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Original Article

Increased risk of dialysis and end-stage renal disease among HIV patients in Denmark compared with the background population

Magnus G. Rasch[1,2],
Marie Helleberg[1,2],
Bo Feldt-Rasmussen[3],
Gitte Kronborg[4],
Carsten S. Larsen[5],
Court Pedersen[6],
Gitte Pedersen[7],
Jan Gerstoft[1]
and Niels Obel[1]

[1]Faculty of Health Sciences, University of Copenhagen, 1455 København K, Denmark,
[2]Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark,
[3]Department of Nephrology, Copenhagen University Hospital, Rigshospitalet, Denmark,
[4]Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark,
[5]Department of Infectious Diseases, Aarhus University Hospital, Skejby, Aarhus, Denmark,
[6]Department of Infectious Diseases, Odense University Hospital, Odense, Denmark and
[7]Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark

Correspondence and offprint requests to: Magnus G. Rasch; E-mail: magnus.rasch@gmail.com

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ABSTRACT

Background. HIV patients have increased risk of impaired renal function. We aimed to estimate the incidence of any renal replacement therapy (aRRT) and start of chronic renal replacement therapy (cRRT) among HIV patients compared with population controls.

Methods. In a nationwide, population-based cohort study we analysed incidence rates (IR), incidence rate ratios (IRR) and risk factors for aRRT and cRRT among HIV patients compared with an age- and gender-matched population control cohort using Poisson regression.

Results. We identified 5300 HIV patients and 53 000 population controls. The IRs per 10 000 person-years of aRRT and cRRT among HIV patients were 15.9 (95% CI: 12.5–20.1) and 4.4 (95% CI: 2.8–6.9), respectively. The IRR was 4.7 (95% CI: 3.5–6.2) for aRRT and 3.6 (95% CI: 2.2–6.0) for cRRT compared with population controls. Risk of aRRT was increased during the first year after HIV diagnosis [IRR 3.5 (95% CI: 1.5–8.1)], after a diagnosis of AIDS [IRR 2.3 (95% CI: 1.3–3.9)], in intravenous drug users [IRR 6.0 (95% CI: 2.9–12.2)] and in patients with hypertension [IRR 7.0 (95% CI: 3.7–13.2)]. Factors associated with increased risk of cRRT were hypertension [IRR 20 (95% CI: 6.8–61)] and baseline eGFR < 60 mL/min pr. 1.73 m^2 [IRR 7.8 (95% CI: 1.2–50)]. Exposure to tenofovir and/or atazanavir was not associated with risk of aRRT or cRRT.

Conclusions. The risk of aRRT is increased more than 4-fold and the risk of cRRT is increased more than 3-fold in HIV patients in Denmark compared with the background population. We found no association between exposure to tenofovir, atazanavir or the combination of the two and risk of aRRT or cRRT.

INTRODUCTION

After the introduction of highly active antiretroviral therapy (HAART), the mortality and morbidity of HIV patients have decreased dramatically and with aging of this patient

population the incidence of comorbidity has increased [1, 2]. HIV patients lose kidney function faster than the background population [3, 4], but the mechanism of this decline is not fully understood. Exposure to antiretrovirals (ARVs) (indinavir, atazanavir and tenofovir) has been associated with deterioration of renal function [5–7]. Furthermore, HIV replicates in other cells than CD4 cells, e.g. renal epithelial cells [8]. This seems to be directly associated with HIV-associated nephropathy (HIVAN) [9].

Although the increased incidence of mild-to-moderate renal impairment in HIV patients is well documented, few studies have addressed the prevalence and incidence of renal replacement therapy (dialysis or renal transplantation) [10, 11]. Only a few studies have evaluated ARVs as risk factors of renal replacement therapy [12].

In the present study, we aimed to assess the risk and risk factors for renal replacement therapy in the HIV population in Denmark compared with an HIV-negative control population. We evaluated risk of any renal replacement therapy (aRRT) including dialysis because of acute kidney failure and as a marker of end-stage renal disease we estimated risk of chronic renal replacement therapy (cRRT).

PATIENTS AND METHODS

In a nationwide, population-based cohort we evaluated risk factors for aRRT and cRRT among HIV patients compared with an age- and gender-matched cohort of population controls.

