Deteriorating renal function and clinical outcomes in HIV-positive persons

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Objectives: To determine the relationship between measures of renal function [current estimated glomerular filtration rate (eGFR) and proportion of follow-up with a low eGFR (%FU ≤60 ml/min)] and fatal/ nonfatal AIDS, non-AIDS events and all-cause mortality.

Design: An observational, longitudinal cohort study of 12 155 persons from EuroSIDA.

Methods: Persons with at least one eGFR measurement after 1 January 2004, using the CKD-EPI formula, were included. Poisson regression analyses were used to determine whether current eGFR or %FU of 60 ml/min or less were independent prognostic markers for clinical events.

Results: During 61 425 person-years of follow-up (PYFU), the crude incidence of deaths was 11.1/1000 PYFU [95% confidence interval (CI) 10.0–12.1] at current eGFR more than 90 ml/min and 199.6 (95% CI 1144.3–254.3/1000 PYFU) when current eGFR was 30 ml/min or less. Corresponding figures for AIDS were 12.2 (11.1–13.3) and 63.9 (36.5–103.7) and for non-AIDS were 16.0 (14.8–17.3) and 203.6 (147.7–259.5). After adjustment, current eGFR of 30 ml/min or less was a strong predictor of death [adjusted incidence rate ratios (aIRR) 4.35; 95% CI 3.20–5.91] and non-AIDS events (3.63; 95% CI 2.57–5.13), although the relationship with AIDS was less strong (1.45; 95% CI 1.01–2.08). After adjustment, %FU of 60 ml/min or less was associated with a 22% increased incidence of death (aIRR 1.22 per 10% longer; 95% CI 1.18–1.27), a 13% increased incidence of non-AIDS events (95% CI 1.08–1.18) and a 15% increased incidence of AIDS events (95% CI 1.06–1.24).

Conclusion: Both current eGFR and %FU of 60 ml/min or less were associated with death and non-AIDS events in HIV-positive persons. Our findings highlight the association between underlying renal dysfunction and morbidity and mortality in HIV infection, although reverse causality cannot be excluded.

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Introduction

Much is known about the morbidity and mortality in HIV-positive persons, both overall and within current $CD4^+$ cell count or viral load strata. For example, for fatal and nonfatal non-AIDS events, there is an increasing incidence as $CD4^+$ cell count decreases [1–6], but less marked than seen for AIDS and a less strong relationship with viral load [4,6,7]. In the general population, it is known that persons with different levels of impaired renal function have an increased risk of not only end-stage renal disease (ESRD) and death [8,9] but also a wide range of other events related to impaired immune function including infectious complications [10]. Further, short-term positive or negative changes in renal function were associated with a higher rate of ESRD and mortality than those with a stable renal function [11,12]. Among HIV-positive persons associations between decreasing or low eGFR and cardiovascular disease, all-cause mortality and AIDS [13–19] has been described. However, the spectrum of clinical events seen across a wide range of renal function, as measured by current estimated glomerular filtration rate (eGFR) and other measures of renal function, has not been well described in HIV-positive persons. This information would be relevant for routine patient management and monitoring, and could additionally be used to refine risk-prognosis scores and models, such as those previously developed by EuroSIDA [20] or the more recently developed VACS index [21].

The aims of this analysis were therefore to describe the incidence of both fatal and nonfatal AIDS and non-AIDS events in a diverse and heterogeneous HIV-positive cohort according to current eGFR strata and whether current eGFR or other measures of renal insufficiency were independent predictors of these clinical events.

Method

Persons

The EuroSIDA study is a prospective, observational cohort of 18 295 HIV-positive persons in 108 centres across 33 European countries, including Israel and Argentina. The study has been described in detail previously [22]. In brief, persons were enrolled into nine cohorts from May 1994 onwards. Information is collected on a standardized data collection form every 6 months, including all $CD4^+$ cell counts and viral loads measured since the last follow-up and starting and stopping dates of all antiretrovirals. Dates of diagnosis of all clinical AIDS-defining illnesses are recorded using the 1993 clinical definition of AIDS from the Centers for Disease Control [23], as well as all deaths, with cause of death determined by the Coding Causes of Death in HIV (CoDe) protocol and by applying a standardized algorithm [24,25]. Cardiovascular disease, non-AIDS defining malignancies, end-stage hepatic encephalopathy, pancreatitis and ESRD were included as non-AIDS defining events, as previously described [7]. All serum creatinine measured during routine care have been collected since 1 January 2004.

