

1 **Title page**

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

3 **Running title:** eGFR and Cardiovascular Disease in HIV

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

5 **Word count abstract:** 200 words

6 **Word count text:** 3456 words

7
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42 **Abstract** (200 words)

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

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

49 **Results** During 8.0 years median follow-up (Interquartile range 5.4-8.9) 1,357 of 35,357 developed CVD
50 (incidence 5.2/1000 person-years [95%confidence interval, CI [5.0-5.5]). Confirmed baseline eGFR and CVD
51 were closely related with 1.8% [95%CI 1.6-2.0%] estimated to develop CVD at five years at eGFR>90
52 ml/min/1.73m², increasing to 21.1% [95%CI 6.6-35.6%] at eGFR \leq 30 ml/min/1.73m². The strong univariate
53 relationship between low current eGFR and CVD was primarily explained by increasing age in adjusted
54 analyses, although all eGFRs \leq 80 ml/min/1.73m² remained associated with 30-40% increased CVD rates and
55 particular high rates at eGFR \leq 30 ml/min/1.73m² (3.08 [95%CI 2.04-4.65]).

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

60
61 **Keywords:** eGFR, renal impairment, kidney disease, cardiovascular disease, myocardial infarction, stroke,
62 invasive cardiovascular procedures, sudden cardiac death, HIV

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Text (3456 words)

65 **Introduction**

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

74 Renal impairment is projected to become more prevalent among HIV-positive individuals in future years
75 due to ageing and an accumulating burden of comorbidities and lifestyle related risk factors.

76 CVD is furthermore now one of the leading causes of non-AIDS death in HIV-positive individuals [14]. A
77 better understanding of the rates of CVD among HIV-positives individuals with renal impairment is
78 therefore warranted to assist identification of those at highest risk with a need for intensified monitoring
79 and initiation of preventive measures [15]

80 The relationship between renal impairment and CVD is complex and may be mediated through a variety of
81 different pathways [3, 6, 14]. These include accelerated coronary- and cerebrovascular atherosclerosis
82 which may be mediated in part by increased inflammation and oxidative stress, atrial fibrillation and
83 ventricular hypertrophy, which are common at severe levels of renal impairment and may, similar to
84 electrolyte abnormalities, promote dysrhythmias resulting in stroke or sudden cardiac death [3, 15-20].

85 Finally renal impairment and CVD are known to share a common underlying risk factor profile which include
86 hypertension, diabetes, dyslipidemia, smoking, injecting drug use, obesity, on-going inflammation and black
87 African origin [20, 21]. CVD, renal impairment, and many of the underlying shared individual risk factors,

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

93 **Methods**

94 *Study population*

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

103 *Endpoint definition*

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

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

115 *Statistical methods*

116 D:A:D Study participants with ≥ 2 eGFR measurements after 1/2/2004 (baseline for initiation of systematic
117 creatinine collection) were included and followed until the earliest of first CVD event, death, six months
118 after last visit or 1/2/2015. Persons with less than three months follow-up from the first to last eGFR were
119 excluded. The Cockcroft-Gault equation [25], standardized for body surface area [26], was used to estimate
120 creatinine clearance, a surrogate for eGFR in this analysis [27, 28]. As several cohorts participating in D:A:D
121 are prohibited from collecting ethnicity information, the Cockcroft-Gault equation was used rather than an
122 equation including ethnicity. Where eGFR measurements were carried out more frequently than every 28
123 days, the median value was used and assigned to the median date. Confirmed baseline and time-updated
124 (current) eGFR levels were defined using two consecutive eGFR measurements, regardless of time between
125 measurements (per definition minimum 28 days). The confirmed baseline and current eGFR values were
126 subsequently allocated to the following eGFR strata: >90 , $>60\text{-}\leq 90$, $>30\text{-}\leq 60$ and ≤ 30 ml/min/1.73m². Where
127 two consecutive eGFR values ($<15\%$ of all values) did not fall within the same eGFR strata, the mean of two
128 eGFR values carried forward was used to assign an eGFR category.

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

132 Incidence rates were calculated per 1000 person years of follow-up (PYFU). Kaplan-Meier estimation was
133 used to investigate time to CVD, stratified according to confirmed baseline eGFR levels (eGFR >90 , $\leq 90\text{-}>60$,
134 $\leq 60\text{-}>30$, ≤ 30 ml/min/1.73m²).