Setting

Denmark has a population of 5.5 million, with an estimated HIV prevalence of 0.09% among adults in January 2010. HIV patients are treated in eight specialized HIV care centres and are seen as outpatients at intended intervals of 12 weeks. A letter specifying a date for a new appointment reminds patients who miss a planned visit. Antiretroviral treatment is provided at the centres free of charge. The national criteria for initiating HAART have been described previously [13].

Data sources

The unique 10-digit personal identification number assigned to all Danish citizens at birth or immigration was used to avoid multiple registrations and to track individuals in the following registries.

The Danish HIV Cohort Study (DHCS) is a prospective study of all HIV patients 16 years or older at diagnosis, who were treated at Danish HIV centres after 1 January 1995. Patients are consecutively enrolled. Data are collected annually and include demographics, date of HIV diagnosis, AIDS-defining events, date and cause of death and ARV treatment. CD4 cell counts and viral loads (VL) are extracted electronically from laboratory data files. The study is described in detail elsewhere [13].

Date of cRRT was defined as the first date of chronic dialysis or renal transplantation as registered in the Danish Nephrology Registry (DNR). DNR contains data on all Danish patients who have received chronic dialysis or renal transplantation, and the underlying causes [categorized according to International Classification of Diseases 10th revision (ICD-10)], after 1 January 1990. Chronic dialysis was defined as dialysis during a minimum of 3 months for a minimum of 12 times. More than 99% of patients in Denmark with cRRT are included in DNR [14, 15].

For both HIV patients and controls diagnoses of dialysis (ICD-10: BJFD00-BJFD27), diabetes [categorized according to ICD-10 as Type 1, Type 2 and other diabetes (ICD10: DE10.0-DE14.9)] and hypertension (ICD1: DI10-DI5.9) were extracted from the Danish National Hospital Registry (DNHR) [16].

Data on vital status, residency and migration were extracted from the Danish Civil Registration System (DCRS) which were established in 1968 and stores information on all Danish residents.

Serum creatinine measurements were extracted from electronic laboratory databases. All serum creatinines were standardized according to the Jaffe method as described by the local laboratories (data not published). We calculated eGFR using the modification of diet in renal disease (MDRD) formula [17]. Baseline eGFR was defined as the eGFR closest to—and within 6 months of—index date (defined below). In analyses only including time after start of HAART, baseline eGFR was calculated as the eGFR closest to initiation of HAART.

Study population

We included all HIV patients who had a Danish person identification number and were aged ≥16 years at HIV diagnosis. The index date was defined as 1 January 1995, the date of HIV diagnosis or date of immigration whichever came last. Patients with a diagnosis of aRRT or cRRT before index date were excluded from the analyses.

Population control cohort. From DCRS, we identified 10 population controls for each HIV patient matched on date of birth and gender. The population controls were assigned the same index date as the HIV patient, to whom they were matched.

Study outcomes

Outcomes were (i) time to first date of aRRT and (ii) time to cRRT. cRRT was defined as described above and aRRT was defined as the first date an individual was registered with dialysis in DNHR (with ICD codes as stated above) or cRRT, and thereby includes patients who receive RRT because of acute kidney failure. As a consequence, all patients with cRRT will by definition have an outcome in the analyses of time to aRRT.

Statistics

Time was calculated from the index date to 1 January 2010, emigration, death, loss to follow-up or first date of aRRT/cRRT whichever occurred first.

Because death and emigration can be considered events competing with the events of interest (aRRT and cRRT), we used Cumulative Incidence Functions to construct survival

curves for aRRT and cRRT (taking into account these competing risks) and Poisson regression analyses to estimate incidence rate ratios (IRR) of aRRT and cRRT among HIV patients compared with controls. Separate analyses were conducted for aRRT and cRRT. Further, we analysed risk factors for aRRT and cRRT among HIV patients using Poisson regression. The following variables were included in the model: route of infection [men who have sex with men (MSM), intravenous drug use (IDU), heterosexually infected or other], date of HIV diagnosis (before versus after 1 January 1997, reflecting the pre- and post HAART era), hepatitis C co-infection in non-IDUs (defined as positive hepatitis C