To ensure correct person selection and to verify that accurate data are supplied, members of the coordinating office visit all centres to check the information provided against case-notes for all persons with clinical events and 10% randomly selected persons per year.

Statistical methods

Persons from EuroSIDA with at least one eGFR measurement after 1 January 2004 and with prospective follow-up were included. eGFRs were calculated using the CKD-EPI formula [26], shown in a previous EuroSIDA study to be similar to the Cockcroft–Gault equation in this population [27]. Baseline was defined as the first eGFR measured during prospective follow-up after 1 January 2004, and persons were followed to the latest of last clinic visit, last eGFR or death. All individual clinical events occurring in more than 75 persons were analysed separately. The threshold of 75 events was decided *a priori* to allow multivariate analysis with appropriate adjustment. AIDS events included oesophageal candidiasis, pulmonary and extrapulmonary tuberculosis and AIDS-defining malignancies. Non-AIDS events included ESRD, cardiovascular disease (myocardial infarction, stroke, invasive cardiovascular procedures), non-AIDS defining malignancies, stage III/IV hepatic encephalopathy or pancreatitis, as previously defined [7]. The proportion of follow-up and incidence of clinical events within current eGFR strata was determined, using commonly used eGFR limits of more than 90, 60–90, 30–60 and 30 ml/min or less [28]. More than one event per person was included in analyses, but recurrences of the same event were excluded and persons could contribute more than one event to each category. For example, a person diagnosed with a stroke followed by an invasive cardiovascular procedure would contribute two events to the non-AIDS events category or the analysis of cardiovascular events, but a person with a myocardial infarction followed by a second myocardial infarction would only contribute the first of these two events.

Poisson regression analyses, using generalized estimating equations and repeated measurements to ensure robust standard errors, were used to determine whether current eGFR was an independent prognostic marker for different clinical events, after adjustment for relevant confounding variables. Adjustments were made for HIV-related variables (such as HIV exposure group, hepatitis B and C status, prior AIDS event, use of antiretroviral treatment, $CD4^+$ cell nadir, current $CD4^+$ cell count and viral load) in addition to demographic variables (age, sex, region of origin) and variables that were likely associated with eGFR (prior non-AIDS diagnosis, diabetes, anaemia, hypertension and smoking status,

defined previously [7]). In addition to including current eGFR, models also investigated whether current nadir eGFR was an important predictor of clinical disease independently of current eGFR and whether proportion of follow-up time spent with renal impairment, defined as an eGFR of 60 ml/min or less (%FU $\leq$ 60 ml/min) and included as a time-updated variable, was also a significant and independent prognostic marker. Sensitivity analyses investigated the robustness of the results using Cockcroft–Gault to estimate eGFR rather than CKD-EPI, only including follow-up for a maximum of 6 months after the last eGFR measurement, time-lagging eGFR measurements by 6 or 12 months and allowing for competing risks. All analyses were performed in SAS (Statistical Analysis Software Version 9.3; Cary, North Carolina, USA).

Results

Of 18 722 persons enrolled in EuroSIDA, 12 155 were included in this analysis (64.9%); 4051 persons were excluded, as they had died or were lost to follow-up prior to 1 January 2004 and 885 because they had no eGFR measurement available. Three hundred and twenty-nine persons were excluded, as they had no prospective follow-up after baseline (first eGFR after 1 January 2004) and 1302 were excluded as they had no $CD4^+$ cell count or viral load measured in the 6 months prior to baseline. Excluded persons were more likely to be hepatitis B and C antibody positive, originate from Eastern or Central Europe compared with Southern Europe, to have lower $CD4^+$ cell counts, higher viral loads and to have been recruited to EuroSIDA later. The 12 155 persons contributed 161 145 eGFR measurements during a median follow-up 5.7 [interquartile range (IQR) 2.8–7.6] years and a median of 13 (IQR 5–19) eGFR measurements per person a median time of 3.7 (IQR 2.8–5.5) months apart. The median (IQR) number of eGFR measurements was 12 (6–18), 12 (6–18) and 13 (5–19) measured a median time (IQR) time apart of 3.7 (2.8–5.5), 3.7 (2.8–5.5) and 3.5 (2.6–5.3) months in those with baseline eGFRs at least 90, 60–90 and less than 60 ml/min, respectively. Characteristics of the 12 155 included persons are summarized in Table 1; of 387 persons with an eGFR of less than 60 ml/min at baseline, only 35 (9.0%) were 30 ml/min or less. The median eGFR at baseline was 100 (IQR 85–111 ml/min). As expected, a higher proportion of persons with lower eGFR at baseline (<60 ml/min) had diabetes, hypertension and were significantly older.

