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ORIGINAL RESEARCH

End-stage renal disease and dialysis in HIV-positive patients: observations from a long-term cohort study with a follow-up of 22 years

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Objectives

Renal disease is a common and serious complication in HIV-infected patients.

Methods

A retrospective cohort analysis for the period 1989–2010 was carried out to determine the prevalence, incidence and risk factors for end-stage renal disease (ESRD). ESRD was defined as initiation of renal replacement therapy. Three time periods were defined: 1989–1996 [pre-highly active antiretroviral therapy (HAART)], 1997–2003 (early HAART) and 2004–2010 (late HAART).

Results

Data for 9198 patients [78.2% male; 88.9% Caucasian; cumulative observation time 68 084 patient-years (PY)] were analysed. ESRD was newly diagnosed in 35 patients (0.38%). Risk factors for ESRD were Black ethnicity [relative risk (RR) 5.1; 95% confidence interval (CI) 2.3–10.3; $P < 0.0001$], injecting drug use (IDU) (RR 2.3; 95% CI 1.1–4.6; $P = 0.02$) and hepatitis C virus (HCV) coinfection (RR 2.2; 95% CI 1.1–4.2; $P = 0.03$). The incidence of ESRD decreased in Black patients over the three time periods [from 788.8 to 130.5 and 164.1 per 100 000 PY of follow-up (PYFU), respectively], but increased in Caucasian patients (from 29.9 to 41.0 and 43.4 per 100 000 PYFU, respectively). The prevalence of ESRD increased over time and reached 1.9 per 1000 patients in 2010. Mortality for patients with ESRD decreased nonsignificantly from period 1 to 2 (RR 0.72; $P = 0.52$), but significantly from period 1 to 3 (RR 0.24; $P = 0.006$), whereas for patients without ESRD mortality decreased significantly for all comparisons. ESRD was associated with a high overall mortality (RR 9.9; 95% CI 6.3–14.5; $P < 0.0001$).

Conclusion

As a result of longer survival, the prevalence of ESRD is increasing but remains associated with a high mortality. The incidence of ESRD declined in Black but not in Caucasian patients. IDU and HCV were identified as additional risk factors for the development of ESRD.

Keywords: chronic kidney disease, haemodialysis, HIV-associated nephropathy, renal failure, renal replacement therapy

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Introduction

The prevention and treatment of cardiovascular, liver and kidney diseases have increasingly been the focus of attention in attempts to reduce the morbidity and mortality of HIV-infected individuals [1]. Renal disease of any stage is

a common complication in HIV-infected patients, affecting up to 30% of patients, and is associated with increased morbidity and mortality [2–4]. Once established, end-stage renal disease (ESRD) and chronic renal replacement therapy (RRT) substantially increase the risk of death and cardiovascular events in the general and HIV-infected populations [5–7]. The causes of kidney disease in HIV-infected patients are heterogeneous and include diseases related to HIV [HIV-associated nephropathy (HIVAN), immune complex glomerulonephritis and thrombotic microangiopathy], chronic hepatitis virus coinfection and factors not directly related to HIV (drug toxicity, age, diabetes mellitus and hypertension). Traditional risk factors for ESRD are likely to increase over time with aging of the HIV-infected population [8–10].

In the USA, HIV-associated ESRD has become epidemic among Black patients [11,12]. Black individuals are more prone to kidney disease than any other ethnic group in the general [13,14] and HIV-infected populations, possibly as a consequence of predisposing genetic polymorphisms [15]. The risk of ESRD in Black HIV-infected individuals has been reported to be three- to six-fold higher than in Caucasian HIV-infected patients [7,16,17], reflecting the susceptibility of Black patients to develop HIVAN. The introduction of highly active antiretroviral therapy (HAART) has reduced the incidence of HIVAN and ESRD among Black patients [18–20], but the prevalence of ESRD is projected to further increase [11,12]. Earlier studies, mainly from the USA, concluded that, almost exclusively in Black patients, HIVAN is one of the major causes of ESRD [6,21,22], but histological confirmation of HIVAN is infrequent and the diagnosis is usually made clinically. More recent studies have reported an increasing relevance of traditional risk factors as well as chronic hepatitis C virus (HCV) coinfection in the development of ESRD in HIV-infected patients [7,23].

