MAJOR ARTICLE

Diminished Impact of Ethnicity as a Risk Factor for Chronic Kidney Disease in the Current HIV Treatment Era

Annelot F. Schoffelen,[1] Colette Smit,[2] Steven F. L. van Lelyveld,[1,7] Liffert Vogt,[3] Martijn P. Bauer,[8] Peter Reiss,[2,4,5,6] Andy I. M. Hoepelman,[1] and Roos E. Barth[1]; on behalf of the ATHENA National Observational HIV Cohort[a]

[1]Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht, [2]Stichting HIV Monitoring, [3]Department of Nephrology, [4]Department of Global Health, [5]Division of Infectious Diseases, Academic Medical Centre, University of Amsterdam, [6]Amsterdam Institute for Global Health and Development, [7]Department of Internal Medicine, Kennemer Gasthuis, Haarlem, and [8]Department of Infectious Diseases, Centre for Infectious Diseases, Leiden University Medical Centre, The Netherlands

Background. Chronic kidney disease (CKD) is an important comorbidity during human immunodeficiency virus (HIV) infection. Historically, HIV-associated nephropathy has been the predominant cause of CKD and has primarily been observed in people of African ancestry. This study aims to investigate the role of ethnicity in relation to CKD risk in recent years.

Methods. Analyses were performed including 16 836 patients from the Dutch AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. Baseline was defined as the first available creatinine level measurement after 1 January 2007; CKD was defined as a glomerular filtration rate of <60 mL/min/1.73 m^2. The associations between ethnicity and both prevalent CKD at baseline and incident CKD during follow-up were analyzed.

Results. The prevalence of baseline CKD was 2.7% (460 of 16 836 patients). Birth in a sub-Saharan African country (hereafter, "SSA origin") was significantly associated with baseline CKD (adjusted odds ratio 1.49; 95% confidence interval [CI], 1.04–2.13). During follow-up (median duration, 4.7 years; interquartile range, 2.4–5.2), the rate of incident CKD was 6.0 events per 1000 person-years. The risk of newly developing CKD was similar between patients of SSA origin and those born in Western Europe, Australia, or New Zealand (adjusted hazard ratio, 1.00; 95% CI, .63–1.59).

Conclusions. Among HIV-infected patients in the Netherlands, being of SSA origin was associated with a higher baseline CKD prevalence but had no impact on newly developing CKD over time. This suggests a shift in the etiology of CKD from HIV-associated nephropathy toward other etiologies.

Keywords. HIV; ethnicity; chronic kidney disease; sub-Saharan African origin; genetic predisposition; estimated glomerular filtration rate; renal function.

Chronic kidney disease (CKD) is an important comorbidity in people living with human immunodeficiency virus (HIV). In the past, the main cause of renal function impairment in HIV-infected people was HIV-associated nephropathy, characterized by high-level proteinuria and rapid decline to end-stage renal disease (ESRD). Fortunately, the introduction of combination antiretroviral therapy (cART) has markedly decreased the incidence of HIV-associated nephropathy [1, 2].

However, the spectrum of HIV-related CKD has changed, and new kidney-related conditions have emerged instead since the introduction of antiretroviral therapy (ART). With the improved effectiveness of treatment, HIV infection has become a chronic disease, with patients needing lifelong ART. Various nephrotoxic effects of cART have been described, such as tubular dysfunction associated with tenofovir use [3, 4]. Moreover, it has been suggested that people with HIV

Received 9 November 2014; accepted 9 January 2015; electronically published 18 January 2015.

Presented in part: State of the cART-II, Amsterdam, The Netherlands, October 2013; 7th Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention, and Treatment, Amsterdam, The Netherlands, 19 November 2013.

[a]Study group members are listed at the end of the text.

Correspondence: Annelot F. Schoffelen, MD, Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht, PO Box 85500, F.02.126, 3508 GA Utrecht, The Netherlands (a.f.schoffelen@umcutrecht.nl).

The Journal of Infectious Diseases® 2015;212:264–74

DOI: 10.1093/infdis/jiv026

infection age more rapidly than people without HIV infection [5, 6]. Various processes, including chronic inflammation, immune dysregulation, and thrombotic activation, may lead to accelerated atherosclerosis [7, 8]. As a result, cardiovascular risk factors and comorbidities, such as hypertension and dyslipidemia, are seen more often in people with HIV infection, leading to microvascular disease and decline of renal function. This shift toward a different origin of HIV-associated CKD has come to light in recent years, owing to the increased aging of HIV-infected individuals [1].

Throughout the HIV epidemic, racial differences have been described as playing a role in the susceptibility to renal failure. CKD was predominantly observed in individuals of African ancestry, who progress more rapidly to ESRD, compared with people of non-African ancestry [9, 10].

It is less clear, however, whether and how the impact of ethnicity on the risk of developing CKD may have changed with time. Various observational studies regarding CKD among HIV-infected patients and the role of ethnicity have been published in the past 5 years. Most of these studies were performed in the United States and were conducted in the early years after the introduction of cART, when HIV-associated nephropathy still accounted for a substantial part of renal impairment [10–12]. We therefore undertook an analysis to assess the impact of ethnicity on the development of CKD in HIV-infected patients enrolled in the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort in the Netherlands.