At baseline, the proportions of persons exposed to tenofovir (3302, 27.2%), atazanavir (1131, 9.3%), lopinavir (3217, 26.5%) and indinavir (4284, 35.2%) were all significantly higher in those with low than in those with high baseline eGFRs ($P < 0.05$). For example, 25.3% of those with a baseline eGFR at least 90 mL/min had been exposed to tenofovir, increasing to 34.9% of those with a baseline eGFR less than 60 ml/min. In addition, among those who started the antiretroviral by baseline, cumulative exposure to both tenofovir and indinavir was significantly higher in those with eGFR less than 60 ml/min ($P < 0.0001$), but not for lopinavir and atazanavir ($P > 0.15$). For example, among persons started tenofovir at baseline, median exposure was 13 months (IQR 6–24 months) in those with baseline eGFR at least 90 ml/min and 20 months (IQR 10–31 months) in those with baseline eGFR less than 60 ml/min.

Incidence of clinical events and renal function

There was a wide range of clinical events observed during 61 425 person-years of follow-up (PYFU), the most common being non-AIDS defining events. There was a steady increase in the incidence of clinical events as current eGFR declined (Table 2), which was particularly striking for deaths and non-AIDS events. The crude incidence of deaths was 11.1/1000 PYFU [95% confidence interval (CI) 10.0–12.1] at current eGFR more than 90 ml/min and 199.6 (95% CI 144.3–254.9/1000 PYFU) when current eGFR was 30 ml/min or less. Corresponding figures for AIDS were 12.2 (95% CI 11.1–13.3) and 63.9 (95% CI 36.5–103.7) and for non-AIDS events were 16.0 (95% CI 14.8–17.3) and 203.6 (95% CI 147.7–259.5). The incidence of deaths and a new AIDS-defining event was similar in those with current eGFR more than 90 and 60–90 ml/min.

A similar pattern was seen for the crude incidence rates stratified by the %FU of 60 ml/min or less (Table 2). The crude incidence of death was 0.7/1000 PYFU (95% CI 9.8–11.6) in those with zero %FU of 60 ml/min or less, and 126.5/1000 PYFU (95% CI 99.3–153.7) in those in whom %FU of 60 ml/min or less was at least 50%. Rates were similar for non-AIDS events, but were less variable for AIDS events, increasing from 12.3/1000 PYFU (95% CI 11.4–13.2) to 36.6/1000 PYFU (95% CI 22.0–51.2), respectively. Despite these striking differences in event rates, the median eGFR immediately before a clinical event was, on average, high, and the median %FU of 60 ml/min or less was low. The median eGFR prior to death was 95 ml/min (IQR 69–110), measured a median time of 2.3 months prior to the event (IQR 0.6–5.8 months). The corresponding figures for AIDS and non-AIDS events were 101 (83–112) and 93 (73–105), respectively, measured a median time of 1.8 (0.5–4.8) and 2.2 (0.8–4.8) months prior to the events. For all events, the median and IQR of %FU of 60 ml/min or less was zero.

Renal function as a predictor of clinical events

After adjustment, a low current eGFR ($\leq$30 ml/min) was a strong predictor of death, a new AIDS or non-AIDS event, as shown in Fig. 1a. The eGFR categories 60–90 and more than 90 ml/min were combined, as the adjusted incidence rate ratios (aIRRs) were very similar for any

Table 1. Baseline characteristics of included persons.