The epidemiology of ESRD outside the USA has not been extensively studied [24–27] but could provide new insights, as most US cohorts consist of a high proportion of Black patients with coeval injecting drug use (IVDU). Conversely, European cohorts consist of mostly Caucasian HIV-infected patients with various proportions of IDU and far fewer Black patients with almost no IDU [19,26,28].

Thus, the aim of our study was to evaluate the incidence, prevalence and outcome of patients with ESRD since the initiation of a chronic renal replacement therapy (RRT) programme in a large, single German HIV-infected cohort.

Methods

Data for all HIV-infected patients treated from January 1989 to December 2010 in the Frankfurt HIV Cohort (FHC) were evaluated for this study. Patients are routinely followed every 3 – 4 months with the use of paper charts and a standardized electronic database. ESRD was defined as initiation of chronic RRT for more than 3 months. Demographic, clinical and laboratory parameters of all patients included in the FHC and those with ESRD were compared. Chronic hepatitis B virus (HBV) coinfection was defined as a detectable HBV surface (HBs) antigen persisting for at least 6 months; HCV coinfection was diagnosed when patients tested positive for HCV antibodies. Three time periods, 1989–1996 (pre-HAART), 1997–2003 (early HAART) and 2004–2010 (late HAART), were defined to describe changes over time.

Continuous variables were expressed as mean ± standard deviation (SD) or as proportions, as appropriate. Continuous and categorical variables were compared for univariate analysis between groups using the *t*-test or Wilcoxon test and the χ^2 or Fisher exact test, respectively. All *P* values reported are two-sided and confidence intervals (CIs) are 95% intervals. Statistical significance was defined as $P \leq 0.05$. The association between the presence of ESRD and demographic and clinical variables was estimated by Poisson regression analysis [relative risk (RR) and confidence interval (CI)]. Kaplan–Meier estimates were used to analyse the survival of ESRD patients.

Results

Study population

Between 1 January 1989 and 31 December 2010, a total of 9198 patients were followed in the cohort, with a cumulative observation time of 68 084 patient-years (PY). The majority were male (78.2%), Caucasian (88.9%) and men who have sex with men (MSM) (49.9%). In the entire cohort, the percentage of Black patients, those with heterosexual acquisition of HIV infection, and those with HBV and HCV coinfection increased from the pre-HAART (1989–1996) to the late HAART (2004–2010) time period ($P < 0.01$ for all comparisons), whereas such a change could not be detected in the group of patients with ESRD. The percentage of male patients, the percentage of patients with IDU, the percentage of those with previous AIDS, and mortality significantly decreased in the entire cohort ($P < 0.01$ for all comparisons) (Table 1).

Prevalence and incidence of ESRD

Over the whole observation period, between 1989 and 2010, 39 patients in our cohort had ESRD, with a mean prevalence of 0.12%. ESRD was more prevalent in Black patients compared with Caucasians (mean prevalence 0.6 *vs.* 0.09%, respectively). The prevalence of ESRD continu-

Table 1 Demographic data and clinical characteristics of the Frankfurt HIV cohort (FHC) and patients with end-stage renal disease (ESRD) stratified for the different time periods