135 Poisson regression models stratified according to the confirmed current eGFR level were used to model the
136 CVD incidence rate ratios, overall and stratified by individual CVD events. Potential confounders included in
137 multivariate models were age (per 10 years older), gender, ethnicity, D:A:D enrolment cohort, nadir CD4
138 count, mode of HIV acquisition and family history of CVD. All remaining variables were adjusted for as
139 time-updated, including HBV/HCV co-infection, HIV-RNA (per \log_{10}), CD4 count, prior AIDS, hypertension
140 ($>150/>100$ or receipt of antihypertensive treatment), diabetes (confirmed diagnosis of DM or receipt of
141 anti-diabetic treatment), confirmed eGFR strata, smoking status (current, previous, never), dyslipidemia
142 (total cholesterol >6.2 mmol/l, high-density lipoprotein cholesterol <0.9 mmol/l, triglyceride >2.3 mmol/l,
143 or receipt of lipid-lowering treatment) and prior CVD (confirmed diagnosis). Antiretroviral drug use was
144 fitted as time-updated cumulative use (per five years; zidovudine, didanosine, zalcitabine, stavudine,
145 lamivudine, emtricitabine, tenofovir disoproxil fumerate, abacavir, efavirenz, nevirapine, indinavir,
146 saquinavir, ritonavir, nelfinavir, (fos)ampreavir, atazanavir and darunavir) and current use (currently on and
147 use with last six months; zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine,
148 tenofovir disoproxil fumerate and abacavir).

149 A number of sensitivity analyses were performed to test the robustness of the results. One analysis
150 investigated death as a potential competing risk of CVD. Another analysis excluded all those with a prior
151 CVD event. Other analyses adjusted for the D:A:D CKD risk-score [29] and the predicted CVD risk based on
152 the Framingham CVD prediction model [30] to estimate how much of the CVD risk is explained through
153 common renal and CVD risk factors. The D:A:D CKD risk score is a nine-variable prediction score estimating
154 the five year risk of developing CKD in HIV-positive individuals. Individuals in the low CKD risk group (score
155 <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%)
156 high risk group (score ≥ 5) [29]. A final analysis investigated the association between current nadir eGFR
157 and the percentage of follow-up time spent with $eGFR \leq 60$ ml/min/1.73m² and CVD respectively.

158

159 **Results**

160 *Study population*

161 35,357 persons with follow-up after 2004 and at least two eGFR measurement were included in analysis,
162 Supplementary Figure 1. Included individuals were predominantly Caucasian (48.1%) males (73.9%) with a
163 median age of 41 (interquartile range, IQR, 35-48) years, Table 1. While 41.6% were smokers, 4.0% had
164 diabetes, 8.9% had hypertension and 0.7% had experienced a prior CVD event. At baseline the median
165 estimated five year risk of CKD was low overall (-1 (IQR -3 to4) corresponding to 0.3%) and medium (4 (IQR -
166 1to 9) corresponding to 2.1%) in those developing a CVD event, Table 1. 558 persons were excluded from
167 analysis due to missing CD4 counts or viral load at baseline, or because of insufficient follow-up. Excluded
168 persons were more likely to be young, of Caucasian origin, cART-naïve, HCV-positive, have no family history
169 of CVD and have experienced a prior AIDS event.

170 *Age and eGFR level*

171 Among individuals younger than 40 years 87.0% (n=13,660) had a normal (confirmed eGFR>90
172 ml/min/1.73m²) baseline eGFR, and only 0.04% (n=7) had advanced renal impairment (confirmed baseline
173 eGFR≤30 ml/min/1.73m²). In contrast, among individuals older than 60 years, only 15.8% (n=321) had
174 confirmed baseline eGFR>90ml/min/1.73m² and 0.8% (n=17) confirmed baseline eGFR≤30 ml/min/1.73m².

175 *CVD events*

176 Over a median follow-up time of 8.0 years (IQR, 5.4-8.9, total PYFU 258,480) 1,357 persons developed
177 1,646 CVD events (incidence rate 5.2 per 1000 PYFU [95% confidence interval, CI, 5.0-5.5]). The CVD events
178 included 586 myocardial infarctions (11.1% fatal), 430 strokes (8.6% fatal), 510 coronary angioplasties (1.6%
179 fatal), 96 coronary bypasses (2.1% fatal), 19 carotid endarterectomies (0% fatal) and 5 sudden cardiac
180 deaths respectively. A total of 284 persons (21.0%) experienced more than one CVD event on the same
181 date, most commonly a myocardial infarction and coronary angioplasty (n=259).

