Title page

Title: Renal Impairment and Cardiovascular Disease in HIV-positive Individuals; The D:A:D Study

Running title: eGFR and Cardiovascular Disease in HIV

This project was presented in part at CROI, February 23-26 2015, Seattle, abstract ID: 2099268

Word count abstract: 200 words

Word count text: 3456 words

Authors

Lene Ryom[1], Jens D Lundgren[1], Mike Ross[2], Ole Kirk[1], Matthew Law[3], Philippe Morlat[4], Colette Smit[5], Eric Fontas[6], Christoph A Fux[7], Camilla I Hatleberg[1], Stéphane de Wit[8], Caroline A Sabin[9] and Amanda Mocroft[9] for the D:A:D Study Group

[1]Department of Infectious Diseases, CHIP, Section 2100, Rigshospitalet, University of Copenhagen, Denmark

[2]Division of Nephrology, Mount Sinai School of Medicine, New York, USA

[3]The Kirby Institute, University of New South Wales, Sydney, Australia

[4]Université Bordeaux, INSERM U 897, CHU de Bordeaux, France

[5]Academic Medical Center, Div. of Infectious Diseases and Dept. of Global Health, University of Amsterdam and HIV Monitoring Foundation, Amsterdam, The Netherlands

[6]Nephrology department, Public Health department, CHU Nice, France

[7]Clinic for Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Switzerland

[8]CHU Saint-Pierre, Department of Infectious Diseases, Brussels, Belgium

[9]Research Dept. of Infection and Population Health, UCL, London, United Kingdom

Corresponding author

Lene Ryom, M.D. PhD

Department of Infectious Diseases, CHIP, Section 2100, Rigshospitalet, Finsencentret, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen O

Tel: + 45 35 45 57 65/ Fax: +45 35 45 57 57/ email: lene.ryom.nielsen@regionh.dk

Abstract (*200 words*)

Background While the association between renal impairment and cardiovascular disease (CVD) is well established in the general population, the association remains poorly understood in HIV-positive individuals.

Methods Individuals with ≥2 estimated glomerular filtration rate (eGFRs) after 1/2/2004 were followed until CVD, death, last visit plus six months or 1/2/2015. CVD was defined as centrally validated myocardial infarction, stroke, invasive cardiovascular procedures or sudden cardiac death.

Results During 8.0 years median follow-up (Interquartile range 5.4-8.9) 1,357 of 35,357 developed CVD (incidence 5.2/1000 person-years [95%confidence interval, CI [5.0-5.5]). Confirmed baseline eGFR and CVD were closely related with 1.8% [95%CI 1.6-2.0%] estimated to develop CVD at five years at eGFR>90 ml/min/1.73m^2, increasing to 21.1% [95%CI 6.6-35.6%] at eGFR≤30 ml/min/1.73m^2. The strong univariate relationship between low current eGFR and CVD was primarily explained by increasing age in adjusted analyses, although all eGFRs≤80 ml/min/1.73m^2 remained associated with 30-40% increased CVD rates and particular high rates at eGFR≤30 ml/min/1.73m^2 (3.08 [95%CI 2.04-4.65]).

Conclusions Among HIV-positive individuals in a large contemporary cohort a strong relation between confirmed impaired eGFR and CVD was observed. This finding highlights the need for renal preventive measures and intensified monitoring for emerging CVD, in particular in older individuals with continuously low eGFR.

Keywords: eGFR, renal impairment, kidney disease, cardiovascular disease, myocardial infarction, stroke, invasive cardiovascular procedures, sudden cardiac death, HIV

Text (*3456 words*)

Introduction

The association between impaired renal function and cardiovascular disease (CVD) is well established in the general population, in particular for severe levels of renal impairment [1-6]. As such more than 50% of all deaths in individuals with end-stage renal disease are related to a CVD event [7]. In contrast, most prior studies that have investigated the relation between renal impairment and CVD in HIV-positive individuals have been small, have used relatively broad definitions of CVD, or have focused on single measures of renal function which are subjected to random variation and the transient effects of acute illness [8-13]. The influence of a more sustained impairment of estimated glomerular filtration rate (eGFR) on well-defined CVD events in HIV-positive individuals is less clear.