		All		eGFR ≥90 ml/min		eGFR 60–90 ml/min		eGFR <60 ml/min		
		N	%	*N*	%	*N*	%	*N*	%	*P*
All		12 155	100	8226	67.7	3542	29.1	387	3.2	
Sex	Male	9027	74.3	6198	73.3	2251	72.0	278	71.8	0.0004
	Female	3128	25.7	2028	24.7	991	28.0	109	28.2	
HIV exposure group	MSM	5113	42.1	3993	41.3	1565	44.2	155	40.1	<0.0001
	IDU	2331	19.2	1672	20.3	603	17.0	56	14.5	
	Het	3797	31.2	2554	31.1	1112	31.4	131	33.9	
	Other	914	7.5	607	7.4	262	7.4	45	11.6	
Race	White	10 591	87.1	7089	86.2	3171	89.5	331	85.5	<0.0001
	Other	1564	12.9	1137	13.8	371	10.5	56	14.5	
Region	South	3171	26.1	1965	23.9	1082	30.6	124	32.0	<0.0001
	Central	2880	23.7	1965	23.9	808	22.8	107	27.7	
	North	2828	23.3	1948	23.7	785	22.2	95	24.6	
	East	2820	23.2	2002	24.3	767	21.7	51	13.2	
	Argentina	456	3.7	346	4.2	100	2.8	10	2.6	
Hepatitis B	Negative	9444	77.7	6442	78.3	2703	76.3	299	77.3	0.0073
	Positive	722	5.9	506	6.2	195	5.5	21	5.4	
	Unknown	1989	16.4	1278	15.5	644	18.2	67	17.3	
Hepatitis C	Negative	7501	61.7	4979	60.5	2282	64.4	240	62.0	<0.0001
	Positive	2511	20.7	1818	22.1	617	17.4	76	19.6	
	Unknown	2143	17.6	1429	17.4	643	18.2	71	18.4	
Smoking status	Never	3315	27.3	2012	24.5	1153	32.6	150	38.8	<0.0001
	Current	3707	30.5	2561	31.1	1045	29.5	101	26.1	
	Past	435	3.6	276	3.4	133	3.8	26	6.7	
	Unknown	4698	38.7	3377	41.1	1211	34.2	110	28.4	
									3.2	
Diabetes[a]	No	10 434	85.8	7196	87.5	2954	83.4	284	73.4	<0.0001
	Yes	581	4.8	297	3.6	217	6.1	67	17.3	
	Unknown	1140	9.4	733	8.9	371	10.5	36	9.3	
Hypertension[a]	No	6940	57.1	4919	59.8	1883	53.2	138	35.7	<0.0001
	Yes	3373	28.8	2048	24.9	1127	31.8	198	51.2	
	Unknown	1842	15.1	1259	15.3	532	15.0	51	13.2	
Anaemia[a]	No	6402	53.2	4318	52.5	1976	55.8	168	43.4	<0.0001
	Yes	2710	22.3	1731	21.0	830	23.4	149	38.5	
	Unknown	2983	24.5	2177	26.5	736	20.8	70	18.1	
AIDS	Yes	3459	28.5	2119	25.8	1164	32.9	176	45.5	<0.0001
Non-AIDS[a]	Yes	771	6.3	412	5.0	264	7.5	95	24.6	<0.0001
ARV-naive	Yes	1619	13.3	1269	15.4	393	9.4	17	4.4	<0.0001
Treatment	cART	9996	82.2	6606	80.3	3039	85.8	351	90.7	<0.0001
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	*P*
Age	Years	42	36–49	40	34–46	46	39–54	55	45–64	<0.0001
Baseline	mm/yy	April 2005	June 2004–October 2007	June 2005	June 2004–January 2008	February 2005	June 2004–December 2006	November 2004	June 2004–January 2006	<0.0001
$CD4^+$ cell count	/μl	432	289–619	430	287–615	441	298–631	417	250–595	0.011
Nadir $CD4^+$ cell count	/μl	164	62–278	121	66–284	155	59–266	109	30–195	<0.0001
VL	Log_{10} cp/ml	1.7	1.7–3.5	1.7	1.7–3.7	1.7	1.7–2.9	1.7	1.6–2.6	<0.0001
SCr	mg/dl	0.9	0.8–1.0	0.8	0.7–0.9	1.1	1.0–1.1	1.4	1.3–1.7	<0.0001

IQR, interquartile range; SCr, serum creatinine; VL, HIV RNA viral load.
[a]Defined previously [7].

Table 2. Crude incidence rates (per 1000 PYFU) of deaths, AIDS and non-AIDS: relationship with current eGFR and %FU of 60 ml/min or less.