182

183 *Median eGFR levels and incident CVD*

184 The median eGFR measured in individuals prior to their CVD event was significantly lower (85 (IQR 69-102)
185 ml/min/1.73m²) than the median eGFR measured during follow-up in individuals not experiencing a CVD
186 event (94 (IQR 79-110) ml/min/1.73m², p<0.0001). Likewise, a greater proportion of individuals
187 experiencing a CVD event had some level of confirmed reduced eGFR level, compared to individuals not
188 experiencing an event, Figure 1. When comparing the individual types of CVD events, those experiencing a
189 coronary bypass event had significantly lower confirmed eGFR levels compared to all other CVD event types
190 (p=0.018). When excluding the coronary bypass events there was no statistically significant differences in
191 confirmed eGFR levels prior to a CVD event (p=0.068). Likewise, when comparing those with an invasive
192 cardiovascular procedures (coronary angioplasty, carotid endarterectomy or coronary bypass) to those with
193 a myocardial infarction and/or stroke there was no statistical significant difference (p=0.55), Figure 1.

194 *Confirmed baseline eGFR levels and incident CVD*

195 We observed a clear inverse relationship between confirmed eGFR levels at baseline and incident CVD with
196 1.8% [95% CI 1.6-2.0%] estimated to have progressed to CVD at five years among those with confirmed
197 baseline eGFR>90 ml/min/1.73m², increasing to 4.1% (95% CI 3.5-4.6) for eGFR 60-90 ml/min/1.73m²,
198 10.8% (95% CI 8.7-12.9) for baseline eGFR 30-60 ml/min/1.73m² and 21.1% [95% CI 6.6-35.6%] among
199 those with confirmed baseline eGFR≤30 ml/min/1.73m², Figure 2.

200 Amongst individuals with moderately impaired baseline eGFR (confirmed eGFR≤60 ml/min/1.73m²) who
201 developed a CVD event, we did not observe a statistically significant differences (p=0.63) in time to
202 different CVD events with a median time to CVD event of 45 months (IQR 21-76).

203 *Confirmed current eGFR level and incident CKD*

204 There was a strong and inverse linear relationship between confirmed current eGFR and CVD in univariate
205 analysis; incidence rate ratios (IRRs) increasing from 1.00 at eGFR>90 ml/min/1.73m² to 14.09 [95%CI 9.58-
206 20.74] at eGFR≤30 ml/min/1.73m², Figure 3. Adjusting for increasing age explained most of the relationship

207 between eGFR and CVD at eGFR levels >30 ml/min/ 1.73m^2 , although all eGFRs below 80 ml/min/ 1.73m^2
208 were associated with an increased incidence of CVD of approximately 30-40%. At a confirmed current
209 eGFR ≤ 30 ml/min/ 1.73m^2 a significantly increased incidence of CVD remained independent of age (IRR 4.21
210 [95%CI 2.81-6.30]), Figure 3. Further adjustment for other potential confounders including individual
211 antiretroviral drugs had relatively limited impact on the overall association (IRR 3.08 [95%CI 2.04-4.65] at
212 confirmed eGFR ≤ 30 ml/min/ 1.73m^2 compared to confirmed eGFR ≥ 90 ml/min/ 1.73m^2 , Figure 3. The
213 exclusion of the 240 individuals with a CVD event prior to baseline led to entirely consistent results (data
214 not shown).

215 In a bivariate analysis, adjusting for the Framingham score (as a continuous variable) explained some of the
216 association between confirmed current eGFR and CVD, but not to the same extent as age alone (data not
217 shown). In another analysis adjusting for the estimated five-year D:A:D CKD risk score individuals with a
218 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
219 individuals with a high CKD risk (score ≥ 5) had almost a five-fold increased incidence of CVD (IRR 4.98 [95%
220 CI 4.37 – 5.68]) compared to persons with a low estimated CKD risk (score <0). After adjusting for other
221 potential confounders (as shown in Figure 4) not included in the D:A:D CKD risk score (with the exception of
222 age), those with a medium or high CKD risk score continued to have a significantly higher risk of CVD (IRR
223 1.29 [95%CI 1.10-1.50] and 1.43 [95%CI 1.19-1.71] respectively).