METHODS

The observational ATHENA cohort follows HIV-positive patients registered for care in one of the 27 designated treatment centers in the Netherlands [13]. The ATHENA database includes information on patient demographic characteristics; clinical, immunological, and virological parameters; detailed treatment data; and data on adverse events, AIDS-defining clinical events, and select non–AIDS-defining clinical events during follow-up. Laboratory findings, including creatinine levels, are also collected in the ATHENA database. Creatinine levels have been routinely collected since January 2007 for all patients in the cohort.

All patients aged ≥16 years with available data on creatinine levels between 1 January 2007 and 1 February 2013 and available demographic data were selected for analysis. To ensure that renal function had been evaluated during HIV infection, patients were excluded if their creatinine level was measured >1 month before the registered date of HIV diagnosis (ie, the date on which a positive result of an HIV test was obtained) or the first available $CD4^+$ T-cell count measurement. Kidney function was assessed by estimating creatinine clearance and, as such, the glomerular filtration rate (GFR), using the CG equation (hereafter, CG-eGFR), standardized for body surface area. Results yielded by the body surface area–corrected CG equation were shown to be similar to those yielded by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation among HIV-infected individuals [14, 15]. As a result of the demonstrated outcome resemblances between both estimations for this study population, it was considered appropriate to apply the definitions of the Kidney Disease: Improving Global Outcomes guidelines, which make use of the CKD-EPI equation to assess renal function [16]. Accordingly, CKD was defined as a CG-eGFR of <60 mL/min/1.73 m^2 or on the basis of initiation of renal dialysis or receipt of a kidney transplant. For incident CKD in the follow-up period, a CG-eGFR of <60 mL/min/1.73 m^2 had to be confirmed by a consecutive measurement performed at least 90 days afterward.

Each patient's region of origin, defined as the registered country of birth, was used as proxy for ethnicity. Patients were categorized accordingly into one of the following groups: patients of Western European origin (including Australia and New Zealand), patients of sub-Saharan African (SSA) origin, patients of Asian and Pacific origin, and patients of other origin (ie, Latin America and the Caribbean, Central and Eastern Europe, North America, and North Africa and the Middle East). Subjects were classified as previously in care if they had been in care before 1 January 2007, determined by their date of registration in the ATHENA cohort or the date of their first available $CD4^+$ T-cell count measurement (whichever came first), in contrast to those who came into care after 1 January 2007, who were classified as new to care. The majority of patients new to care were expected to be treatment naive, but they could have started ART before entering the ATHENA database. Baseline was defined as the date of the first available creatinine level measurement after 1 January 2007, regardless of being previously in care or new to care. Both cross-sectional analyses at baseline and longitudinal analyses were performed to evaluate the association between ethnicity and both prevalent and incident CKD.

Cross-sectional Analysis

Logistic regression models were used to determine the association between region of origin and the prevalence of CKD at baseline. Adjusted odds ratios (aORs) were calculated by adjusting for demographic variables (age at the time of HIV diagnosis and sex), mode of HIV transmission, coinfection with hepatitis B virus (HBV; defined on the basis of HBV surface antigen positivity) and hepatitis C virus (HCV; defined on the basis of HCV RNA positivity or, if missing, HCV-antibody positivity), and well-known cardiovascular risk factors, including hypertension (registered as having hypertension by a treating physician or use of antihypertensive medication), dyslipidemia (registered as having dyslipidemia by a treating physician or use of lipid-level-lowering medication), previous cardiovascular event, diabetes mellitus, and smoking. Furthermore, aORs were adjusted for the use of nonantiretroviral nephrotoxic medication, previous start of cART, concurrent use of atazanavir and tenofovir,

HIV load, and $CD4^+$ T-cell count. All time-dependent variables were assessed at baseline. Baseline $CD4^+$ T-cell count was used instead of nadir $CD4^+$ T-cell count, because patients new to care only had one $CD4^+$ T-cell count measurement available at baseline. Separate subgroup analyses were performed for patients previously in care and those new to care, to investigate whether already being in care influences the prevalence of decreased renal function and its related factors.

Longitudinal Analysis

Incident CKD was evaluated by performing longitudinal analysis among patients with a CG-eGFR of >60 mL/min/1.73 m^2 at baseline. Baseline was defined as described previously. End of follow-up was defined as the last visit date before 1 February 2013, development of CKD, or death. Patients with an CG-eGFR of <60 mL/min/1.73 m^2 at baseline were excluded for the purpose of this analysis. Incidence rates of CKD were calculated per 1000 person-years of follow-up.

The association between region of origin and CKD incidence was evaluated by using Cox proportional hazards models. Adjusted hazard ratios (aHRs) were calculated by correcting for baseline CG-eGFR and other independent variables, which included mostly the same variables described for cross-sectional analysis. For incidence analysis, we used nadir $CD4^+$ T-cell count. Moreover, the use of tenofovir was examined more thoroughly by examining the influence of both prior and current exposure to tenofovir. Again, subgroup analyses were performed on patients previously in care and those new to care. Furthermore, patients with a baseline CG-eGFR of >90 mL/min/1.73 m^2 were analyzed separately from those with a baseline value of 60–90 mL/min/1.73 m^2, to gain more insight into the influence of baseline CG-eGFR on CKD incidence rates and the association with other independent variables.