Table 1. Characteristics of the study population

	HIV patients (aRRT/cRRT)[a]	Controls (aRRT/cRRT)[a]
Number	5300	53 000
Number of events (%)	68 (1.3)/19 (0.4)	182 (0.3)/66 (0.1)
Follow-up, median (IQR), years	8.0 (3.1–13.7)/8.0 (3.1–13.8)	11.2 (5.8–15.0)/11.2 (5.8–15.0)
Lost to follow-up (%)	22 (0.4)	98 (0.2)
Emigrated during follow-up (%)	219 (4.1)	2037 (3.8)
Died during study period (%)	1338 (25.2)	2454 (4.7)
Age at study inclusion, median (IQR), years	37 (30–44)	37 (30–44)
Male (%)	4036 (76.2)	40 360 (76.2)
Race		
Caucasian	4167 (78.6)	–
African	683 (12.9)	–
Other/unknown	450 (6.7)	–
Route of infection		
MSM (%)	2407 (45.5)	–
IDU (%)	563 (10.6)	–
Heterosexually (%)	1928 (36.4)	–
Others (%)	402 (5.6)	–
HIV diagnosis after 1 January 1997	2486 (46.9)	–
Diabetes during study period (%)	131 (2.5)/132 (2.5)	1303 (2.5)/1309 (2.4)
Type 1 (%)	36 (0.7)	230 (0.4)/232 (0.5)
Type 2 (%)	80 (1.5)	975 (1.8)/979 (1.8)
Other (%)	15 (0.3)/16 (0.3)	117 (0.2)/117 (0.2)
Hypertension during study period (%)	219 (4.1)/220 (4.1)	2557 (4.8)/2574 (5.0)
Hepatitis C co-infection (non-IDU)	354 (6.7)	–
AIDS diagnosis during study period (%)	788 (14.8)/790 (14.9)	–
CD4 cell count at baseline (IQR)	290 (120–480)	–
eGFR baseline (mL/min pr. 1.73 m^2)		
>90 (%)	1776 (33.5)	–
60–90 (%)	1177 (22.2)	–
≤60 (%)	69 (1.3)	–
Missing (%)	2278 (43)	–

aRRT, any renal replacement therapy; cRRT, start of chronic renal replacement therapy; IQR, interquartile range; MSM, men who have sex with men; IDU, intravenous drug users; eGFR, estimated glomerular filtration rate.
[a]Presented if there is a difference between aRRT and cRRT.

antibodies or positive PCR for hepatitis C RNA in non-IDU patients), CD4 cell count at baseline (<200 versus ≥200 cells/μL), viral load at baseline (copies/mL) (<5000, 5000–100 000 and >100 000), baseline eGFR (≥90, 60–90 and <60 mL/min pr. 1.73 m^2), race (Caucasian, African or other) and gender. The following were included as time-updated variables: HAART exposure, diabetes (yes/no), hypertension (yes/no) and AIDS (yes/no), after the date 1 year after diagnosis, age (5-year intervals) and year after index date (5-year intervals). The African population was categorized as West/Central African, East African or unspecified.

We analysed the association between treatment with tenofovir, atazanavir and the combination tenofovir/atazanavir and risk of first dialyses by including exposure of the ARVs as time-updated variables in the Poisson regression model (in three separate analyses). Exposure to the specific drugs was calculated from date of initiation until 1 year after discontinuation. In this analysis, time on tenofovir or atazanavir was stopped once the combination tenofovir/atazanavir was started.

We performed a sensitivity analysis in which only time after 1 January 2000 was included as no tenofovir was used in Denmark before that date. Statistical analyses were performed using SPSS for Windows (Norusis; SPSS Inc., Chicago, IL, version 13.0) and STATA (Stata Corporation, College Station, TX, version 11.0).

RESULTS

We identified 5300 HIV patients and 53 000 population controls. The African population accounted for 13% of the HIV population and the majority of the African HIV population were from East Africa (69%), 24% were from Western and Central regions and 7% were from unknown or other regions. Characteristics of the study population are summarized in Table 1.

Among HIV patients, there were 68 cases of aRRT during 42 833 person years of follow-up (PY) [IR 15.9/10 000 PY (95% CI: 12.5–20.1)]. Among population controls, there were 182 cases of aRRT during 534 282 PY [IR 3.4/10 000 PY (95% CI: 2.9–3.9)]. The IRR of aRRT was 4.7 (95% CI: 3.5–6.2) among HIV patients compared with the population control cohort (Figure 1a). In two sensitivity analyses, we included only (i) individuals diagnosed after 1 January 1995 [IRR 5.0 (95% CI: 3.3–7.4)] and (ii) non-IDUs and non-Africans [IRR 3.5 (95% CI: 2.5–4.8)]. The incidence of aRRT was highest during the first year after HIV diagnosis [IR 24.8/10 000 PY (95% CI: 12.4–49.5)] compared with the period >1 year after HIV diagnosis [IR 15.2/10 000 PY (95% CI: 11.8–19.5)].