	Period 1, pre-HAART, 1989–1996	Period 2, early HAART, 1997–2003	Period 3, late HAART, 2004–2010
FHC	(*n* = 4 022)	(*n* = 4 810)	(*n* = 5 592)
Age (years) (mean ± SD)	36.5 ± 9.8	39.0 ± 10.1	42.7 ± 10.6
Male gender [*n* (%)]	3 285 (81.7)	3 646 (75.8)	4 381 (77.7)
Ethnicity [*n* (%)]			
Caucasian	3 830 (95.2)	4 266 (88.7)	4 792 (85.7)
Black	131 (3.3)	384 (8.0)	548 (9.8)
Other	61 (1.5)	160 (3.3)	252 (4.5)
Risk behaviour for HIV acquisition [*n* (%)]			
MSM	2 177 (54.1)	2 240 (46.6)	2 894 (51.8)
MSW	348 (8.7)	847 (17.6)	1091 (19.5)
IDU	928 (23.1)	830 (17.3)	672 (11.9)
Other	111 (2.8)	137 (2.8)	113 (2.0)
Unknown	458 (11.4)	756 (15.7)	829 (14.8)
CD4 lymphocyte nadir (cells/μL) (mean ± SD)	206 ± 254	223 ± 197	282 ± 204
AIDS [*n* (%)]	1 516 (37.7)	1 158 (24.1)	1 323 (23.8)
HBV coinfection [*n* (%)]			
Positive	159 (4.0)	247 (5.1)	296 (5.3)
Negative	1 132 (28.1)	2 942 (61.2)	3 858 (69.0)
Unknown	2 731 (67.9)	1 621 (33.8)	1 438 (25.7)
HCV coinfection [*n* (%)]			
Positive	373 (9.3)	759 (15.8)	85 (14.4)
Negative	1 015 (25.2)	2 735 (56.9)	4 038 (72.2)
Unknown	2 634 (65.5)	1 316 (27.4)	749 (13.4)
Mortality (per 10 000 patient-years)	851.3	143.8	87.7
ESRD	(*n* = 9)	(*n* = 13)	(*n* = 22)
Age (years) (mean ± SD)	34.8 ± 6.4	40.9 ± 6.5	46.8 ± 12.0
Male gender [*n* (%)]	9 (100)	12 (92.3)	16 (72.7)
Ethnicity [*n* (%)]			
Caucasian	6 (66.6)	10 (76.9)	17 (77.3)
Black	3 (33.3)	3 (23.1)	5 (22.7)
Risk behaviour for HIV acquisition [*n* (%)]			
MSM	4 (44.4)	5 (38.5)	5 (22.7)
MSW	0	0	7 (31.8)
IDU	4 (44.4)	5 (38.5)	6 (27.3)
Other	0	1 (7.7)	1 (4.5)
Unknown	1 (11.1)	2 (15.4)	3 (13.6)
CD4 lymphocyte nadir (cells/μL) (mean ± SD)	135.2 ± 128.3	75.1 ± 86.3	150 ± 134
AIDS [*n* (%)]	4 (44.4)	9 (69.2)	6 (27.3)
HBV coinfection [*n* (%)]			
Positive	2 (22.2)	2 (15.4)	1 (4.5)
Negative	7 (77.8)	11 (84.6)	21 (95.5)
HCV coinfection [*n* (%)]			
Positive	4 (44.4)	6 (46.1)	6 (27.3)
Negative	5 (55.6)	7 (53.9)	16 (72.2)
Mortality (per 10 000 patient-years)	5 714.7	4 100.5*	1 369.4
Age at death (years) (mean ± SD)	35.1 ± 7.0	42.4 ± 7.7	57.3 ± 8.5
Survival on RRT (months) (mean ± SD)	18.2 ± 13.5	19.6 ± 14.3	26.0 ± 16.1

HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; MSM, men who have sex with men; MSW, men who have sex with women; IDU, injecting drug use; RRT, renal replacement therapy; SD, standard deviation.
*Two patients were lost to follow-up.

ously increased over time from 0.08% in the first defined time period to 0.19% in the third time period. While prevalence increased in Caucasian patients (from 0.05 to 0.17%), in Black patients it was highest in 1995, at 2.6%, and decreased thereafter to 0.38% in the third time period.

Incidence was calculated for 35 of the 39 patients, because one patient had ESRD before he became HIV-infected and three patients were referred to our centre for the initiation of RRT and thus entered the cohort after they had developed ESRD. The overall incidence of ESRD was 51.5 per 100 000 PY of follow-up (PYFU) (95% CI 35.9–71.6) and was significantly higher for Black compared with Caucasian patients. The incidence of ESRD in Black patients decreased substantially over the three defined time

Table 2 Demographic data and clinical characteristics of the Frankfurt HIV cohort (FHC) and patients with end-stage renal disease (ESRD)