Patient characteristics were described by calculating medians (with interquartile ranges [IQRs]) for continuous variables and proportions (as percentages) for categorical variables. Continuous data were compared between regions of origin, using the Student *t* test or the Mann–Whitney *U* test. The distributions of categorical variables were compared using the χ^2 test. For all multivariable analyses, determinants associated with the outcome that had a *P* value of <.10 in univariate analysis were included. A *P* value of < .05 was considered statistically significant. Assumptions of proportional hazards with respect to region of origin were evaluated and met. Statistical analyses were done using SPSS, version 20.0. Data were analyzed and reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist for observational studies [17].

RESULTS

For the purpose of the current analyses, 16 900 HIV-infected patients were selected, all with at least 1 available creatinine level measurement between 1 January 2007 and 1 February 2013. Sixty-four patients (0.4%) were excluded because the date of first available creatinine level measurement was >1 month before the registered date of HIV diagnosis or the first available $CD4^+$ T-cell count measurement, resulting in 16 836 subjects available for analysis. Thirty-eight percent of patients (6424 of 16 836) were new to care after 1 January 2007, with 91% (5869 of 6424) who were treatment naive, and 62% (10 412 of 16 836) were previously in care, including 19% (1952 of 10 412) who were treatment naive.

Two-thirds of patients (11 125 of 16836) were of Western European origin and 13% (2232/16 836) originated from SSA. Compared with patients of Western European origin, patients of SSA origin included more females (50.1% [1118 of 2232] vs 8.9% [992 of 11 125]; $P < .05$), were younger (36.9 years [IQR, 30.5–43.5 years] vs 44.0 years [IQR, 37.1–51.1 years]; $P < .05$), and had more-compromised immune systems, as shown by the lower baseline $CD4^+$ T-cell count (380 cells/μL [IQR, 230–540 cells/μL] vs 460 cells/μL [IQR, 302–640 cells/μL]; $P < .05$). A more detailed description of the subjects can be found in Table 1.

Cross-sectional Analysis

Cross-sectional analysis of CKD at baseline showed a prevalence of 2.7% (460 of 16 836). The proportion of patients having a CG-eGFR of <60 mL/min/1.73 m^2 among those new to care was lower than that among patients previously in care (1.9% [121 of 6424] vs 3.3% [339 of 10 412]; $P < .05$). The prevalence among SSA patients (2.8% [63 of 2232]) was similar to that among patients of Western European origin (2.6% [286 of 11 125]), with an OR for having CKD of 1.10 (95% CI, .84–1.45; $P = .50$).

For multivariable analysis, 958 of 16 836 patients (5.7%) were excluded because of missing values, predominantly regarding HBV and HCV coinfection, and fewer because of missing data on baseline $CD4^+$ T-cell count and start date of cART. Multivariable logistic regression analysis was therefore performed on 15 878 patients, 425 (2.7%) of whom had a CG-eGFR of <60 mL/min/1.73 m^2.

In contrast to univariate analysis, multivariable analysis showed an association between SSA origin and CKD prevalence after adjustment for multiple independent variables (aOR, 1.49; 95% CI, 1.04–2.13). Patients originating from Asia or the Pacific also showed a higher risk of having a CG-eGFR of <60 mL/min/1.73 m^2, compared with patients of Western European origin (aOR, 2.27; 95% CI, 1.46–3.55). Several other factors were associated with the prevalence of CKD at baseline (Table 2). Although there was an association between prior start of cART and CKD prevalence in univariate analysis, this was no longer present in multivariable analysis. HIV load was excluded from multivariable analysis, because of interaction with the covariate "prior start of cART." Repeated