		Deaths			AIDS			Non-AIDS		
	PYFU	Events	Rate	95% CI	Events	Rate	95% CI	Events	Rate	95% CI
Current eGFR (ml/min)										
>90	39955	442	11.1	10.0–12.1	488	12.2	11.1–13.3	640	16.0	14.8–17.3
60–90	18839	213	11.3	9.8–12.8	228	12.1	10.5–13.7	396	21.0	19.0–23.1
30–60	2381	92	38.6	30.7–46.5	45	18.9	13.4–24.4	120	50.4	41.4–59.4
≤30	251	50	199.6	144.3–254.9	16	63.9	36.5–103.7	51	203.6	147.7–259.5
%FU ≤ 60 ml/min										
0	55491	593	10.7	9.8–11.6	683	12.3	11.4–13.2	955	17.2	16.1–18.3
0–10	2721	54	19.8	14.6–25.1	38	14.0	9.5–18.4	77	28.3	22.0–34.6
10–50	2557	67	26.2	19.9–32.5	32	12.5	8.2–16.9	96	37.5	30.0–45.1
≥50	656	83	126.5	99.3–153.7	24	36.6	22.0–51.2	79	120.4	93.9–147.0

CI, confidence interval; PYFU, person-years of follow up.

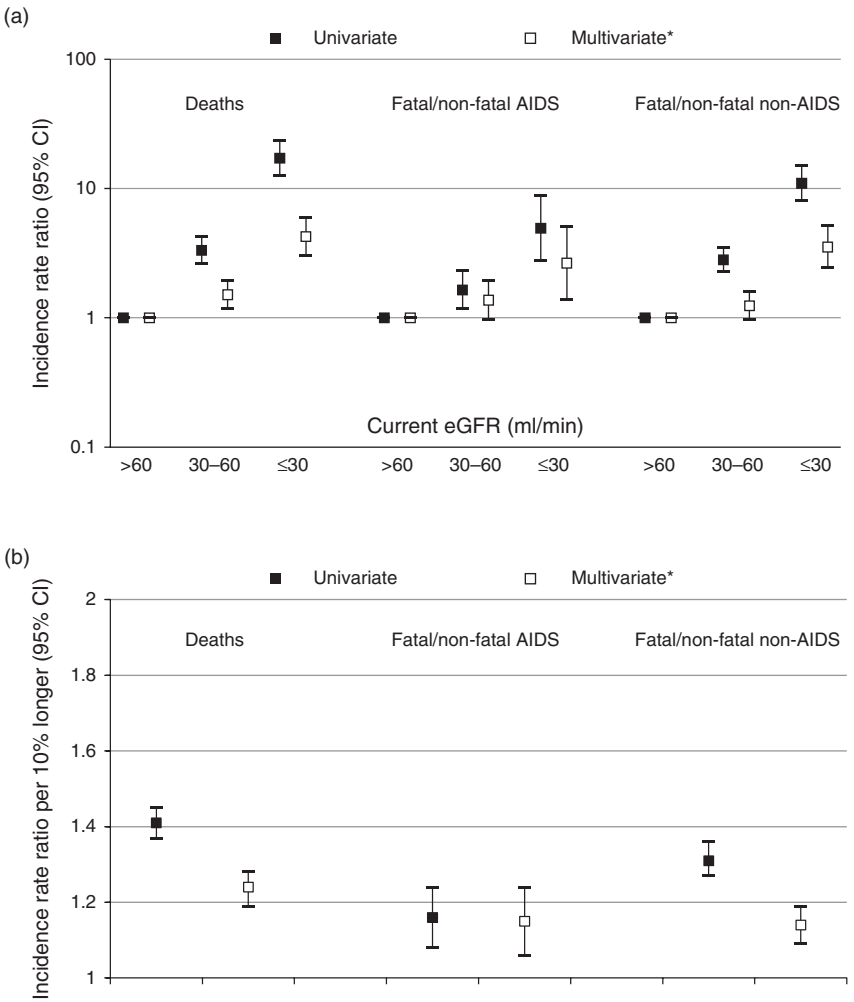

Fig. 1. Incidence rate ratios of clinical events. (a) Current eGFR. [a]Adjusted for sex, race, region of Europe, age, $CD4^+$ cell count nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, $CD4^+$ cell count, viral load and development of a non-AIDS event as time-updated variables (AIDS events) or AIDS (non-AIDS events). (b) %FUeGFR ≤ 60 ml/min. [b]Adjusted for sex, race, region of Europe, age, $CD4^+$ cell count nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, $CD4^+$ cell count, viral load and development of a non-AIDS event as time-updated variables (AIDS events) or AIDS (non-AIDS events).

clinical event. The relationship was strongest for death, wherein there was over a four-fold increased incidence of death in those with a current eGFR of 30 ml/min or less (aIRR 4.35; 95% CI 3.20–5.91). The %FU of 60 ml/min or less, included as a continuous variable, was also a good predictor of the clinical event with the strongest relationship seen for deaths. %FU of 60 ml/min or less was associated with a 24% increased incidence of death per 10% longer (aIRR 1.22; 95% CI 1.18–1.27).