Of the 68 cases of aRRT among HIV patients, 19 (28%) progressed to cRRT during 42 879 PY [IR 4.4/10 000 PY (95% CI: 2.8–6.9)], none of these patients had received renal transplantation (for underlying causes of cRRT, see Supplementary data, Table S1). Of the 182 cases of aRRT among controls, 66 (36%) progressed to cRRT during 534 476 PY [IR 1.2/10 000 PY (95% CI: 1.0–1.6) pr. 10 000 PY], IRR 3.6 (95% CI: 2.2–6.0) (Figure 1b).

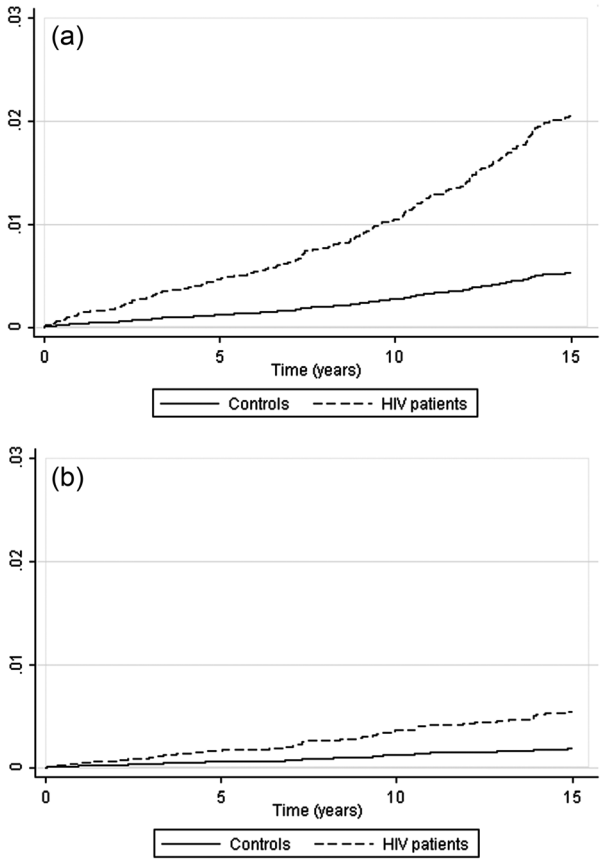

FIGURE 1: (**a**) Time to any renal replacement therapy (aRRT). (**b**) Time to chronic renal replacement therapy (cRRT).

Factors associated with increased risk of aRRT were, age, IDU, hypertension and AIDS. HAART exposure, hepatitis C co-infection in non-IDU patients and baseline eGFR <60 mL/min pr. 1.73 m^2 were also associated with the increased risk of aRRT, although associations did not reach the statistical significance (Table 2).

Factors associated with the increased risk of cRRT were hypertension and baseline eGFR <60 mL/min pr. 1.73 m^2 (Table 2).

Neither tenofovir, atazanavir nor their combination was associated with increased risk of aRRT (Table 3). A sensitivity analysis including only time after 1 January 2000 did not change the estimates substantially.

DISCUSSION

In this Danish, nationwide, population-based cohort study we found that the risk of aRRT was increased more than 4-fold and the risk of cRRT was increased more than 3-fold in HIV patients compared with the background population. The risk of aRRT was highest the first year after HIV diagnosis. Factors associated with increased risk of aRRT were IDU, hypertension and AIDS-defining illness. Risk factors for cRRT were hypertension and baseline eGFR. We found no association

Table 2. Risk factors for aRRT–Poisson regression analyses and cRRT–Poisson regression analyses