Table 1. Cohort Description at Baseline

Characteristic	Overall	Western Europe, Australia, N Zealand	Sub-Saharan Africa	Asia and the Pacific	Other[a]
Patients, no. (%)	16 836	11 125 (66.1)	2232 (13.3)	621 (3.7)	2858 (17.0)
Age, y	42.2 (35.1–49.1)	44.0 (37.1–51.1)	36.9 (30.5–43.5)	38.6 (32.8–46.1)	40.0 (33.2–46.1)
Female sex	2823 (16.8)	992 (8.9)	1118 (50.1)	191 (30.8)	522 (18.3)
Weight, kg	74 (65.5–83)	75 (67.3–84.0)	71.5 (63.0–80.9)	60 (54–69.5)	72 (64–80.6)
BMI[b]	23.4 (21.3–25.9)	23.1 (21.2–25.4)	24.9 (22.4–27.9)	22.1 (20.2–24.3)	23.7 (21.5–26.4)
Mode of HIV transmission					
Homosexual sex	10 388 (61.7)	8332 (74.9)	134 (6.0)	338 (54.4)	1584 (55.4)
Heterosexual sex	4887 (29.0)	1859 (16.7)	1812 (81.2)	221 (35.6)	995 (34.8)
IDU or blood (products)	481 (2.9)	368 (3.3)	7 (0.3)	15 (2.4)	91 (3.2)
Other[c]	1080 (6.4)	566 (5.1)	279 (12.5)	47 (7.6)	188 (6.6)
New to care[d]	6424 (38.2)	4244 (38.1)	750 (33.6)	243 (39.1)	1187 (41.5)
cART history					
Started before baseline	8950 (53.4) (n = 16 771)	5725 (51.6) (n = 11 097)	1384 (62.4) (n = 2218)	343 (55.4) (n = 619)	1498 (52.8) (n = 2837)
History of receipt at baseline, y[e]	5.9 (2.6–9.3) (n = 8950)	6.7 (2.9–9.8) (n = 5725)	4.4 (2.3–6.9) (n = 1384)	5.6 (2.3–8.5) (n = 343)	5.2 (2.1–8.6) (n = 1498)
$CD4^+$ T-cell count, cells/μL					
Nadir	210 (90–320) (n = 16 787)	220 (100–328) (n = 11 095)	167 (70–270) (n = 2221)	170 (50–281) (n = 621)	210 (80–330) (n = 2850)
At baseline	440 (280–620) (n = 16 796)	460 (302–640) (n = 11 095)	380 (230–540) (n = 2230)	380 (230–560) (n = 620)	420 (260–620) (n = 2851)
HIV load, $\log_{10}$ copies/mL	3.00 (1.70–4.73) (n = 16 685)	3.26 (1.70–4.80) (n = 11 027)	1.99 (1.70–4.35) (n = 2208)	2.54 (1.70–4.62) (n = 616)	3.19 (1.70–4.63) (n = 2834)
CG-eGFR, mL/min/1.73 m^2[f]					
>90	13 713 (81.5)	9094 (81.7)	1895 (84.9)	406 (65.4)	2318 (81.1)
80–90	1377 (8.2)	922 (8.3)	143 (6.4)	80 (12.9)	232 (8.1)
70–80	838 (5.0)	538 (4.8)	91 (4.1)	71 (11.4)	138 (4.8)
60–70	448 (2.7)	285 (2.6)	40 (1.8)	32 (5.2)	91 (3.2)
<60	460 (2.7)	286 (2.6)	63 (2.8)	32 (5.2)	79 (2.8)
HBsAg positive	1031 (6.4) (n = 16 221)	585 (5.5) (n = 10 682)	212 (9.8) (n = 2163)	53 (8.8) (n = 602)	181 (6.5) (n = 2774)
HCV positive[g]	1213 (7.6) (n = 15 976)	865 (8.2) (n = 10 571)	86 (4.1) (n = 2076)	47 (8.0) (n = 590)	215 (7.8) (n = 2739)
Hypertension[h]	1636 (9.7)	1107 (10.0)	226 (10.1)	43 (6.9)	260 (9.1)
Dyslipidemia[i]	1093 (6.5)	866 (7.8)	55 (2.5)	35 (5.6)	137 (4.8)
Past history of cardiovascular event	296 (1.8)	234 (2.1)	15 (0.7)	13 (2.1)	34 (1.2)
Diabetes mellitus	537 (3.2)	321 (2.9)	84 (3.8)	18 (2.9)	114 (4.0)
History of smoking	8126 (48.3)	6030 (54.2)	453 (20.3)	251 (40.4)	1392 (48.7)
Nephrotoxic medication use[j]	6088 (36.2)	3867 (34.8)	945 (42.3)	248 (39.9)	1028 (36.0)
Tenofovir use	4244 (25.2)	2735 (24.6)	583 (26.1)	171 (27.5)	755 (26.4)
Atazanavir use	984 (5.8)	636 (5.7)	126 (5.6)	36 (5.8)	186 (6.5)

Data are no. (%) of patients or median value (interquartile range). Baseline is defined as the date of first available creatinine level measurement after 1 January 2007. In case of missing data, the no. of included subjects is given.

Abbreviations: cART, combination antiretroviral therapy; HBsAg, hepatitis B virus surface antigen; HIV, human immunodeficiency virus; IDU, injection drug use.

[a] Defined as Latin America and the Caribbean, Central and Eastern Europe, North America, and North Africa and the Middle East.

[b] Body mass index (BMI) is defined as the weight in kilograms divided by the height in meters squared.

[c] Defined as vertical transmission, unknown, or other.

[d] Defined as having come into care after 1 January 2007.

[e] Data are for patients receiving cART at baseline.

[f] The glomerular filtration rate was estimated by the Cockcroft-Gault formulation (CG-eGFR) and is standardized for body surface area.

[g] Defined as positive for hepatitis C virus (HCV) RNA or, if missing, as positive for HCV antibody.

[h] Registered as having hypertension by a physician at the treatment center or use of antihypertensive medication.

[i] Registered as having dyslipidemia by a physician at the treatment center or use of lipid-lowering medication.

[j] Defined as nonantiretroviral medication with potential nephrotoxicity.