Renal impairment is projected to become more prevalent among HIV-positive individuals in future years due to ageing and an accumulating burden of comorbidities and lifestyle related risk factors.
CVD is furthermore now one of the leading causes of non-AIDS death in HIV-positive individuals [14]. A better understanding of the rates of CVD among HIV-positives individuals with renal impairment is therefore warranted to assist identification of those at highest risk with a need for intensified monitoring and initiation of preventive measures [15]

The relationship between renal impairment and CVD is complex and may be mediated through a variety of different pathways [3, 6, 14]. These include accelerated coronary- and cerebrovascular atherosclerosis which may be mediated in part by increased inflammation and oxidative stress, atrial fibrillation and ventricular hypertrophy, which are common at severe levels of renal impairment and may, similar to electrolyte abnormalities, promote dysrhythmias resulting in stroke or sudden cardiac death [3, 15-20]. Finally renal impairment and CVD are known to share a common underlying risk factor profile which include hypertension, diabetes, dyslipidemia, smoking, injecting drug use, obesity, on-going inflammation and black African origin [20, 21]. CVD, renal impairment, and many of the underlying shared individual risk factors,

are more prevalent among HIV-positive individuals than in the general population, hence the association between renal impairment and CVD may be stronger in HIV-positive individuals [22, 23]. The aim of this analysis is to investigate the nature and relationship of various levels of sustained eGFR impairment with centrally adjudicated CVD endpoints in a large heterogeneous and contemporary cohort of primarily Caucasian HIV-positive individuals.

Methods

Study population

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study is a large, prospective cohort collaboration established in 1999 following more than 49,000 HIV-1-positive persons from 11 cohorts in Europe, the United States and Australia; details have been published previously [17]. Data on centrally validated clinical events including myocardial infarction, sudden cardiac death, stroke, invasive cardiovascular procedures, end-stage renal disease and fatal cases is collected in real-time during routine clinical care. Information on socio-demographic factors, antiretroviral treatment, HIV viral load, CD4 counts, AIDS events, viral hepatitis, creatinine and other laboratory biomarkers and cardiovascular risk factors is collected electronically at enrolment and every six months.

Endpoint definition

CVD events are reported using designated event forms (more information at www.chip.dk/Studies/DAD/Study-Documents) and are defined as centrally validated fatal and non-fatal myocardial infarction, stroke, coronary angioplasty, coronary bypass, carotid endarterectomy and sudden cardiac death. A fatal CVD event is defined as one of the above events leading to death within 28 days. Adjudication of CVD events is made in accordance with predefined algorithms, and only confirmed events are included in analysis. Sudden cardiac death is defined as a sudden death event in which the underlying cause of death could not be established as a myocardial infarction due to the lack of data on symptoms,

electrocardiogram findings and changes in cardiac biomarker, but with cardiovascular risks present at time of death according to the WHO MONICA Dundee score [24], and no evidence of other non-atherosclerotic or non-cardiovascular causes of death. All sudden cardiac deaths in the D:A:D study are reviewed by an external cardiologist.

Statistical methods

D:A:D Study participants with ≥2 eGFR measurements after 1/2/2004 (baseline for initiation of systematic creatinine collection) were included and followed until the earliest of first CVD event, death, six months after last visit or 1/2/2015. Persons with less than three months follow-up from the first to last eGFR were excluded. The Cockcroft-Gault equation [25], standardized for body surface area [26], was used to estimate creatinine clearance, a surrogate for eGFR in this analysis [27, 28]. As several cohorts participating in D:A:D are prohibited from collecting ethnicity information, the Cockcroft-Gault equation was used rather than an equation including ethnicity. Where eGFR measurements were carried out more frequently than every 28 days, the median value was used and assigned to the median date. Confirmed baseline and time-updated (current) eGFR levels were defined using two consecutive eGFR measurements, regardless of time between measurements (per definition minimum 28 days). The confirmed baseline and current eGFR values were subsequently allocated to the following eGFR strata: >90, >60-≤90, >30-≤60 and ≤30 ml/min/1.73m^2. Where two consecutive eGFR values (<15% of all values) did not fall within the same eGFR strata, the mean of two eGFR values carried forward was used to assign an eGFR category.

Individuals with a prior CVD event were included, but only the first CVD event experienced during prospective follow-up after baseline was included as an event. Individuals could however experience two or more different types of CVD event on the same date.

Incidence rates were calculated per 1000 person years of follow-up (PYFU). Kaplan-Meier estimation was used to investigate time to CVD, stratified according to confirmed baseline eGFR levels (eGFR>90, ≤90->60, ≤60->30, ≤30 ml/min/1.73m^2).

Poisson regression models stratified according to the confirmed current eGFR level were used to model the CVD incidence rate ratios, overall and stratified by individual CVD events. Potential confounders included in multivariate models were age (per 10 years older), gender, ethnicity, D:A:D enrolment cohort, nadir CD4 count, mode of HIV acquisition and family history of CVD. All remaining variables were adjusted for as time-updated, including HBV/HCV co-infection, HIV-RNA (per $\log_{10}$), CD4 count, prior AIDS, hypertension (>150/>100 or receipt of antihypertensive treatment), diabetes (confirmed diagnosis of DM or receipt of anti-diabetic treatment), confirmed eGFR strata, smoking status (current, previous, never), dyslipidemia (total cholesterol >6.2 mmol/l, high-density lipoprotein cholesterol <0.9 mmol/l, triglyceride >2.3 mmol/l, or receipt of lipid-lowering treatment) and prior CVD (confirmed diagnosis). Antiretroviral drug use was fitted as time-updated cumulative use (per five years; zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, tenofovir disoproxil fumerate, abacavir, efavirenz, nevirapine, indinavir, saquinavir, ritonavir, nelfinavir, (fos)ampreavir, atazanavir and darunavir) and current use (currently on and use with last six months; zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, tenofovir disoproxil fumerate and abacavir).

