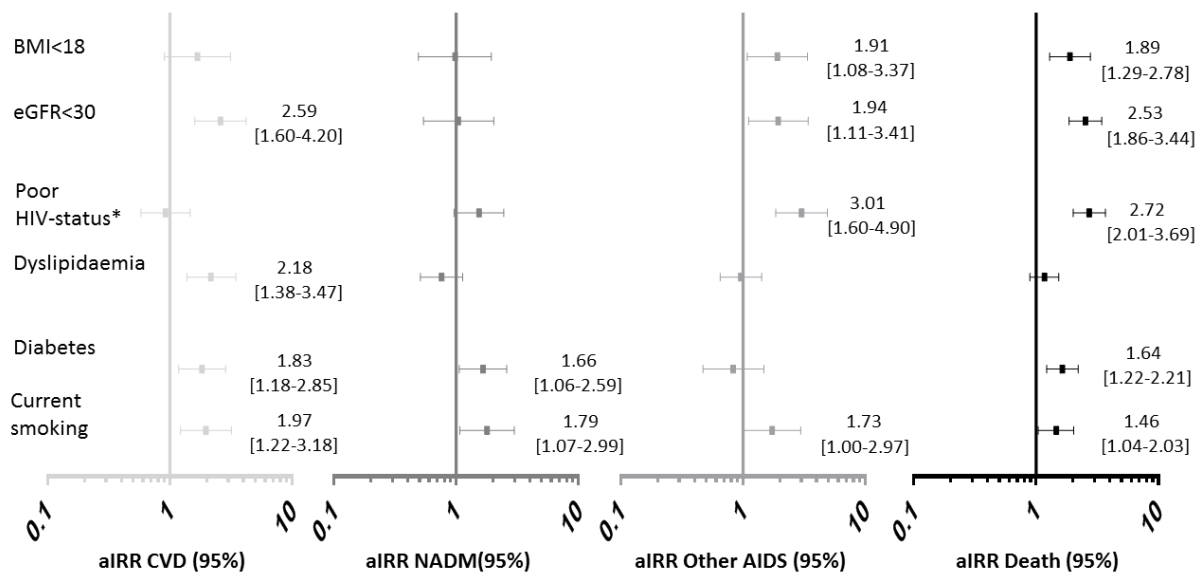


Figure 3. Population Attributable Fraction of Risk Factors for individual SCE After CKD

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.

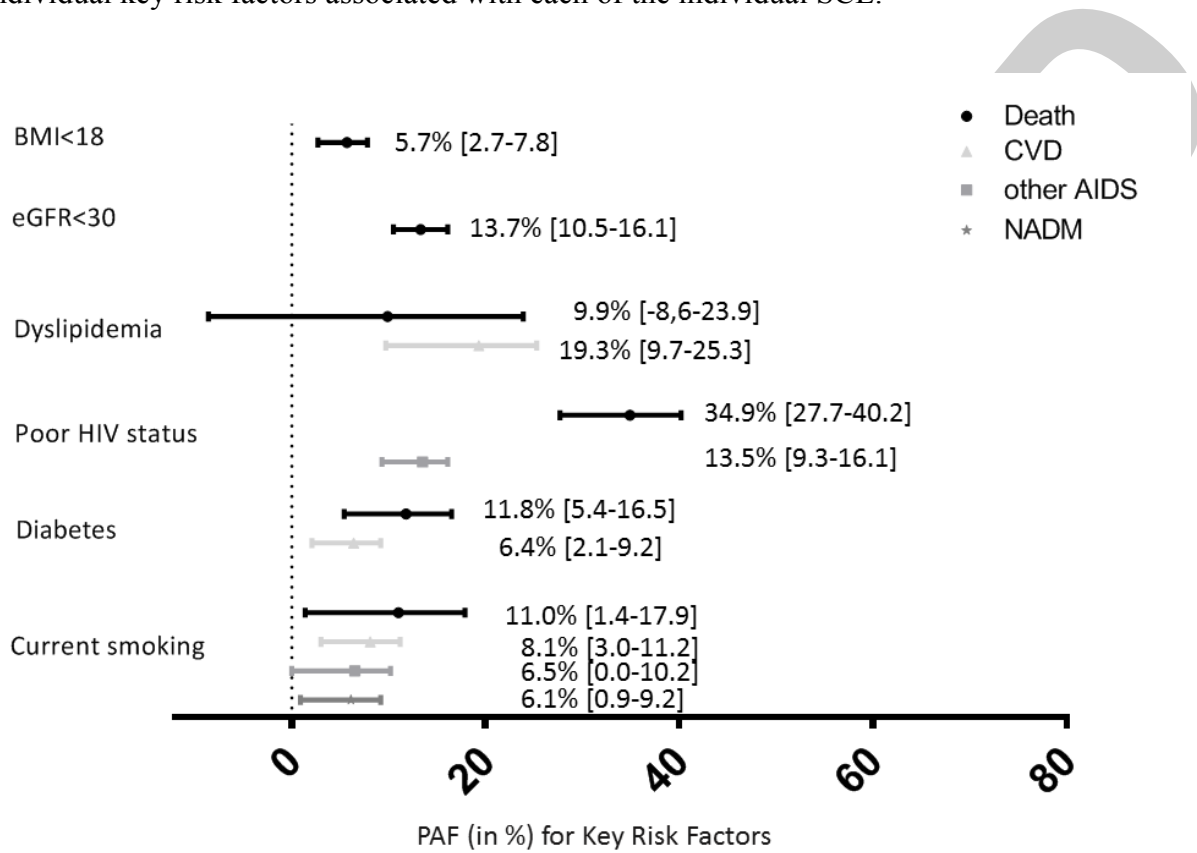


Figure 4. Crude SCE Incidence Rate Ratios in PLWH with & without CKD