Table 2. Prevalence Analysis of Chronic Kidney Disease (CKD), by Patient Characteristic at Baseline

	Univariate Analysis		Multivariable Analysis	
Determinant	OR (95% CI)	*P* Value[a]	Adjusted OR (95% CI)	*P* Value[a]
Age, y	1.10 (1.09–1.11)	<.001	1.09 (1.08–1.10)	<.001
Female sex	2.09 (1.70–2.57)	<.001	2.11 (1.59–2.81)	<.001
Region of origin				
Western Europe, Australia, New Zealand	1.00 (Reference)	. . .	1.00 (Reference)	. . .
Sub-Saharan Africa	1.10 (.84–1.45)	.50	1.49 (1.04–2.13)	.03
Asia and the Pacific	2.06 (1.42–3.00)	<.001	2.27 (1.46–3.55)	<.001
Other[b]	1.08 (.84–1.39)	.56	1.26 (.94–1.70)	.12
Mode of HIV transmission				
Homosexual sex	1.00 (Reference)	. . .	1.00 (Reference)	. . .
Heterosexual sex	2.34 (1.89–2.88)	<.001	1.33 (.98–1.79)	.07
IDU or blood (products)	4.61 (3.17–6.70)	<.001	2.30 (1.36–3.88)	.002
Other[c]	3.70 (2.76–4.96)	<.001	1.96 (1.37–2.81)	<.001
New to care[d]	0.57 (.46–.70)	<.001	0.88 (.59–1.30)	.51
Started cART before baseline	2.25 (1.83–2.76)	<.001	1.31 (.89–1.92)	.18
$CD4^+$ T-cell count, cells/μL				
≥350	1.00 (Reference)	. . .	1.00 (Reference)	. . .
200–350	1.90 (1.51–2.39)	<.001	1.78 (1.38–2.31)	<.001
100–200	2.65 (1.97–3.56)	<.001	2.26 (1.60–3.19)	<.001
50–100	3.06 (2.03–4.62)	<.001	3.12 (1.94–5.02)	<.001
<50	3.97 (2.86–5.51)	<.001	5.18 (3.39–7.90)	<.001
HIV load, $\log_{10}$ copies/mL	0.85 (.80–.90)	<.001		
HBsAg positive	1.31 (.92–1.85)	.13		
HCV positive[e]	2.18 (1.66–2.86)	<.001	1.54 (1.06–2.24)	.03
Hypertension[f]	7.70 (6.35–9.34)	<.001	3.31 (2.58–4.25)	<.001
Dyslipidemia[g]	3.73 (2.94–4.74)	<.001	1.16 (.85–1.59)	.35
Past history of cardiovascular event	6.57 (4.69–9.21)	<.001	1.21 (.78–1.87)	.39
Diabetes mellitus	4.28 (3.17–5.77)	<.001	0.99 (.69–1.44)	.97
History of smoking	1.01 (.84–1.21)	.93		
Nephrotoxic medication use[h]	3.95 (3.24–4.82)	<.001	1.43 (1.09–1.86)	.009
Tenofovir use	1.36 (1.12–1.67)	.002	0.95 (.74–1.22)	.69
Atazanavir use	2.31 (1.73–3.08)	<.001	1.39 (.99–1.97)	.06

There were 425 cases of CKD, defined as an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2, at baseline among 15 878 patients evaluated. Univariate and multivariable analyses were performed using a logistic regression model. Baseline is defined as the date of first available creatinine level measurement after 1 January 2007. The GFR was estimated by the Cockcroft-Gault formulation (CG-eGFR) and is standardized for body surface area.

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HBsAg, hepatitis B virus surface antigen; HIV, human immunodeficiency virus; IDU, injection drug use; OR, odds ratio.

[a] Statistically significant differences were those with a *P* value of <.05.

[b] Defined as Latin America and the Caribbean, Central and Eastern Europe, North America, and North Africa and the Middle East.

[c] Defined as vertical transmission, unknown, or other.

[d] Defined as having come into care after 1 January 2007.

[e] Defined as positive for hepatitis C virus (HCV) RNA or, if missing, as positive for HCV antibody.

[f] Registered as having hypertension by a physician at the treatment center or use of antihypertensive medication.

[g] Registered as having dyslipidemia by a physician at the treatment center or use of lipid-lowering medication.

[h] Defined as nonantiretroviral medication with potential nephrotoxicity.

multivariable analyses with HIV load included instead of "prior start of cART" showed similar results, and it was not associated with CKD.

Subgroup analyses among the groups previously in care and new to care showed similar results, although there was no significant association between CKD prevalence and SSA origin in the group of patients previously in care after adjustment for covariates, (aOR 1.25 [95% CI, .80–1.93, *P* = .33]), but SSA patients new to care still had an increased risk of having a CG-eGFR of <60 mL/min/1.73 m^2 (aOR, 1.91; 95% CI, 1.06–3.45).

Longitudinal Analysis

Longitudinal analysis of CKD incidence was performed after excluding the 460 patients with a CG-eGFR of <60 mL/min/1.73 m^2 at baseline. The median duration of follow-up was 4.7 years (IQR, 2.4–5.2 years), resulting in a total follow-up duration of 62 192 person-years.

During follow-up, CKD occurred in 374 patients (2.3%), resulting in an incidence of 6.0 events per 1000 person-years. Median time of follow-up for the patients developing CKD was 5.1 years (IQR, 4.6–5.5 years), which was somewhat longer than in the group that did not develop CKD (4.6 years [IQR, 2.3–5.2 years]; $P < .05$).

Cox proportional hazards analysis was performed on 15 160 patients, resulting from the total group of 16 836 patients minus the 460 patients with decreased CG-eGFR at baseline and minus 1216 patients (7.2%) with missing data (mainly on HBV or HBC coinfection). Among those 15 160 subjects, 348 (2.3%) developed CKD during follow-up.

In univariate analysis, SSA origin was not a risk factor for developing CKD, compared with Western European origin. Surprisingly, patients of SSA origin even showed a reduced HR of 0.49 (95% CI, .32–.74) for development of CKD.