A number of sensitivity analyses were performed to test the robustness of the results. One analysis investigated death as a potential competing risk of CVD. Another analysis excluded all those with a prior CVD event. Other analyses adjusted for the D:A:D CKD risk-score [29] and the predicted CVD risk based on the Framingham CVD prediction model [30] to estimate how much of the CVD risk is explained through common renal and CVD risk factors. The D:A:D CKD risk score is a nine-variable prediction score estimating the five year risk of developing CKD in HIV-positive individuals. Individuals in the low CKD risk group (score <0) have a 1:393 (0.3%) five year CKD risk, rising to 1:47 (2.1%) in the medium (score 0-4) and 1:6 (16.7%) high risk group (score $\geq$5) [29]. A final analysis investigated the association between current nadir eGFR and the percentage of follow-up time spent with eGFR$\leq$60 ml/min/1.73m^2 and CVD respectively.

Results

Study population

35,357 persons with follow-up after 2004 and at least two eGFR measurement were included in analysis, Supplementary Figure 1. Included individuals were predominantly Caucasian (48.1%) males (73.9%) with a median age of 41 (interquartile range, IQR, 35-48) years, Table 1. While 41.6% were smokers, 4.0% had diabetes, 8.9% had hypertension and 0.7% had experienced a prior CVD event. At baseline the median estimated five year risk of CKD was low overall (-1 (IQR -3 to4) corresponding to 0.3%) and medium (4 (IQR -1to 9) corresponding to 2.1%) in those developing a CVD event, Table 1. 558 persons were excluded from analysis due to missing CD4 counts or viral load at baseline, or because of insufficient follow-up. Excluded persons were more likely to be young, of Caucasian origin, cART-naïve, HCV-positive, have no family history of CVD and have experienced a prior AIDS event.

Age and eGFR level

Among individuals younger than 40 years 87.0% (n=13,660) had a normal (confirmed eGFR>90 ml/min/1.73m^2) baseline eGFR, and only 0.04% (n=7) had advanced renal impairment (confirmed baseline eGFR$\leq$30 ml/min/1.73m^2). In contrast, among individuals older than 60 years, only 15.8% (n=321) had confirmed baseline eGFR>90ml/min/1.73m^2 and 0.8% (n=17) confirmed baseline eGFR$\leq$30 ml/min/1.73m^2.

CVD events

Over a median follow-up time of 8.0 years (IQR, 5.4-8.9, total PYFU 258,480) 1,357 persons developed 1,646 CVD events (incidence rate 5.2 per 1000 PYFU [95% confidence interval, CI, 5.0-5.5]). The CVD events included 586 myocardial infarctions (11.1% fatal), 430 strokes (8.6% fatal), 510 coronary angioplasties (1.6% fatal), 96 coronary bypasses (2.1% fatal), 19 carotid endarterectomies (0% fatal) and 5 sudden cardiac deaths respectively. A total of 284 persons (21.0%) experienced more than one CVD event on the same date, most commonly a myocardial infarction and coronary angioplasty (n=259).

Median eGFR levels and incident CVD

The median eGFR measured in individuals prior to their CVD event was significantly lower (85 (IQR 69-102) ml/min/1.73m^2) than the median eGFR measured during follow-up in individuals not experiencing a CVD event (94 (IQR 79-110) ml/min/1.73m^2, p<0.0001). Likewise, a greater proportion of individuals experiencing a CVD event had some level of confirmed reduced eGFR level, compared to individuals not experiencing an event, Figure 1. When comparing the individual types of CVD events, those experiencing a coronary bypass event had significantly lower confirmed eGFR levels compared to all other CVD event types (p=0.018). When excluding the coronary bypass events there was no statistically significant differences in confirmed eGFR levels prior to a CVD event (p=0.068). Likewise, when comparing those with an invasive cardiovascular procedures (coronary angioplasty, carotid endarterectomy or coronary bypass) to those with a myocardial infarction and/or stroke there was no statistical significant difference (p=0.55), Figure 1.

Confirmed baseline eGFR levels and incident CVD

We observed a clear inverse relationship between confirmed eGFR levels at baseline and incident CVD with 1.8% [95% CI 1.6-2.0%] estimated to have progressed to CVD at five years among those with confirmed baseline eGFR>90 ml/min/1.73m^2, increasing to 4.1% (95% CI 3.5-4.6) for eGFR 60-90 ml/min/1.73m^2, 10.8% (95% CI 8.7-12.9) for baseline eGFR 30-60 ml/min/1.73m^2 and 21.1% [95% CI 6.6-35.6%] among those with confirmed baseline eGFR$\leq$30 ml/min/1.73m^2, Figure 2.