Nadir eGFR was not a strong predictor of any of the clinical events after adjustment and so was not included in further analyses. The strongest relationship was seen for deaths. For example, a 10 ml/min lower nadir eGFR was associated with a 22% increased incidence of death in univariate analyses (aIRR 1.22; 95% CI 1.18–1.26), but this reduced to an 8% increased incidence after adjustment for current eGFR and other factors (aIRR 1.08; 95% CI 1.02–1.36). It was not possible to adjust for both current eGFR and %FU of 60 ml/min or less owing to the strong correlation between these two variables (correlation coefficient −0.45, $P < 0.0001$).

Individual events occurring in more than 75 persons were also considered (Fig. 2), comparing current eGFR categories. For fatal and nonfatal AIDS events [oesophageal candidiasis ($N = 114$), pulmonary and extrapulmonary tuberculosis ($N = 166$) and malignancies ($N = 131$)], the aIRRs were all close to 1, although the 95% CIs were quite wide. In contrast, those with a current eGFR of 30 ml/min or less had a raised incidence of the different types of fatal and nonfatal non-AIDS events, including malignancies, cardiovascular disease and end-stage hepatic encephalopathy. Similar results were seen for %FU of 60 ml/min or less. After adjustment, %FU of 60 ml/min or less was associated with a significantly increased incidence of cardiovascular disease ($N = 406$ events, aIRR 1.17 per 10% longer; 95% CI 1.09–1.25), end-stage hepatic encephalopathy ($N = 165$ events, aIRR 1.17 per 10% longer; 95% CI 1.03–1.33), but not malignancies ($N = 538$ events, aIRR 1.03 per 10% longer; 95% CI 0.95–1.12).

Fatal versus nonfatal events

The relationship between the two measures of renal function and both AIDS and non-AIDS events was considerably stronger in fatal events than in nonfatal events, summarized in Table 3. After adjustment, a current eGFR of 30 ml/min or less was associated with over a four-fold increased incidence of fatal AIDS events (aIRR 4.38; 95% CI 1.56–12.34), but only a small, nonsignificant increased incidence of nonfatal AIDS events (aIRR 1.14; 95% CI 0.77–1.68). In contrast, after adjustment, a current eGFR of 30 ml/min or less was associated with over a five-fold increased incidence of fatal non-AIDS events (aIRR 5.23; 95% CI 2.92–9.34), and over a three-fold increased incidence of nonfatal non-AIDS events (aIRR 3.26; 95% CI 2.20–4.83). The %FU of 60 ml/min or less was not significantly associated with either nonfatal non-AIDS or nonfatal non-AIDS events.

Discussion

This large study of over 11 000 HIV-positive persons found that the incidence of a wide range of clinical events increased as current eGFR decreased, and also that after adjustment for other potential confounders, a low current eGFR of 30 ml/min or less was a strong predictor of mortality and fatal and nonfatal non-AIDS defining events and a weaker predictor of fatal and nonfatal AIDS

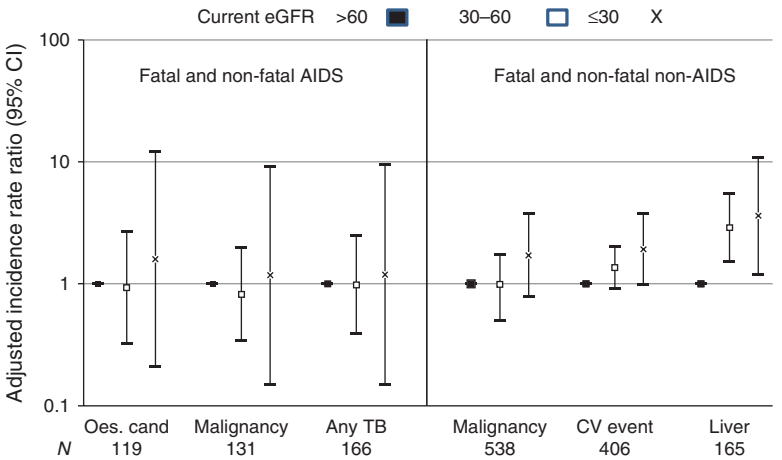

Fig. 2. Adjusted incidence rate ratios of individual ($n > 75$) events and current estimated glomerular filtration rate. [a]Adjusted for sex, race, region of Europe, age, $CD4^+$ cell count nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, $CD4^+$ cell count, viral load and development of a non-AIDS event as time-updated variables (AIDS events) or AIDS (non-AIDS events).