Baseline CG-eGFR was strongly associated with a risk for incident CKD during follow-up. The proportion of patients new to care had a lower CKD incidence than those previously in care. Older and female subjects were also more prone to develop CKD. In contrast to atazanavir, on univariate analysis concurrent use of tenofovir was associated with a lower risk of developing CKD, compared with patients who had never used tenofovir or those previously exposed to but not currently receiving tenofovir. Start of cART prior to the event date (or the end of follow-up) was not associated with CKD incidence.

After adjustment for all included variables in multivariable analysis, no association between originating from SSA and risk of CKD was found, compared with patients of Western European origin (aHR, 1.00 [95% CI, .63–1.59]; $P = .98$).

CG-eGFR at baseline remained strongly associated with CKD incidence. Being new to care was not related to a lower incidence of CKD anymore. After adjustment for independent variables, concurrent use of tenofovir was no longer associated with CKD incidence, while previous exposure was related to lower CKD incidence. All outcomes from both uni- and multivariable analyses are presented in Table 3.

Subgroup analyses of the subjects new to care versus those previously in care did not show any other risk factors for developing CKD among both groups, compared with the total group analysis.

Subgroup analyses were also performed on the patients with a CG-eGFR of >90 mL/min/1.73 m^2 at baseline, in contrast to those with a CG-eGFR of 60–90 mL/min/1.73 m^2 at baseline. Obviously, the incidence of CKD was much lower among the first group, with an incidence of 0.5% of patients (64 of 13 713) and 1.2 events per 1000 person-years, compared with 11.6% (310 of 2663) and 29.2 events per 1000 person-years. Again, after further analysis of the subgroups, patients from SSA did not have a higher risk for developing CKD, and no other new risk factors were identified.

DISCUSSION

This Dutch observational cohort study shows that HIV-infected patients originating from SSA had a higher baseline prevalence of impaired CG-eGFR (<60 mL/min/1.73 m^2) but did not have an increased risk of newly developing CKD, compared with patients of Western European origin, in the current cART era.

These new findings are in contrast to past observations, when black ethnicity was shown to be a risk factor for developing renal insufficiency among HIV-infected people. This is the first report to describe this subject in a well-defined large cohort with a substantial duration of follow-up, which reflects the actual incidence rates of CKD in recent years.

Various publications from the United States, starting follow-up in the 1990s, have reported a higher incidence of CKD among African American HIV-infected patients, as well as a higher risk for developing ESRD once diagnosed with chronic renal impairment [9–12]. Two studies from the United Kingdom, starting in 1998 and 1996, also described a higher rate of kidney disease progression and ESRD incidence among individuals of African ancestry, compared with patients of non-African ancestry [18, 19].

In contrast to those earlier reports, the follow-up in our study started more recently (in 2007), while most other studies describe cohorts originating from the 1990s, the earlier years of the HIV era. In that time, a substantial part of renal disease was attributable to HIV-associated nephropathy, which has been shown to be independently associated with African ethnicity, as host factors play a role in the occurrence of HIV-associated nephropathy. Certain *APOL1* genetic variants are known to cause increased genetic susceptibility for development of glomerulosclerosis in advanced HIV infection among Africans [20–22]. Fortunately, the incidence of HIV-associated nephropathy has decreased substantially since the introduction of cART. However, other causes of kidney disease have emerged, such as toxicity of antiretroviral medication and long-term effects of HIV infection.

The impact of ethnicity on kidney diseases such as HIV-associated nephropathy among new-to-care and thus mostly cART-naive HIV-infected people from SSA is reflected in this study, which shows that those patients are more likely to have impaired CG-eGFR at baseline. On the other hand, possibly, genetic susceptibility is of minor importance in the occurrence of CKD of other nature than HIV-associated nephropathy. This could explain the observation that patients of SSA origin and those of Western European origin have similar risks regarding newly developing CKD, despite the numbers at baseline.

Table 3. Incidence Analysis of Chronic Kidney Disease (CKD), by Patient Characteristic at the Time of CKD Diagnosis or the End of Follow-up