Amongst individuals with moderately impaired baseline eGFR (confirmed eGFR$\leq$60 ml/min/1.73m^2) who developed a CVD event, we did not observe a statistically significant differences (p=0.63) in time to different CVD events with a median time to CVD event of 45 months (IQR 21-76).

Confirmed current eGFR level and incident CKD

There was a strong and inverse linear relationship between confirmed current eGFR and CVD in univariate analysis; incidence rate ratios (IRRs) increasing from 1.00 at eGFR>90 ml/min/1.73m^2 to 14.09 [95%CI 9.58-20.74] at eGFR$\leq$30 ml/min/1.73m^2, Figure 3. Adjusting for increasing age explained most of the relationship

between eGFR and CVD at eGFR levels >30 ml/min/1.73m^2, although all eGFRs below 80 ml/min/1.73m^2 were associated with an increased incidence of CVD of approximately 30-40%. At a confirmed current eGFR$\leq$30 ml/min/1.73m^2 a significantly increased incidence of CVD remained independent of age (IRR 4.21 [95%CI 2.81-6.30]), Figure 3. Further adjustment for other potential confounders including individual antiretroviral drugs had relatively limited impact on the overall association (IRR 3.08 [95%CI 2.04-4.65] at confirmed eGFR$\leq$30 ml/min/1.73m^2 compared to confirmed eGFR$\geq$90 ml/min/1.73m^2, Figure 3. The exclusion of the 240 individuals with a CVD event prior to baseline led to entirely consistent results (data not shown).

In a bivariate analysis, adjusting for the Framingham score (as a continuous variable) explained some of the association between confirmed current eGFR and CVD, but not to the same extent as age alone (data not shown). In another analysis adjusting for the estimated five-year D:A:D CKD risk score individuals with a medium CKD risk (score 0-4) had a 2.56-fold increased incidence of CVD (IRR 2.56 [95%CI 2.22 – 2.95]) and individuals with a high CKD risk (score $\geq$5) had almost a five-fold increased incidence of CVD (IRR 4.98 [95% CI 4.37 – 5.68]) compared to persons with a low estimated CKD risk (score <0). After adjusting for other potential confounders (as shown in Figure 4) not included in the D:A:D CKD risk score (with the exception of age), those with a medium or high CKD risk score continued to have a significantly higher risk of CVD (IRR 1.29 [95%CI 1.10-1.50] and 1.43 [95%CI 1.19-1.71] respectively).

There was no strong evidence suggesting that the observed association between confirmed current eGFR levels and CVD differed amongst the individual types of CVD events. When restricting the analysis to fatal CVD events only, all observed associations were further strengthened (data not shown). Our findings were furthermore consistent in different age groups (test for interaction, p=0.88), and after accounting for death as a possible competing risk for CVD (data not shown). The association between CVD and confirmed eGFR seen in the primary analyses was largely unchanged by fitting renal function as current nadir eGFR and as

the percentage of follow-up spent with moderately impaired eGFR (eGFR≤60 ml/min/1.73m^2) (data not shown).

Confirmed current eGFR levels and number of CVD events

Individuals with higher confirmed current eGFR levels experienced two or more CVD events (at the same date) more frequently than those with lower eGFR levels (24.7% at eGFR>90 ml/min/1.73m^2 vs.4.2% at eGFR≤30 ml/min/1.73m^2, p=0.0034), most commonly a myocardial infarction and coronary angioplasty. Furthermore, the proportion of individuals experiencing a fatal CVD event (death within 28 days following the event) was strongly related to the confirmed current eGFR level, increasing from 4.4% in individuals with a confirmed current eGFR>90 ml/min/1.73m^2 to 25.0% in individuals with a confirmed current eGFR≤30 ml/min/1.73m^2 (p<0.0001).

Discussion

In this large heterogeneous cohort of HIV-positive individuals we found a strong association between centrally adjudicated CVD events and advanced levels of renal impairment (confirmed eGFR≤30 ml/min/1.73m^2).

Almost 60% of all individuals experiencing a CVD event had eGFR≤90 ml/min/1.73m^2, based on the latest median eGFR before the event, compared to less than 40% of those without an event. We further showed that development of a CVD event was considerately faster among those with a severely impaired eGFR at baseline. Among HIV-positive individuals with confirmed baseline eGFR≤30 ml/min/1.73m^2 over 20% were estimated to have developed CVD after five years.