	FHC ($n = 9\,198$)	ESRD ($n = 39$)	*P* value
Age at HIV diagnosis(years) (mean ± SD)	36.5 ± 9.9	35.7 ± 10.5	0.76
Male gender [*n* (%)]	7 189 (78.2)	32 (82.1)	0.69
Ethnicity [*n* (%)]			
Caucasian	8 180 (88.9)	29 (74.4)	<0.000001
Black	683 (7.4)	10 (25.6)	0.000006
Other	335 (3.6)	0 (0%)	0.43
Risk behaviour for HIV acquisition [*n* (%)]			
MSM	4 593 (49.9)	11 (28.2)	0.011
IDU	1 478 (16.1)	13 (33.3)	0.0067
Other	217 (2.4)	2 (5.1)	0.54
MSW	1 474 (16.0)	8 (20.5)	0.59
Unknown	1 436 (15.6)	5 (1.8)	0.79
CD4 lymphocyte nadir (cells/μL)			
(mean ± SD)	201 ± 215	131 ± 127	0.07
AIDS [*n* (%)]	2 764 (30.1)	17 (43.6)	0.095
HBV coinfection [*n* (%)]			
Positive	386 (4.2)	5 (12.8)	0.46
Negative	4 296 (46.7)	34 (87.2)	
Unknown	4 516 (49.1)	0 (0)	
HCV coinfection [*n* (%)]			
Positive	1 008 (11.0)	15 (38.5)	0.037
Negative	4 330 (47.1)	24 (61.5)	
Unknown	3 860 (42.0)	0 (0)	
Mortality (per 10 000 patient-years)	258.8	2550.5*	<0.000001

HBC, hepatitis B virus; HCV, hepatitis C virus; MSM, men who have sex with men; MSW, men who have sex with women; IDU, injecting drug use; SD, standard deviation.
*Two patients were lost to follow-up.

periods, from 788.8 to 130.5 and 164.1 per 100 000 PYFU, respectively, but increased in Caucasian patients, from 29.8 to 41.0 and 43.4 per 100 000 PYFU, respectively.

Risk factors for ESRD and mortality

Compared with the entire cohort, patients with ESRD were also mostly male (82.1 *vs.* 78.2%; $P = 0.69$) but were more likely to be Black (25.6 *vs.* 7.4%; $P < 0.0001$), IDUs (33.3 *vs.* 16.1%; $P = 0.0067$) and HCV-coinfected (38.5 *vs.* 11.0%; $P = 0.037$). HBV coinfection (12.8 *vs.* 4.2%; $P = 0.46$) and previous AIDS (43.6 *vs.* 30.1%; $P = 0.095$) were also more frequent in patients with ESRD but the difference was not stastically significant (Table 2). In the univariate analysis, risk factors for the development of ESRD were Black ethnicity (RR 5.1; 95% CI 2.3–10.3; $P < 0.0001$), IDU (RR 2.4; 95% CI 1.1–4.7; $P < 0.02$) and HCV coinfection (RR 1.7; 95% CI 1.1–4.2; $P < 0.03$). In the multivariate regression analysis, Black ethnicity (RR 6.7; 95% CI 2.8–14.8; $P < 0.00001$) and IDU (RR 5.0; 95% CI 1.4–16.9; $P = 0.014$) but not HCV coinfection (RR 0.84; 95% CI 0.23–2.9; $P = 0.79$) remained significantly associated with the development of ESRD (Table 3). No association was found between age, gender, nadir CD4 lymphocyte count or previous AIDS-defining disease and ESRD. In separate analysis of Caucasian and Black patients, we found that prior AIDS was not a risk factor for ESRD in either Black (RR 2.6; 95% CI 0.65–8.96; $P = 0.15$) or Caucasian patients (RR 1.6; 95% CI 0.61–3.6; $P = 0.31$).

ESRD was associated with an overall high risk of mortality (RR 9.9; 95% CI 6.3–14.5; $P < 0.0001$). The mortality of patients with ESRD decreased over the three defined time periods, from 5714.7 per 10 000 PY in the pre-HAART (period 1) to 4100.5 per 10 000 PY in the early HAART (period 2) and finally to 1369.4 per 10 000 PY in the late HAART period (3). The corresponding RR of death for patients with ESRD decreased insignificantly from period 1 to 2 (RR 0.72; $P = 0.52$), but significantly from period 1 to 3 (RR 0.24; $P = 0.006$), whereas in patients without ESRD, mortality decreased significantly for both comparisons (period 1 *vs.* 2: RR 0.17; $P < 000001$, and period 1 *vs.* 3: RR 0.10; $P < 0.000001$). Figure 1 shows the Kaplan–Meier survival plot for patients with ESRD for the three defined time periods ($P = 0.069$ for the log rank test). The median survival time was 15.8, 20.7 and 28.8 months in the three time periods, respectively.