	Events	IR pr. 10 000 PY (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR[a] (95% CI)
aRRT				
HIV patients compared to controls				
Controls	182	3.4 (2.9–3.9)	Ref.	–
HIV patients	68	16 (13–20)	4.7 (3.5–6.2)	–
Only including the HIV patients				
Female gender	14	13 (7.6–22)	0.8 (0.4–1.4)	0.8 (0.4–1.5)
Age (pr. 5 year interval)	–	–	1.07 (1.04–1.09)	1.06 (1.03–1.08)
Race				
Caucasian	57	17 (13–22)	Ref.	Ref.
African	6	11 (4.9–24)	0.7 (0.3–1.5)	1.2 (0.4–3.0)
Other	5	16 (6.8–39)	1.0 (0.4–2.5)	1.4 (0.6–3.7)
HAART exposed—time updated	59	20 (16–26)	3.0 (1.5–6.0)	2.0 (0.9–4.5)
Route of infection				
MSM	23	12 (7.7–17)	Ref.	Ref.
IDU	15	34 (20–56)	2.9 (1.5–5.6)	5.3 (2.6–11.0)
Heterosexual	23	15 (9.6–22)	1.3 (0.7–2.2)	1.4 (0.7–2.8)
Other	7	27 (13–56)	2.3 (1.0–5.3)	1.6 (0.6–4.0)
Time of diagnosis				
After 1 January 1997	27	16 (11–23)	Ref.	Ref.
Before 1 January 1997	41	16 (12–22)	1.0 (0.6–1.6)	0.8 (0.4–1.9)
Comorbidity				
Diabetes—time updated	7	73 (35–153)	5.0 (2.3–10.9)	1.2 (0.5–3.0)
Hypertension—time updated	16	151 (83–247)	12.2 (7.0–21.3)	6.7 (3.5–13.0)
Hepatitis C co-infection (non-IDU)	7	22 (11–46)	1.4 (0.7–3.1)	2.1 (0.9–4.8)
AIDS—time updated	23	34 (22–51)	2.7 (1.6–4.5)	2.2 (1.3–3.8)
CD4 cell count baseline (cells/μL)				
>200	15	20 (11–33)	Ref.	Ref.
<200	33	15 (11–22)	1.4 (0.7–2.7)	0.6 (0.3–1.4)
Viral load at baseline (copies/mL)				
<5000	1	4 (0.6–31)	Ref.	Ref.
5000–100 000	9	15 (8–28)	3.3 (0.4–26.2)	2.5 (0.3–19.8)
>100 000	12	22 (13–39)	5.0 (0.6–38.4)	2.9 (0.4–23.4)
Baseline eGFR (mL/min pr. 1.73 $m^{2)}$)				
>90	25	18 (12–26)	Ref.	Ref.
60–90	18	18 (11–28)	1.0 (0.6–1.9)	0.8 (0.4–1.6)
<60	3	94 (30–293)	5.4 (1.6–17.8)	2.0 (0.5–7.5)
First year after HIV diagnosis	8	25 (12–50)	1.6 (0.8–3.4)	3.4 (1.5–8.1)

Continued

Table 2. Continued

	Events	IR pr. 10 000 PY (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR[a] (95% CI)
cRRT				
HIV patients compared to controls				
Controls	66	1.2 (1.0–1.6)	Ref.	–
HIV patients	19	4.4 (2.8–6.9)	3.59 (2.15–5.98)	–
Only including the HIV patients				
Female gender	3	2.8 (0.9–8.6)	0.6 (0.2–1.9)	0.3 (0.1–2.4)
Age (pr. 5 year interval)	–	–	1.06 (1.02–1.10)	1.03 (0.97–1.08)
Race				
Caucasian	14	4.1 (2.4–6.9)	Ref.	Ref.
African	3	5.4 (1.8–17)	1.3 (0.4–4.6)	2.8 (0.6–13)
Other	2	6.5 (1.6–26)	1.6 (0.4–7.1)	3.4 (0.7–17)
HAART exposed—time updated	15	5.1 (3.1–8.4)	1.7 (0.6–5.1)	1.1 (0.3–3.9)
Route of infection				
MSM	8	4.0 (2.0–8.0)	Ref.	Ref.
IDU	2	4.5 (1.1–18)	1.1 (0.2–5.3)	2.0 (0.4–11)
Heterosexual	8	5.0 (2.5–10)	1.3 (0.5–3.3)	1.3 (0.4–4.4)
Other	1	3.8 (0.5–27)	0.9 (0.1–7.5)	0.7 (0.1–6.4)
Time of diagnosis				
After 1 January 1997	7	4.1 (2.0–8.7)	Ref.	Ref.
Before 1 January 1997	12	4.6 (2.6–8.1)	1.1 (0.4–2.8)	1.5 (0.3–7.4)
Comorbidity				
Diabetes—time updated	3	31 (10–96)	8.1 (2.4–28)	1.6 (0.4–6.7)
Hypertension—time updated	8	75.0 (38–150)	29 (12–71)	19 (6.2–56)
Hepatitis C co-infection (non-IDU)	2	6.3 (1.6–25)	1.5 (0.3–6.3)	2.2 (0.5–11)
AIDS—time updated	5	7.3 (3.0–18)	1.9 (0.7–5.2)	1.6 (0.5–5.0)
CD4 cell count baseline (cells/μL)				
>200	5	3.6 (1.5–8.7)	Ref.	Ref.
<200	4	5.3 (2.0–14)	1.5 (0.4–5.4)	0.7 (0.2–3.3)
Viral load at baseline (copies/mL)				
<5000	0	–	Ref.	Ref.
5000–100 000	3	4.9 (1.6–15)	–	–
>100 000	3	5.5 (1.8–17)	–	–
Baseline eGFR (mL/min pr. 1.73 m^2)				
>90	6	4.2 (1.9–9.4)	Ref.	Ref.
60–90	7	7.0 (3.3–14)	1.7 (0.6–4.9)	1.3 (0.4–4.3)
<60	2	61 (15–24)	14 (2.9–72)	7.8 (1.2–50)
First year after HIV diagnosis	1	3.1 (0.5–22)	0.7 (0.1–5.1)	0.8 (0.1–6.5)