In previous studies from D:A:D we have investigated the inverse relation between CVD events and eGFR, focusing on CVD as a risk factor of various levels of chronic renal impairment [28, 29, 31]. Interestingly, these previous data also supported a strong association between CVD and renal function which significantly diminished after accounting for other risk factors suggesting an underlying biological mechanism at least

partly mediated by other factors. We have also previously showed an association between the use of certain antiretroviral drugs and CVD and renal impairment [28, 30, 32]. The results of this analysis are entirely consistent with these prior findings, and adjustment for the use of individual antiretroviral drugs did not have any major impact on the association between impaired eGFR and CVD. Data from this analysis points towards increasing age as the main underlying driver of the inverse relationship between eGFR and CVD, in particular at mild to moderately impaired eGFR levels [14]. At more advanced levels of renal impairment (eGFR$\leq$30 ml/min/1.73m^2) there are additional pathways between renal impairment and CVD, not immediately related to any of the known common risk factors on the shared causal pathway such as diabetes, hypertension and immunosuppression. Regardless of the underlying pathology the high rates of CVD observed in older individuals with mild to moderate renal impairment highlight the need for intensified monitoring and search for effective prophylactic measures for impaired renal function and CVD in the ageing HIV-population.

In other studies of HIV-positive individuals, a smaller cross-sectional analysis in the FRAM study did not confirm an association between carotid intima-medial thickness and eGFR after accounting for older age, gender and ethnicity [13]. Likewise, a British study did not find an association between eGFR as a continuous variable and coronary heart disease, although those with eGFR<75 mL/min already had more than a 4-fold increased incidence [9]. In a recent EuroSIDA study both the follow-up time with a low eGFR and eGFR$\leq$30 ml/min/1.73m^2 were predictive of non-AIDS events including CVD, but power was limited [12]. An older large cohort study among HIV-positive US veterans showed an almost 6-fold higher association between eGFR$\leq$30 ml/min, albuminuria and CVD, although this study also included peripheral artery disease and heart failure [10].

Our findings do not suggest that the association between declining renal function and CVD is stronger, or starts at higher eGFR levels in HIV-positive persons than in the general population, as was hypothesised based on the higher occurrence of common renal and CVD risk factors and increased immune activation [1,

4, 33, 34]. There is, however, ongoing ambiguity, in the general population, regarding the strength of the association between impaired renal function and CVD. Some studies report only on an association with CVD at advanced levels of renal impairment (eGFR≤30 ml/min/1.73m^2) while others report of associations already at higher eGFR levels [1, 4, 5, 9, 10, 14, 33, 34]. However, the definitions of CVD differ considerately in these studies ranging from subclinical imaging-verified diagnoses of atherosclerosis to various clinical events ascertained with different levels of certainty. The differences in the incidence of common risk factors and of CVD and renal impairment may also partly explain the conflicting results. Importantly, the D:A:D study focuses on 'hard' clinical CVD events exclusively and information on non-fatal heart failure or milder forms of ischemic CVD such as angina pectoris is not collected. This methodology may explain why more severe levels of renal impairment are necessary to establish an association with CVD. Interestingly, none of the widely accepted CVD risk prediction models currently include renal impairment in the estimates [30, 32], but the proportion of individuals with advanced renal impairment may be too limited to date.

We also found that fatal outcomes of a CVD event were more common at lower compared to higher eGFR levels, which may be related to a more severe clinical event or to the fact that those with advanced levels of renal impairment provide a more fragile phenotype with less ability to cope with CVD complications. Likewise, fewer multiple CVD events occurred on the same date among those with lower eGFR levels. This finding may be related to the increased fatality rate at lower eGFR levelsor that those with lower eGFR levels are less likely to undergo invasive cardiovascular procedures as secondary prophylaxis, due to concerns about radiocontrast induced nephrotoxicity. Interestingly, there was no evidence of a relation between the eGFR level and type of CVD outcome i.e. a myocardial infarction did not seem to occur at different eGFR levels to other CVD events, with the exception of coronary bypass. Coronary bypass was more commonly carried out at lower eGFR levels, compared to the other CVD events, which may suggest more advanced atherosclerosis with multiple vessel disease in this population.

The potential limitations of the analysis should be acknowledged. We may have underestimated the proportion of individuals with an impaired eGFR level as those excluded from analysis were more likely to have common renal risk factors; hence the provided relation between eGFR and CVD is of a conservative nature. Proteinuria is a potential source of unmeasured confounding as it not collected systematically in the D:A:D study, and may further have moderating effects as it is a strong independent risk factor for both CVD and CKD [35].Furthermore, renal impairment may have developed secondary to a CVD event as part of a cardiorenal syndrome, with potentials of reverse causality. However, in this analysis eGFR impairment proceeded all prospectively investigated CVD events [36]. Finally, non-ischemic events such as cardiac arrhythmias and ventricular hypertrophy were not directly included in the CVD definition, but may have contributed more indirectly via stroke and sudden cardiac death events.