Spectrum of renal disease and renal replacement therapy

In 34 of our 39 patients developing ESRD, the underlying cause of renal disease could be established. Diagnosis was

Table 3 Risk factors for end-stage renal disease (ESRD) in the uni- and multivariate analyses

	Univariate		Multivariate	
Variable	**RR (95% CI)**	***P* value**	**RR (95% CI)**	***P* value**
Sex				
Male	1	0.76		
Female	0.87 (0.35–1.90)			
Ethnicity				
Caucasian	1	<0.0001	1	<0.00001
Black	5.08 (2.33–10.27)		6.68 (2.82–14.83)	
Risk for HIV acquisition				
No IDU	1	0.02	1	<0.016
IDU	2.37 (1.13–4.73)		4.99 (1.42–16.87)	
AIDS				
No AIDS	1	0.09		
AIDS	1.85 (0.87–3.69)			
HBV coinfection				
Negative	1	0.20		
Positive	1.86 (0.63–4.38)			
HCV coinfection				
Negative	1	0.03	1	0.79
Positive	2.16 (1.06–4.23)		0.84 (0.24–2.86)	

HBV, hepatitis B virus; HCV, hepatitis C virus; RR, relative risk; CI, confidence interval; IDU, injecting drug use.

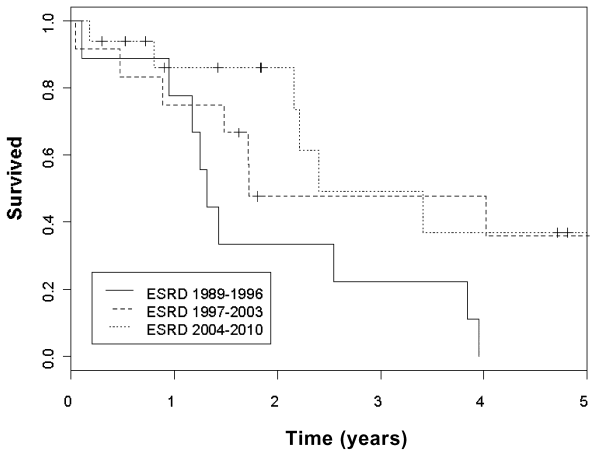

Fig. 1 Kaplan–Meier survival estimates from the diagnosis of end-stage renal disease (ESRD) stratified for pre- (1989–1996), early (1997–2003) and late HAART (2004–2010) time periods; $P = 0.069$ for log rank test.

based on renal biopsy in 31 cases and was made by other diagnostic means in three cases (e.g. by ultrasound findings in two patients with a known family history of autosomal dominant polycystc kidney disease). The spectrum of renal disease observed was highly heterogeneous, with diabetic nephropathy being the most frequent cause of ESRD (nine of 34 patients; 26.5%), whereas HIVAN was rather uncommon (four of 34 patients; 11.8%). Haemodialysis was the treatment of choice for RRT in all patients. The mean time from the first positive HIV antibody test to initiation of RRT was 81.2 ± 74.5 months, and RRT was initiated prior to or within 4 weeks of HIV diagnosis in eight patients (20.5%). The mean observation time on RRT was 32.1 ± 30.2 months. Two patients moved abroad and were lost to follow-up. Comorbidities were frequent: one-third of the patients with ESRD had cardiovascular disease and one-fourth had malignancies. Causes of death were mainly attributable to infections (30.4%), followed by malignancies (21.7%) and cardiovascular disease (17.4%). Mean age at death was 45.2 ± 12.2 years. Demographic data and clinical characteristics are shown in Table 4.

Discussion

The prevalence of ESRD found in our cohort was slightly lower compared with those of other European HIV-infected cohorts, which have been found to range from 0.31 to 0.5% [26,27]. This prevalence appears low, especially when compared with studies conducted in cohorts with higher rates of Black patients [7,18]. Nevertheless, in a comparison with data from the German ESRD Registry [29], the prevalence (0.19 *vs.* 0.08%, respectively) and incidence (51.5 *vs.* 21.3 per 100 000 PYFU, respectively) of ESRD in the last time period were more than two times higher in HIV-infected patients than in HIV-negative individuals. The HIV-infected patients were more than 25 years younger compared with patients from the general German population at the time at which ESRD was diagnosed (median age 42.3 *vs.* 70 years, respectively) [29], underlining a higher risk for ESRD in HIV-infected patients. This difference compared with the general German population is not solely explained

Table 4 Clinical characteristics of patients with end-stage renal disease (ESRD)