aRRT, any renal replacement therapy; cRRT, chronic renal replacement therapy; IR, incidence rate; PY, person years at risk; IRR, incidence risk ratio; MSM, men who have sex with men; IDU, intravenous drug users; eGFR, estimated glomerular filtration rate.
[a]Adjusted for: HAART, route of infection, time of diagnosis, first year after diagnosis, diabetes, hypertension, hepatitis C co-infektion, AIDS, CD4 count at baseline, baseline eGFR, age, year after index date, race and gender.

Table 3. Associations between tenofovir and atazanavir and risk of aRRT

	Events	PY	IR pr. 10 000 PY (95% CI)	Unadjusted IRR[a] (95% CI)	Adjusted IRR[a,b] (95% CI)
Including only time after initiation of HAART					
HAART exposed but not tenofovir/atazanavir exposed	46	23 674	19.4 (14.6–25.9)	Ref.	Ref.
Tenofovir exposed	5	3181	15.7 (6.54–37.8)	0.77 (0.31–1.91)	0.63 (0.25–1.59)
Atazanavir exposed	5	1520	32.9 (13.7–79.0)	1.70 (0.68–4.26)	1.67 (0.65–4.29)
Atazanavir/tenofovir exposed	3	1111	27.0 (8.71–83.8)	1.37 (0.43–4.37)	1.10 (0.34–3.60)
Including only time after 1 January 2000					
HAART exposed but not tenofovir/atazanavir exposed	42	19 613	21.4 (15.8–29.0)	Ref.	Ref.
Tenofovir exposed	5	3181	15.7 (6.54–37.8)	0.70 (0.27–1.75)	0.68 (0.27–1.73)[c]
Atazanavir exposed	5	1520	32.9 (13.7–79.0)	1.57 (0.63–3.94)	1.50 (0.58–3.78)[c]
Atazanavir/tenofovir exposed	3	1111	27.0 (8.71–83.8)	1.26 (0.39–4.04)	1.07 (0.33–3.50)[c]

PY, person-years at risk; IR, incidence rate; CI, confidence interval; IRR, incidence rate ratio; eGFR, estimated glomerular filtration rate.
[a]The Poisson regression model.
[b]Adjusted for route of infection, year of diagnosis, diabetes, hypertension, hepatitis C co-infection, AIDS, CD4 count at baseline, eGFR at initiation of HAART, age, 1 year after diagnosis, year after index date, race and gender.
[c]Adjusted for eGFR at initiation of tenofovir rather than at start of HAART.

between tenofovir, atazanavir or the combination atazanavir/tenofovir and risk of aRRT or cRRT.