Conclusion

In a large, contemporary cohort of HIV-positive individuals we observed a strong relationship between confirmed impaired renal function and incident CVD. More than one in five of those with advanced levels of renal impairment were estimated to have developed CVD by five years, with an increasing 28-day CVD fatality rate as eGFR declined. Our findings highlight the need for an intensified monitoring for emerging CVD, in particular in older individuals with continuously low eGFR levels. Our findings also call for an increased focus on applying different renal and cardiovascular preventive measures in HIV-positive individuals.

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 Stiching 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 Espanã [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 Beirn 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.

Conflicts of Interests

L. Ryom, J.D. Lundgren, M. Ross, E. Fontas, C. Smit, C.I. Hatleberg, and S. De Wit have reported no conflicts of interest. 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. P. Morlat has received honoraria, speaker fees, travel support or honoraria from AbbVie, Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck & Co Inc. and Janssen Pharmaceuticals. C.A. Fux is an advisory board member for Gilead Sciences and MSD, has pending grants from Gilead Sciences and Abbott and received payment for lectures by Gilead HIV and the body. M. Law has received research grants from Boehringer Ingelheim, Bristol Myer Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Merck, Pfizer and Hoffman-LaRoche. C. Sabin received personal fees from Gilead Sciences, Bristol-Myers Squibb, Janssen Pharmaceuticals, Abbott Pharmaceuticals, and ViiV Healthcare. A. Mocroft has received consultancy fees/honoraria/speaker fees from Bristol-Myers Squibb, Pfizer, Merck, Boehringer Ingelheim, and Gilead Sciences.

Acknowledgements

D:A:D participating cohorts: AHOD (Australia), Aquitaine (France), Athena (The Netherlands), BASS (Spain), CPCRA (USA), EuroSIDA (multi-national), HivBivus (Sweden), ICONA (Italy), Nice (France), SHCS (Switzerland) and St. Pierre (Belgium)

D:A:D Steering Committee: Names marked with *, Chair with #

Cohort PIs: W. El-Sadr* (CPCRA), G. Calvo* (BASS), F. Dabis* (Aquitaine), O. Kirk* (EuroSIDA), M. Law* (AHOD), A. d'Arminio Monforte* (ICONA), L. Morfeldt* (HivBIVUS), C. Pradier* (Nice), P. Reiss* (ATHENA), R. Weber* (SHCS), S. De Wit* (Brussels)

Members of the D:A:D SC from the Oversight Committee: B. Powderly*, N. Shortman*, C. Moecklinghoff *, G. Reilly*, X. Franquet*

D:A:D Central Coordination: C.I. Hatleberg, L. Ryom, C.A. Sabin*, D. Kamara, CJ. Smith, A. Phillips*, A. Mocroft*, A. Bojesen, A.L. Grevsen, C. Matthews, D. Raben, J.D. Lundgren#

D:A:D Cohort coordinators and data managers: A. Lind-Thomsen (coordinator), R. Salbøl Brandt, M. Hillebreght, S. Zaheri, F.W.N.M. Wit (ATHENA), F. Schöni-Affolter (SHCS) A. Travelli, I. Fanti (ICONA), O. Leleux (Aquitaine), E. Thulin, A. Sundström (HivBIVUS), G. Bartsch, G. Thompsen (CPCRA), M. Delforge (Brussels), E. Fontas, C. Caissotti, K. Dollet (Nice), S. Mateu, F. Torres, (BASS), R. Puhr (AHOD), D. Kristensen (EuroSIDA)

Verification of Endpoints: A. Sjøl (CVD), P. Meidahl (oncology), J. Helweg-Larsen (hematology), J. Schmidt Iversen (nephrology) **Kidney working group:** L. Ryom, A. Mocroft, O. Kirk*, P. Reiss*, C. Smit, M. Ross, C.A. Fux, P. Morlat, E. Fontas, D.A. Kamara, C.J. Smith, J.D. Lundgren#

Mortality working group: C.J. Smith, L. Ryom, C. I. Hatleberg, A. Phillips*, R. Weber*, P. Morlat, C. Pradier*, P. Reiss*, F.W.N.M. Wit, N. Friis-Møller, J. Kowalska, J.D. Lundgren#

Cancer working group: C. Sabin*, M. Law*, A. d'Arminio Monforte*, F. Dabis*, F. Bonnet*, P. Reiss*,

F.W.N.M. Wit, CJ. Smith, D.A. Kamara, J. Bohlius, M. Bower, G. Fätkenheuer, A. Grulich, L. Ryom, C.I.Hatleberg, J.D. Lundgren#

For a complete list of acknowledgements for the members of the 11 Cohorts in the D:A:D Study, please see Supplementary Document 2

References

1. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis.BMJ **2010**; 341:c4249.

2. Shara NM, Wang H, Mete M, et al. Estimated GFR and incident cardiovascular disease events in American Indians: the Strong Heart Study Am J Kidney Dis. **2012**; 60:795-803.