Age (years) (mean ± SD)	42.9 ± 11.1
at HIV diagnosis	35.7 ± 10.5
at ESRD	42.3 ± 11.3
Time HIV to ESRD diagnosis (months) (mean ± SD)	81.2 ± 74.5
Male gender [*n* (%)]	32 (82.1)
Ethnicity [*n* (%)]	
Black	10 (25.6)
Caucasian	29 (74.4)
Risk behaviour for HIV acquisition [*n* (%)]	
MSM	11 (28.2)
IDU	13 (33.3)
Other	2 (5.1)
MSW	8 (20.5)
Unknown	5 (12.8)
CD4 lymphocyte nadir (cells/μL) (mean ± SD)	131 ± 127
AIDS [*n* (%)]	17 (43.6)
Renal disease [*n* (%)]	
Diabetic nephropathy	9 (23.1)
Nephrosclerosis	4 (10.4)
HIVAN	4 (10.3)
Membranous GN	3 (7.7)
Membranoproliferative GN	3 (7.7)
Other GN	5 (12.2)
Amyloidosis	4 (10.3)
Congenital	3 (7.7)
Unknown	4 (10.3)
HBV coinfection [*n* (%)]	5 (12.2)
HCV coinfection [*n* (%)]	15 (38.5)
Outcome	
Time alive on RRT (months) (mean ± SD)	32.1 ± 30.2
Mortality [*n* (%)]	23 (62.2)*
Causes of death [*n* (%)]	
Cardiovascular disease	4 (17.4)
Infection	7 (30.4)
Malignancy	5 (21.7)
Renal	2 (8.7)
HIV encephalopathy	2 (8.7)
Other	3 (13)
Age at death (years) (mean ± SD)	45.2 ± 12.2
Time HIV diagnosis to death (years) (mean ± SD)	113.0 ± 77.2
Comorbidity [*n* (%)]	
Diabetes mellitus	10 (25.6)
Type 1	3 (7.7)
Type 2	7 (17.9)
Cardiovascular morbidity	13 (33.3)
Coronary heart disease	7 (17.9)
Myocardial infarction	5 (12.8)
Stroke	4 (10.3)
Peripheral occlusive vascular disease	7 (17.9)
Malignancy	10 (25.6)
HIV-related	7 (17.9)
Non-HIV-related	5 (12.8)
Liver cirrhosis	2 (5.1)
AIDS-defining infections	
Prior RRT	12 (30.8)
Under RRT	8 (20.5)

SD, standard deviation; MSM, men who have sex with men; MSW, men who have sex with women; IDU, injecting drug use; HIVAN, HIV-associated nephropathy; GN, glomerulonephritis; RRT, renal replacement therapy.
*Two patients were lost to follow-up.

by a higher proportion of Black patients in the HIV-infected cohort, because the prevalence (0.17 *vs.* 0.08%, respectively) and incidence (43.4 *vs.* 21.3 per 100 000 PYFU, respectively) of ESRD for Caucasian HIV-infected patients were still higher compared with the German ESRD Registry [29]. This finding is contrary to results from a North American study demonstrating that the incidence of ESRD among Caucasians with HIV infection was similar to that among Caucasian patients without HIV infection [16]. This difference might be explained by the finding that most Caucasian patients with ESRD in our cohort were IDU and HCV-coinfected, whereas in most North American studies IDU and HCV coinfection were less prevalent in Caucasian patients with ESRD [19,21,28].

Accordingly, HCV and IDU were both identified as risk factors for ESRD in the univariate analysis of our cohort. HCV coinfection has been associated with an increased incidence and accelerated progression of chronic kidney disease (CKD) [19,23,30,31]. Thus, a role in the development of ESRD as the terminal stage of CKD seems plausible. However, in the multivariate analysis, IDU but no longer HCV coinfection was significantly associated with ESRD. Due to the co-linearity of HCV coinfection and IDU, these risk factors can hardly be separated since 94.8% of IDUs were also HCV antibody positive, not only in our cohort [19,22,25,27].

One important limitation of our analysis is that there were few data from the pre-HAART era concerning the proportion of patients with HCV coinfection, as HCV coinfection was diagnosed by positive HCV antibodies and the antibody assay just became commercially available during this period. For the same reason, we were unable to include HCV polymerase chain reaction (PCR) results in our analysis. A recent analysis from the EuroSIDA cohort demonstrated an association between higher HCV copy numbers as measured by PCR and a higher risk of CKD, suggesting a direct effect of HCV viraemia on CKD [23]. Vice versa, individuals with positive HCV antibodies and negative HCV PCR (resolved HCV coinfection) had a comparable CKD risk compared with HCV antibody-negative individuals [23]. Thus, in our analysis the effect of a viraemic HCV coinfection on ESRD could have been underestimated.