We found an overall incidence of cRRT of 4.4 pr. 10 000 PY, which is comparable with the findings in a large German cohort study who found an incidence of 5.2 pr. 10 000 PY [10]. A study performed in a US veteran cohort by Choi *et al.* [11] found an incidence of 39.1 pr. 10 000 PY, which is almost 10 times higher than in our study. However, the latter study included a much larger proportion of both diabetics and Afro-Americans than our study (2.4 versus 14.4% and 12.9 versus 53.6%, respectively), and the study subjects were older (median age 49 versus 37 years) which may explain some of the difference. No patients in the study population received renal transplantation; however, during the study period two Danish HIV patients were registered with transplantation, these were excluded from the analysis because they had a diagnosis of aRRT prior to HIV diagnosis.

HIV-infected individuals have a faster decline in renal function than the background population, but estimates of the magnitude of this difference varies [3, 4, 18]. The increased risk of impaired renal function may both be related to a direct effect of the HIV infection and to toxic effects of the ARVs. HIV itself can cause impaired renal function as HIVAN, HIV-associated thrombotic microangiopathy and HIV-associated immunomediated glomerulonephritis [19, 20] and in these cases HAART can improve renal function. Tenofovir and atazanavir have been associated with increased risk of impaired renal function [3, 21, 22]. This effect seems to be reversible when the drugs are discontinued [23]. We found that AIDS-defining illness, but not baseline CD4<200 cells/μL was associated with risk of aRRT. It is possible that the increased risk of aRRT is caused by hypotension, dehydration or intensive care treatment during the acute phase of some AIDS-defining diseases.

Tenofovir was introduced in 2001 and the first case report of acute renal failure associated with exposure to tenofovir was published in December 2002 [24]. Several studies have shown an association between tenofovir exposure and decline in eGFR and risk of chronic kidney disease [25–27]. It is difficult to assess the risk of adverse events associated with specific ARVs in observational studies due to the risk of confounding by indication. In the present study, we found no indication of association between tenofovir and risk of aRRT or cRRT. In our analyses, time of exposure to tenofovir, atazanavir and the combination tenofovir/atazanavir was calculated from date of first exposure of the drug to the date 1 year after discontinuation. The 'tail' of 1 year was included since a previous study showed that the effect of drug exposure wanes and is no longer significant 1 year after discontinuation, suggesting that the nephrotoxic effect is reversible [23]. The lack of association between tenofovir and aRRT/cRRT in the present study may be due to the fact that clinicians, knowing the nephrotoxic effects of tenofovir, discontinued the drug in patients who developed mild-to-moderate impairment in renal function and thereby prevented further decrease in renal function and descent to renal failure.

Though previous studies have shown increased risk of HIVAN in African HIV-infected individuals, we found no association between African race and the risk of aRRT or cRRT. The increased risk of end-stage renal disease in African populations has been shown to be associated with the Apol1 gene [28], which is more frequent in Western and Central regions of Africa [29]. The majority of the African population

in the present study were from East Africa (~69%) and only ~24% were from Western and Central regions. This may to some extent explain why we did not find increased risk of either aRRT or cRRT among Africans. It is, however, also possible that the lack of association between race and risk of aRRT/cRRT in our analyses was explained by unmeasured confounders.

Major strengths of the study are the population-based, nationwide design. The use of DCRS, which assign a personal identification number to all Danish citizens and the well-organized structure of Danish national registers allowed us to generate a well-matched population-based control cohort with long and almost complete follow-up. Also this system enabled us to extract data on study outcomes from two well-validated Danish databases, the DNHR [16, 30] and the DNR[14]. Data on study outcomes were extracted from the same data sources for both HIV patients and the control cohort, which decrease the risk of differential misclassification and thereby leads to a negligible impact on estimates of relative risks. Also our study did not use surrogate markers for impaired renal function but hard and indisputable end points as dialyses. There are some limitations in the study. The number of cRRT events was relatively small, which limits statistical power of analyses. We did not have information of race in the population control group, but analyses restricted to HIV patients of Danish origin yielded similar results. We were unable to assess socioeconomic and lifestyle-related factors, which may influence the risk of renal disease.

Our study has several clinical implications. It demonstrates that HIV patients have substantially increased risk of aRRT and cRRT, compared with an age- and gender-matched control population, and are especially vulnerable to these conditions in the first year after HIV diagnosis. Important risk factors are, an AIDS-defining illness, being IDU and having hypertensive disease. Furthermore, it illustrates that in a setting with regularly monitoring of renal function, treatment with tenofovir or atazanavir or their combination does not seem to increase the risk of severe and irreversible renal disease.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

None declared.

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