Table 3. Relationship between markers of renal function and fatal or nonfatal events: Current eGFR and %FU of 60 ml/min or less.

	Fatal events	Nonfatal events
AIDS		
Current eGFR[a]		
>60	1.00	1.00
30–60	2.35 (1.27–4.38); 0.0068	0.85 (0.38–1.91); 0.52
≤30	4.38 (1.56–12.34); 0.0051	1.14 (0.77–1.68); 0.52
%FU ≤ 60 ml/min (per 10% longer)		
Multivariate[a]	1.39 (1.26–1.53); <0.0001	0.98 (0.88–1.08); 0.66
Non-AIDS		
Current eGFR[a]		
>60	1.00	1.00
30–60	1.50 (0.98–2.31); 0.064	1.21 (0.95–1.55); 0.13
≤30	5.23 (2.92–9.34); <0.0001	3.26 (2.20–4.83); <0.0001
%FU ≤ 60 ml/min (per 10% longer)		
Multivariate[a]	1.17 (1.09–1.26); <0.0001	1.03 (0.99–1.07); 0.17

[a]Figures presented are adjusted incidence rate ratios (95% confidence intervals); *P* value. eGFR, estimated glomerular filtration rate. Adjusted for sex, race, region of Europe, age, $CD4^+$ cell count nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, $CD4^+$ cell count and viral load as time-updated variables [7]. AIDS was adjusted for the development of non-AIDS as a time-updated covariate, and non-AIDS was adjusted for the development of AIDS as a time-updated variable.

events. Another measure of renal function, %FU of 60 ml/min or less, was also a strong predictor of clinical events, particularly death and non-AIDS events.

These two measures of renal function were strongly associated with mortality, while nadir eGFR was not a strong predictor after adjustment. Nadir eGFR was strongly correlated with current eGFR, which may explain its lack of significance. Results from the HIV-negative population show the latest eGFR to be a strong marker for ESRD rather than nadir eGFR [29], while Turin *et al.* [11] showed that the change in the year prior to death was an important predictor in HIV-negative persons. Chronic kidney disease (CKD) is a known risk factor for CVD in both HIV-negative and positive individuals [14,30,31] and may suggest that a low eGFR increases cardiovascular risk factors [32]. In addition, HIV-positive persons with a low eGFR may have ongoing chronic illnesses, as seen in both HIV-negative and positive populations, which in turn contributes to increased mortality [33,34]. Deteriorating renal function, measured as lower eGFR, presence of proteinuria/albuminuria, elevated serum creatinine, albumin:creatinine ratio or cystatin C has previously been shown to be associated with mortality in HIV-positive [13,16,17,19, 34,35] and HIV-negative persons [9,36–38]. Reduced renal function in HIV-negative persons can be associated with a number of factors including increased inflammation and immune activation [36,39], although HIV infection in itself has also been shown to affect the same pathways [40,41].

Our two measures of impaired renal function were also strong markers for non-AIDS events. We had sufficient numbers to investigate cardiovascular disease, malignancies and end-stage hepatic encephalopathy individually, and impaired renal function was associated with cardiovascular disease and end-stage hepatic encephalopathy, and to a lesser extent malignancies. The relationship was stronger for fatal than for nonfatal events. Previous studies [9,14,36,42] have shown renal function to be associated with cardiovascular disease in both HIV-positive and negative persons. Cardiovascular and renal disease share is known to share number of risk factors, but Jotwani *et al.* [43] found no association between subclinical atherosclerosis and renal function, suggesting this may not be a major pathway linking renal disease and cardiovascular risk in HIV infection. Low current eGFR was independently associated with end-stage liver disease. Previous research from the INSIGHT study group showed that hepatitis B and C coinfection were both associated with CKD [44], and in EuroSIDA, chronic hepatitis C coinfection was associated with a two-fold risk of CKD [45], although liver-related deaths have been shown to be higher in those with hepatitis coinfection [46]. There are many hepatitis-related nephropathies, most commonly membranoproliferative glomerulonephritis [47,48], which may contribute to the pathogenesis of renal disease. Alternatively, liver impairment may contribute to the low eGFR by inducing hepatorenal syndrome [49].