IDU has long been linked to kidney disease, but potential pathological mechanisms are diverse and generally unclear [32]. HIV-negative IDUs had a 2.3-fold higher risk of RRT than expected from age-matched rates in the general African-American population, arguing for a role of IDU as a risk factor for ESRD. Nevertheless, many studies on CKD and IDU were carried out before HCV and HIV were even discovered. Further taking into account that most IDUs consume more than one substance of variable, uncontrolled purity, it becomes clear that a retrospective study

like ours can only be descriptive. The combination of HIV infection with IDU seems to further increase the risk for CKD, as demonstrated by one study that found a higher prevalence of proteinuria when comparing HIV-infected and uninfected IDUs [33].

We observed an overall increasing prevalence of ESRD from 1989 to 2010, mainly as a result of longer survival of patients with ESRD. Despite a significant increase in the proportion of Black patients in the entire cohort over time, the prevalence of ESRD among Black patients decreased, suggesting a strong reduction of HIVAN as a consequence of HAART. Vice versa, the prevalence of ESRD increased over time in Caucasian patients despite a significant decrease of IDU in the entire cohort. This finding is in contrast to that of a previous study [26] and might be explained by a longer observation period as well as an increased survival time on RRT, especially in the late HAART period. Similarly to our results, other studies reported no significant improvement in survival in the early HAART era [21,28], possibly because HAART was not or could not be effectively prescribed in patients with ESRD [21]. Newer drugs and strategies to combine these without the need for dose adjustments became available in the late HAART era. Thus, effective antiretroviral treatment became easier and safer for patients with renal impairment only very recently. The survival time of patients with ESRD was longer in our study compared with other studies, but lower rates of IDU (33.3% *vs*. 50 – 65%, respectively) and HCV coinfection (38.5% *vs*. 67–68%, respectively) are the most likely explanations for this difference [19,21,22,28].

It is well established that HAART lowers the incidence of HIVAN and thus ESRD in Black patients [16,18,19,34] but it is unclear whether this is true in Caucasian patients [25–27]. In our study, the proportion of Caucasian patients with ESRD was higher than in most studies (74.4%) [16,22,24,26–28]. We could not find any influence of HAART on the incidence of ESRD in Caucasians throughout the observation time. Furthermore, we did not find advanced immunodeficiency, as reflected by a low nadir CD4 lymphocyte count or previous AIDS, to be a risk factor for ESRD in the Caucasian patients, which is contrary to previously published reports on mainly Black patients [19,26,28,35–37]. Given the large diversity of the mostly biopsy-confirmed underlying renal diseases in our cohort, it appears questionable whether immunodeficiency or HAART will play a major role in preventing ESRD, as proposed by others [16].

In addition to those already discussed, our study has several more limitations. First, the study population was small and resided in a single metropolitan area with a high proportion of IDUs and Black patients compared with other German sites [38]. Thus, our results cannot be generalized to HIV-infected populations in other cohorts. As Black ethnicity, IDU and HCV coinfection were risk factors for ESRD, results from individual cohorts will greatly depend on their patient composition. Secondly, we did not assess details of antiretroviral regimens, as many patients started, stopped, changed and resumed antiretroviral therapy during the time periods, making it difficult to draw definite conclusions with such low numbers of ESRD cases. Thirdly, other known risk factors for ESRD, such as diabetes, hypertension and dyslipidaemia, were not systematically assessed in the general cohorts and therefore cannot be analysed.

In summary, the prevalence of ESRD in HIV-infected individuals increased over the last two decades, which is explained by increased survival. HAART significantly reduced the incidence of ESRD in Black, but not in Caucasian patients. We found HCV coinfection to be a dependent and IDU an independent risk factor for ESRD. The underlying mechanisms are currently unknown and warrant further investigation.

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Author contributions: MB and OJ initiated the study, treated patients, analysed the data and wrote the manuscript. EH performed the statistical analysis. WM, OJ and MB collected the data and performed the database analysis. All other authors treated the patients and were substantially involved in the collection and monitoring of data in the electronic database.

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