3. Wang AY, Lai KN. Use of cardiac biomarkers in end-stage renal disease. J Am Soc Nephrol **2008**; 19:1643-52.

4. Di Angelantonio E, Danesh J, Eiriksdottir G, Gudnason V. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. PLoS Med **2007**; 4:e270.

5. Arbel Y, Halkin A, Finkelstein A, et al. Impact of Estimated Glomerular Filtration Rate on Vascular Disease Extent and Adverse Cardiovascular Events in Patients Without Chronic Kidney Disease. Can J Cardiol **2013**.

6. de Bie MK, Buiten MS, Rabelink TJ, Jukema JW. How to reduce sudden cardiac death in patients with renal failure. Heart **2012**; 98:335-41.

7. Collins AJ, Roberts TL, St Peter WL, Chen SC, Ebben J, Constantini E. United States Renal Data System assessment of the impact of the National Kidney Foundation-Dialysis Outcomes Quality Initiative guidelines. Am J Kidney Dis **2002**; 39:784-95.

8. George E, Lucas GM, Nadkarni GN, Fine DM, Moore R, Atta MG. Kidney function and the risk of cardiovascular events in HIV-1-infected patients. AIDS **2010**; 24:387-94.

9. Campbell LJ, Desai M, Hegazi A, et al. Renal impairment is associated with coronary heart disease in HIV-positive men. HIV clinical trials **2012**; 13:343-9.

435 10. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. Association between kidney
436 function and albuminuria with cardiovascular events in HIV-infected persons. Circulation **2010**;
437 121:651-8.
438 11. Serrano-Villar S, Estrada V, Gomez-Garre D, et al. Incipient renal impairment as a predictor of
439 subclinical atherosclerosis in HIV-infected patients. JAIDS **2012**; 59:141-8.
440 12. Mocroft A, Ryom L, Begovac J, et al. Deteriorating renal function and clinical outcomes in HIV-
441 positive persons. AIDS **2014**; 28:727-37.
442 13. Jotwani V, Scherzer R, Choi A, et al. Reduced kidney function and preclinical atherosclerosis in
443 HIV-infected individuals: the study of fat redistribution and metabolic change in HIV infection
444 (FRAM). Am J Nephrol **2011**; 33:453-60.
445 14. Natali A, Boldrini B, Baldi S, et al. Impact of mild to moderate reductions of glomerular
446 filtration rate on coronary artery disease severity. Nutr Metab Cardiovasc Dis **2014**; 24:681-8.
447 15. Spoto B, Mattace-Raso F, Sijbrands E, et al. Association of IL-6 and a functional polymorphism
448 in the IL-6 gene with cardiovascular events in patients with CKD. Clin J Am Soc Nephrol N **2015**;
449 10:232-40.
450 16. Klawitter J, Reed-Gitomer BY, McFann K, et al. Endothelial dysfunction and oxidative stress in
451 polycystic kidney disease. Am J Renal Physiol **2014**; 307:F1198-206.
452 17. Matsushita K, Sang Y, Ballew SH, et al. Cardiac and kidney markers for cardiovascular
453 prediction in individuals with chronic kidney disease: the Atherosclerosis Risk in Communities
454 study. Arterioscler Thromb Vasc Biol **2014**; 34:1770-7.
455 18. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease,
456 renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc
457 Nephrol **2005**; 16:489-95.

19. Baber U, Howard VJ, Halperin JL, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol **2011**; 4:26-32.

20. Gupta SK, Kitch D, Tierney C, Melbourne K, Ha B, McComsey GA. Markers of renal disease and function are associated with systemic inflammation in HIV infection. HIV Med **2015**; 16:591-8.

21. Kong X, Ma X, Cui M, Xu D. Association of clustering of major cardiovascular risk factors with chronic kidney disease in the adult population. Clin Nephrol **2014**; 82:92-7.

22. Schouten J, group oboAHs. comorbidity and ageing with HIV. IAS. Washington DC, USA, **2012**.

23. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab **2007**; 92:2506-12.

24. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation **1994**; 90:583-612.

25. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron **1976**; 16:31-41.

26. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med **1987**; 317:1098.

27. Vrouenraets SM, Fux CA, Wit FW, et al. A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. Clin Nephrol **2012**; 77:311-20.

28. Ryom L, Mocroft A, Kirk O, et al. Association Between Antiretroviral Exposure and Renal Impairment Among HIV-Positive Persons With Normal Baseline Renal Function: the D:A:D Study. JID **2013**; 207:1359-69.

29. Mocroft A, Lundgren JD, Ross M, 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 Med **2015**; 12:e1001809.

30. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation **2008**; 117:743-53.

31. Ryom L, Mocroft A, Kirk O, et al. Predictors of advanced chronic kidney disease and end-stage renal disease in HIV-positive persons. AIDS **2014**; 28:187-99.

32. Friis-Moller N, Ryom L, Smith C, et al. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. Eur J Prev Cardiol y **2015**.

33. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet **2010**; 375:2073-81.

34. Arbel Y, Halkin A, Finkelstein A, et al. Impact of estimated glomerular filtration rate on vascular disease extent and adverse cardiovascular events in patients without chronic kidney disease. Can J Cardiol **2013**; 29:1374-81.

35. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA **2010**; 303:423-9.

36. Lekawanvijit S, Krum H. Cardiorenal syndrome: acute kidney injury secondary to cardiovascular disease and role of protein-bound uraemic toxins. J Physiol **2014**; 592:3969-83.

502 **Table 1, Baseline Characteristics**

		All		Persons developing CVD	
		N	**%**	**N**	**%**
All		35,357	100	1,357	3.8
Gender	Male	26,124	73.9	1,181	87.3
Ethnicity	Caucasian	17,016	48.1	697	51.4
	Black	2,450	6.9	40	3.0
	Other	716	2.0	12	0.9
	Unknown	15,175	42.9	608	44.8
Mode of HIV acquisition	MSM	16,234	45.9	728	53.7
	IDU	4,529	12.8	154	11.4
	Heterosexual	12,436	35.2	386	28.4
	Other	2,158	6.1	89	6.6
HBV[1]	Positive	1,597	4.5	46	3.4
	Negative	31,169	88.2	1,213	89.4
	Unknown	2,591	7.3	98	7.2
HCV[2]	Positive	6,479	18.3	236	17.4
	Negative	25,535	72.2	973	71.7
	Unknown	3,343	9.5	148	10.9
cART	On	26,425	74.7	1,197	88.2
Prior AIDS event	Yes	8,768	24.8	462	34.1
VL<400 (copies/mL)	Yes	20,828	58.9	956	70.4
Smoking	Current	14,715	41.6	688	50.7

BMI (Kg/m^2)	>30	1,830	5.2	78	5.7
CVD Family History	Yes	2,712	7.7	179	13.2
Prior CVD[3]	Yes	240	0.7	72	5.3
Hypertension[4]	Yes	3,133	8.9	264	19.5
Diabetes[5]	Yes	1,425	4.0	163	12.0
eGFR (ml/min/1.73m^2)[6]	>90	24,937	70.5	656	48.3
	>60-<=90	9,378	26.5	559	41.2
	>30-<=60	999	2.8	13.5	10.0
	<=30	43	0.1	7	0.5
Fragminham risk score					
	Low (0-5%)	24,111	68.2	275	18.9
	Moderate (5-10%)	5,821	16.5	290	21.4
	High (>10%)	5,425	15.3	810	59.7
D:A:D CKD risk[7]	Risk score	-1	-3 to 4	4	-1 to 9
(median, IQR)					
Age (median, IQR)	Years	41	35-48	50	44-59
CD4 (median, IQR)	cells/mm^3	44	290-625	441	289-640

Baseline defined as 01/02/2004

1. HBV defined as positive: HBV surface antigen, HBV e antigen, or HBV DNA positive

2. HCV defined as anti-HCV positive and HCV-RNA positive/unknown

3. Prior CVD, as diagnosed on a D:A:D CVD event form

4. Hypertension defined as blood pressure >150/>100 or antihypertensive treatment

5. Diabetes as diagnosis on a D:A:D event form or by use of anti-diabetic treatment

6. eGFR calculated using Cockcroft-Gault

7. Score <0: low 5-year CKD risk (0.3%), Score 0-4: medium 5-year CKD risk (2.1%) and Score $\geq$5: high 5-year CKD risk (16.7%)

Figure 1, Confirmed Current eGFR Level Prior to CVD Event

Confirmed current eGFR level for those with a CVD event is the last measured median eGFR level prior the event. For those without a CVD event confirmed current eGFR level is the last measured median eGFR level during follow-up.

Figure 2, Kaplan-Meier Progression to CVD By Confirmed Baseline eGFR Level

Figure 3, CVD Incidence Rate Ratios by Confirmed Current eGFR Level

Multivariate analysis adjusted for age, gender, ethnicity, D:A:D enrolment cohort, nadir CD4 count, HIV mode of acquisition and family history of CVD at baseline. Time-updated variables include HBV/HCV co-infection, HIV-RNA, CD4 count, prior AIDS, hypertension, diabetes, confirmed eGFR strata, smoking status, dyslipidemia, prior CVD, exposure to antiretroviral drugs fitted as cumulative use (to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, tenofovir disoproxil fumerate, abacavir, efavirenz, nevirapine, indinavir, saquinavir, ritonavir, nelfinavir, (fos)ampreavir, atazanavir and darunavir) and current use (zidovudine, didanosine, zalcitabine, lamivudine, stavudine, emtricitabine, tenofovir disoproxil fumerate and abacavir).

Supplementary Document 1, Figure 1, Inclusion of Individuals in Analysis

Supplementary Document 2, Full cohort acknowledgements