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

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

232 *Confirmed current eGFR levels and number of CVD events*

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

240 **Discussion**

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

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

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

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

265 In other studies of HIV-positive individuals, a smaller cross-sectional analysis in the FRAM study did not
266 confirm an association between carotid intima-medial thickness and eGFR after accounting for older age,
267 gender and ethnicity [13]. Likewise, a British study did not find an association between eGFR as a
268 continuous variable and coronary heart disease, although those with $\text{eGFR} < 75 \text{ mL/min}$ already had more
269 than a 4-fold increased incidence [9]. In a recent EuroSIDA study both the follow-up time with a low eGFR
270 and $\text{eGFR} \leq 30 \text{ ml/min/1.73m}^2$ were predictive of non-AIDS events including CVD, but power was limited
271 [12]. An older large cohort study among HIV-positive US veterans showed an almost 6-fold higher
272 association between $\text{eGFR} \leq 30 \text{ ml/min}$, albuminuria and CVD, although this study also included peripheral
273 artery disease and heart failure [10].

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

277 4, 33, 34]. There is, however, ongoing ambiguity, in the general population, regarding the strength of the
278 association between impaired renal function and CVD. Some studies report only on an association with
279 CVD at advanced levels of renal impairment (eGFR \leq 30 ml/min/1.73m²) while others report of associations
280 already at higher eGFR levels [1, 4, 5, 9, 10, 14, 33, 34]. However, the definitions of CVD differ considerably
281 in these studies ranging from subclinical imaging-verified diagnoses of atherosclerosis to various clinical
282 events ascertained with different levels of certainty. The differences in the incidence of common risk
283 factors and of CVD and renal impairment may also partly explain the conflicting results. Importantly, the
284 D:A:D study focuses on 'hard' clinical CVD events exclusively and information on non-fatal heart failure or
285 milder forms of ischemic CVD such as angina pectoris is not collected. This methodology may explain why
286 more severe levels of renal impairment are necessary to establish an association with CVD. Interestingly,
287 none of the widely accepted CVD risk prediction models currently include renal impairment in the
288 estimates [30, 32], but the proportion of individuals with advanced renal impairment may be too limited
289 to date.

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

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

311 **Conclusion**

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

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323 **Funding**

324 The D:A:D study was supported by the Highly Active Antiretroviral Therapy Oversight Committee (HAART-
325 OC), a collaborative committee with representation from academic institutions, the European Agency for
326 the Evaluation of Medicinal Products, the United States Food and Drug Administration, the patient
327 community, and pharmaceutical companies with licensed anti-HIV drugs in the European Union: AbbVie,
328 Bristol-Myers Squibb, Gilead Sciences Inc., ViiV Healthcare, Merck & Co Inc. and Janssen Pharmaceuticals.
329 Supported also by a grant [grant number DNRF126] from the Danish National Research Foundation (CHIP &
330 PERSIMUNE); by a grant from the Dutch Ministry of Health, Welfare and Sport through the Center for
331 Infectious Disease Control of the National Institute for Public Health and the Environment to Sticking HIV
332 Monitoring (ATHENA); by a grant from the Agence nationale de recherches sur le sida et les hépatites
333 virales [ANRS, Action Coordonnée no.7, Cohortes] to the Aquitaine Cohort; The Australian HIV
334 Observational Database (AHOD) is funded as part of the Asia Pacific HIV Observational Database, a program
335 of The Foundation for AIDS Research, amfAR, and is supported in part by a grant from the U.S. National
336 Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) [grant number U01-
337 AI069907] and by unconditional grants from Merck Sharp & Dohme; Gilead Sciences; Bristol-Myers Squibb;
338 Boehringer Ingelheim; Janssen-Cilag; ViiV Healthcare. The Kirby Institute is funded by The Australian
339 Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, The
340 University of New South Wales; by grants from the Fondo de Investigación Sanitaria [grant number FIS
341 99/0887] and Fundación para la Investigación y la Prevención del SIDA en Españã [grant number FIPSE
342 3171/00], to the Barcelona Antiretroviral Surveillance Study (BASS); by the National Institute of Allergy and
343 Infectious Diseases, National Institutes of Health [grants number 5U01AI042170-10 , 5U01AI046362-03], to
344 the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA); by primary funding provided
345 by the European Union's Seventh Framework Programme for research, technological development and
346 demonstration under EuroCoord grant agreement n° 260694 and unrestricted grants by Bristol-Myers
347 Squibb, Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC, (the participation of centres from

348 Switzerland is supported by The Swiss National Science Foundation (Grant 108787) to the EuroSIDA study;
349 by unrestricted educational grants of AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline,
350 Pfizer, Janssen Pharmaceuticals to the Italian Cohort Naive to Antiretrovirals (The ICONA Foundation); and
351 by a grant from the Swiss National Science Foundation (grant #148522) to the Swiss HIV Cohort Study
352 (SHCS). The content of this publication is solely the responsibility of the authors and does not necessarily
353 represent the official views of any of the institutions mentioned above.