	Univariate Analysis		Multivariable Analysis	
Determinant	HR (95% CI)	*P* Value[a]	Adjusted HR (95% CI)	*P* Value[a]
Age, y	1.12 (1.11–1.13)	<.001	1.05 (1.04–1.07)	<.001
Female sex	1.72 (1.36–2.17)	<.001	1.75 (1.27–2.41)	.001
Region of origin				
Western Europe, Australia, New Zealand	1.00 (Reference)	. . .	1.00 (Reference)	. . .
Sub-Saharan Africa	0.49 (.32–.74)	.001	1.00 (.63–1.59)	.98
Asia and the Pacific	1.27 (.79–2.05)	.32	1.05 (.63–1.74)	.85
Other[b]	1.05 (.80–1.38)	.73	0.98 (.73–1.32)	.90
Mode of HIV transmission				
Homosexual sex	1.00 (Reference)	. . .	1.00 (Reference)	. . .
Heterosexual sex	1.52 (1.21–1.92)	<.001	0.94 (.68–1.30)	.71
IDU or blood (products)	4.62 (3.23–6.61)	<.001	2.28 (1.35–3.84)	.002
Other[c]	2.07 (1.46–2.96)	<.001	1.35 (.92–1.97)	.13
New to care[d]	0.65 (.50–.86)	.002	1.27 (.95–1.71)	.10
cART history				
Started before event date	0.97 (.64–1.47)	.88		
History of receipt before event date, y[e]	0.98 (.96–1.00)	.13		
Nadir $CD4^+$ T-cell count, cells/μL				
≥350	1.00 (Reference)	. . .	1.00 (Reference)	. . .
200–350	1.18 (.77–1.81)	.44	1.29 (.82–2.01)	.27
100–200	1.93 (1.27–2.94)	.002	1.32 (.84–2.06)	.23
50–100	3.21 (2.08–4.95)	<.001	1.73 (1.09–2.75)	.02
<50	3.31 (2.20–5.00)	<.001	1.75 (1.13–2.72)	.01
HIV load, $\log_{10}$ copies/mL	0.92 (.80–1.07)	.27		
CG-eGFR at baseline, mL/min/1.73 m^{2f}	0.90 (.90–.91)	<.001	0.92 (.92–.93)	<.001
HBsAg positive	1.57 (1.09–2.25)	.02	1.45 (1.00–2.11)	.05
HCV positive[g]	1.68 (1.28–2.19)	<.001	1.18 (.81–1.71)	.39
Hypertension[h]	3.52 (2.87–4.31)	<.001	1.41 (1.05–1.88)	.02
Dyslipidemia[i]	2.26 (1.79–2.86)	<.001	0.90 (.69–1.18)	.45
Past history of cardiovascular event	3.71 (2.71–5.09)	<.001	1.07 (.75–1.52)	.72
Diabetes mellitus	3.20 (2.39–4.28)	<.001	1.71 (1.25–2.36)	.001
History of smoking	1.24 (1.01–1.52)	.04	1.29 (1.03–1.60)	.03
Nephrotoxic medication use[j]	3.39 (2.75–4.17)	<.001	1.30 (.98–1.73)	.07
Atazanavir use	1.53 (1.18–1.99)	.001	1.37 (1.04–1.80)	.02
Tenofovir				
Never started	1.00 (Reference)	. . .	1.00 (Reference)	. . .
Started, currently receiving	0.69 (.54–.88)	.003	0.86 (.66–1.12)	.26
Started, not currently receiving	1.12 (.78–1.59)	.54	0.68 (.47–1.00)	.047

There were 348 cases of CKD, defined as an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 (confirmed in a consecutive measurement at least 90 days afterward) or the start of renal dialysis or kidney transplantation, diagnosed between 1 January 2007 and 1 February 2013 among 15 160 patients evaluated. Univariate and multivariable analyses were performed using a Cox proportional hazards model. Event date is defined as the date of CKD diagnosis or the end of follow-up. Baseline is defined as the date of first available creatinine level measurement after 1 January 2007.

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HBsAg, hepatitis B virus surface antigen; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injection drug use.

[a] Statistically significant differences were those with a *P* value of <.05.

[b] Defined as Latin America and the Caribbean, Central and Eastern Europe, North America, and North Africa and the Middle East.

[c] Defined as vertical transmission, unknown, or other.

[d] Defined as having come into care after 1 January 2007.

[e] Data are for patients receiving cART at the event date.

[f] The GFR was estimated by the Cockcroft-Gault formulation (CG-eGFR) and is standardized for body surface area.

[g] Defined as positive for hepatitis C virus (HCV) RNA or, if missing, as positive for HCV antibody.

[h] Registered as having hypertension by a physician at the treatment center or use of antihypertensive medication.

[i] Registered as having dyslipidemia by a physician at the treatment center or use of lipid-lowering medication.

[j] Defined as nonantiretroviral medication with potential nephrotoxicity.

Few earlier studies on smaller cohorts underline our conclusions that HIV-infected patients from African ancestry without decreased eGFR at baseline have comparable hazards for incident CKD and renal function decline as patients of Western European origin [23, 24].

A recent report of the D:A:D study described the association between antiretroviral exposure and other risk factors with the development of renal impairment in HIV-infected patients in cohorts from Europe, the United States, and Australia starting follow-up in 2004 [25]. African ancestry was not associated with CKD, but the power to detect such an association was low, as much information regarding ethnicity was lacking. Here, the region of origin, as a proxy for ethnicity, was known for all patients.

The overall incidence of CKD in our cohort was remarkably higher than the observed incidence in the above mentioned D:A:D cohort (2.3% with 6.0 events per 1000 person-years vs 0.6% with 1.3 cases per 1000 person-years) [25]. However, in the D:A:D cohort study, only patients with a creatinine clearance rate at baseline of >90 mL/min/1.73 m^2 were included, in contrast to our cohort, where all patients had a baseline CG-eGFR of >60 mL/min/1.73 m^2. In the subgroup analysis involving patients with a baseline CG-eGFR of >90 mL/min/1.73 m^2, incidence rates similar to those in the D:A:D study were found. Evidently, patients with a mildly decreased CG-eGFR (60–90 mL/min/1.73 m^2) have a higher risk of progression to CKD during follow-up than those with a CG-eGFR of >90 mL/min/1.73 m^2 at baseline. However, patients with a mildly decreased CG-eGFR account for a substantial part of the HIV-infected population, as can be seen in our study, in which it composed almost 16% of the total group, in line with other reports [4, 26].