The weakest relationship between measures of renal function and clinical disease was seen for AIDS, and this was highly consistent for the three most commonly occurring AIDS events. The relationship was largely driven by the fatal AIDS events, and there was little evidence for a relationship between either of the measures of renal function and AIDS once the fatal events were removed. Evidence from other studies is contradictory [17,18,50]; differences in the study populations, ability to adjust for confounding variables and the ratio of fatal and nonfatal AIDS events likely explain the differences. Our findings are based on observational data, and we cannot rule out reverse causality, wherein the low eGFR is a consequence of illness rather than a cause. The relationships between the measures of renal function

and clinical events were considerably weaker when fatal events were excluded, particularly for AIDS events, suggesting that this is at least partly the explanation for our findings. However, even after time-lagging the eGFR measurements by 6 or 12 months, there was still an association between nonfatal events, especially non-AIDS events, and our measures of renal function (data not shown). In addition, depite the strong relationship between our renal markers and clinical events, the median eGFR immediately before a clinical event was above 90 ml/min and the median %FU of 60 ml/min or less was zero, suggesting that although markers of renal function are an independent prognostic marker for these clinical events, the majority of persons develop clinical events without significant changes in these renal measures. It is possible that individuals with impaired renal function are less healthy overall, and hence, at more risk of events such as AIDS or non-AIDS events, which in turn are related to other measures of health, such as $CD4^+$ cell count, hypertension or hepatitis coinfection.

The use of tenofovir and indinavir, and to a lesser extent atazanavir and lopinavir, has been shown to be associated with changes in eGFRs that may or may not be clinically significant in the long term [51,52]. This study was not adequately powered to consider clinical events separately in those exposed or unexposed to potentially nephrotoxic antiretrovirals. Sensitivity analyses right censoring at the date of starting these antiretrovirals showed similar findings, and there were no significant interactions between measures of renal function and use of antiretrovirals overall, or specific drugs (data not shown). Taken together, these findings suggest that the relationship between renal function and clinical outcomes is similar in those on or off these antiretrovirals.

There are some limitations of this study that should be noted. We used the CKD-EPI formula for estimating eGFR [26], as the CKD-EPI formulae has largely replaced the MDRD formulae and previous analyses from our group demonstrated that both CG and CKD-EPI were similar in terms of predicting mortality and ESRD [27]. The CKD-EPI formula has been shown to be improved by the addition of Cystatin C [53], which is not available in EuroSIDA. In addition, EuroSIDA only recently began collecting information on proteinuria, shown in HIV-negative persons to improve prediction of mortality, myocardial infarction and renal failure [9], and so cannot incorporate these data into these present analyses. We repeated our analyses using Cockcroft–Gault [54], which reduced the number of persons included due to the requirement for weight to be measured, but our results were highly consistent (data not shown). eGFRs are measured in EuroSIDA on average every 4 months, and the analyses presented carry the last observation forward until another becomes available. This could mean that the current eGFR was measured some time ago in an individual in whom measurements were less common. A sensitivity analysis in which the current eGFR was only included if it was measured within the previous 6 months showed similar results (data not shown). Analyses allowing for competing risks also showed consistent results. We included more than one event per person to increase our power, but it is possible that persons with repeated events, particularly malignancies, have a low eGFR as a consequence of treatment of a previous event. Analyses limited to the first event showed similar results (data not shown), but with considerably reduced power and wider CIs for the findings. We included composite endpoints, such as AIDS and non-AIDS events, which may hide the fact that our measures of renal function were associated with some outcomes but not others, although we were also able to perform analyses considering individual events in which we had sufficient power.

To conclude, both current eGFR and %FU of 60 ml/min or less were associated with death and non-AIDS events in HIV-positive persons. The relationship with AIDS was less strong and was mainly explained by fatal AIDS events. Further research to determine whether persons with low eGFR have different underlying diseases is required. Regular monitoring of renal function remains crucial and allows identification of persons at greatest risk of a wide spectrum of clinical disease and aids targeting of additional resources such as management of blood pressure, diabetes, dyslipidaemia and avoidance of potentially nephrotoxic drugs. Our findings highlight the association between underlying renal dysfunction and morbidity and mortality in HIV infection, and that monitoring of renal function should not be overlooked when treating HIV-positive persons for nonrenal morbidities.

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Conflicts of interest

No author has any conflicts of interest.

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