354 **Conflicts of Interests**

355 L. Ryom, J.D. Lundgren, M. Ross, E. Fontas, C. Smit, C.I. Hatleberg, and S. De Wit have reported no conflicts
356 of interest. O. Kirk had prior/present board membership at ViiV Healthcare, Gilead Sciences and Merck,
357 received payment for lectures and/or for development of educational presentations from Abbott, Gilead
358 Sciences and Tibotec and had travel/accommodations/meeting expenses paid by Abbott, BMS, Gilead
359 Sciences, Merck and ViiV Healthcare. P. Morlat has received honoraria, speaker fees, travel support or
360 honoraria from AbbVie, Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck & Co Inc. and Janssen
361 Pharmaceuticals. C.A. Fux is an advisory board member for Gilead Sciences and MSD, has pending grants
362 from Gilead Sciences and Abbott and received payment for lectures by Gilead HIV and the body. M. Law has
363 received research grants from Boehringer Ingelheim, Bristol Myer Squibb, Gilead Sciences, GlaxoSmithKline,
364 Janssen Pharmaceuticals, Merck, Pfizer and Hoffman-LaRoche. C. Sabin received personal fees from Gilead
365 Sciences, Bristol-Myers Squibb, Janssen Pharmaceuticals, Abbott Pharmaceuticals, and ViiV Healthcare. A.
366 Mocroft has received consultancy fees/honoraria/speaker fees from Bristol-Myers Squibb, Pfizer, Merck,
367 Boehringer Ingelheim, and Gilead Sciences.

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369

370

371 **Acknowledgements**

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

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378 R. Weber* (SHCS), S. De Wit* (Brussels)

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385 Leleux (Aquitaine), E. Thulin, A. Sundström (HivBIVUS), G. Bartsch, G. Thompsen (CPCRA), M. Delforge
386 (Brussels), E. Fontas, C. Caissotti, K. Dollet (Nice), S. Mateu, F. Torres, (BASS), R. Pühr (AHOD), D. Kristensen
387 (EuroSIDA)

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390 Fux, P. Morlat, E. Fontas, D.A. Kamara, C.J. Smith, J.D. Lundgren#

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392 P. Reiss*, F.W.N.M. Wit, N. Friis-Møller, J. Kowalska, J.D. Lundgren#

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

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

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

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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
HBV¹	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
HCV²	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/m²)	>30	1,830	5.2	78	5.7
CVD Family History	Yes	2,712	7.7	179	13.2
Prior CVD³	Yes	240	0.7	72	5.3
Hypertension⁴	Yes	3,133	8.9	264	19.5
Diabetes⁵	Yes	1,425	4.0	163	12.0
eGFR (ml/min/1.73m²)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 risk⁷	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

503 Baseline defined as 01/02/2004

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

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

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

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

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

509 6. eGFR calculated using Cockcroft-Gault

510 7. Score <0: low 5-year CKD risk (0.3%), Score 0-4: medium 5-year CKD risk (2.1%) and Score ≥5: high 5-year CKD risk

511 (16.7%)

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Figure 1, Confirmed Current eGFR Level Prior to CVD Event

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Confirmed current eGFR level for those with a CVD event is the last measured median eGFR level prior the event. For

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those without a CVD event confirmed current eGFR level is the last measured median eGFR level during follow-up.

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

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

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Multivariate analysis adjusted for age, gender, ethnicity, D:A:D enrolment cohort, nadir CD4 count, HIV mode of

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acquisition and family history of CVD at baseline. Time-updated variables include HBV/HCV co-infection, HIV-RNA, CD4

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count, prior AIDS, hypertension, diabetes, confirmed eGFR strata, smoking status, dyslipidemia, prior CVD, exposure

522

to antiretroviral drugs fitted as cumulative use (to zidovudine, didanosine, zalcitabine, stavudine, lamivudine,

523

emtricitabine, tenofovir disoproxil fumerate, abacavir, efavirenz, nevirapine, indinavir, saquinavir, ritonavir, nelfinavir,

524

(fos)ampreavir, atazanavir and darunavir) and current use (zidovudine, didanosine, zalcitabine, lamivudine, stavudine,

525

emtricitabine, tenofovir disoproxil fumerate and abacavir).

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

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Supplementary Document 2, Full cohort acknowledgements

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