No association was found between concurrent use of tenofovir and higher CKD risk in multivariable analysis, unlike earlier reports [3, 4, 25]. This is probably due to increased knowledge on tubular toxicity of tenofovir, which may result in keeping only those patients receiving tenofovir without a preexisting high-risk profile for developing kidney disease and who have shown to have stable renal function while using the drug.

Strengths of this study include the use of a well-defined cohort of HIV-infected patients followed prospectively, whose data are recorded in a standardized manner. In addition, the number of patients included in the analyses is large. It is one of the first studies describing CKD incidence in recent years, when the influence of HIV-associated nephropathy has diminished, compared with the earlier years of the HIV epidemic. Only patients with a CG-eGFR of >60 mL/min/1.73 m^2 at baseline were included in longitudinal analyses, giving a realistic view on incidence rates of newly developed CKD in the current era of HIV treatment.

There are some limitations to this study, as well. We used region of origin as a proxy for ethnicity. We expect these factors to greatly overlap, as has been described in literature, but small inconsistencies, causing variety of ethnicity within the compared groups, cannot be ruled out [27]. There was a considerable duration of follow-up, with a median of 4.7 years, but a longer duration of follow-up is warranted to learn more about the long-term CKD incidence during chronic HIV infection. Furthermore, only 1 creatinine level measurement was used for cross-sectional analyses of CKD at baseline, potentially leading to an overestimation of the true prevalence. On the other hand, in incidence analyses, impaired CG-eGFR had to be confirmed in a consecutive measurement, thereby decreasing the chance that certain cases were depicted as CKD while renal function had improved at a later stage. The definition of CKD also included patients starting renal dialysis without having a confirmed CG-eGFR of <60 mL/min/1.73 m^2 after at least 90 days. Possibly, those patients might have developed acute renal failure resulting from acute illness, and thereby the number of CKD cases could have been overestimated. However, only 6 patients started dialysis without having had an impaired CG-eGFR >90 days previously. Another limitation is the lack of data on tubular function. Since subjects receiving treatment with tenofovir could develop proximal tubulopathy without experiencing an eGFR decline, it is possible that not all cases of tenofovir-related toxicity were identified.

In summary, this Dutch observational cohort study shows that SSA origin is no longer a risk factor for the incidence of chronic renal impairment in HIV-infected patients, in contrast to the earlier years of the HIV epidemic. This may be caused by the shift in nature of CKD from HIV-associated nephropathy in the early days toward antiretroviral toxicity, combined with aging and cardiovascular diseases among chronically HIV-infected patients receiving long-term treatment. Host factors, such as those contributing to a higher genetic susceptibility to HIV-associated nephropathy among patients of black ethnicity, seem to be of lesser importance in the etiology of CKD nowadays.

Notes

Acknowledgments. We thank Rebecca Holman and Anouk M. Kesselring, for assisting in data collection; and Susan C. Aitken for contribution to the editing of the final, submitted version of the manuscript.

All authors have contributed to, seen, and approved the final, submitted version of the manuscript.

Financial support. This work was supported by the Netherlands Ministry of Health, Welfare, and Sport (grant to the AIDS Therapy Evaluation in the Netherlands database).

Potential conflicts of interest. A. F. S. reports receiving personal fees from Gilead Sciences and VIIV Healthcare and grants from Boehringer Ingelheim Pharmaceuticals, all outside the submitted work. C. S. reports receiving grants from the Netherlands Ministry of Health, Welfare, and Sport, National Institute for Public Health and the Environment, Centre for Infectious Disease Control during the conduct of the study. S. F. L. v. L. reports receiving personal fees from ViiV Healthcare, Virology Education, BMS, Gilead Sciences, MSD, Janssen-Cilag, all outside the submitted work. P. R. reports receiving grants from the Netherlands Ministry of Health, Welfare, and Sport, National Institute for Public Health and the Environment, Centre for Infectious Disease Control during the conduct of the study; and grants and other support from Gilead Sciences and Janssen Pharmaceutical and grants from ViiV Healthcare, Merck, and Bristol-Myers Squibb, all outside the submitted work. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Mallipattu SK, Salem F, Wyatt CM. The changing epidemiology of HIV-related chronic kidney disease in the era of antiretroviral therapy. Kidney Int **2014**; 86:259–65.
2. Berliner AR, Fine DM, Lucas GM, et al. Observations on a cohort of HIV-infected patients undergoing native renal biopsy. Am J Nephrol **2008**; 28:478–86.
3. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS **2012**; 26:867–75.
4. Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS **2010**; 24:1667–78.
5. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis **2011**; 53:1120–6.
6. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. Clin Infect Dis **2011**; 53:1130–9.
7. Neuhaus J, Jacobs DR Jr, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis **2010**; 201:1788–95.
8. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ **2009**; 338:288–92.
9. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. Racial differences in end-stage renal disease rates in HIV infection versus diabetes. J Am Soc Nephrol **2007**; 18:2968–74.
10. Lucas GM, Lau B, Atta MG, Fine DM, Keruly J, Moore RD. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. J Infect Dis **2008**; 197:1548–57.
11. Kalayjian RC, Lau B, Mechekano RN, et al. Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care. AIDS **2012**; 26:1907–15.
12. Jotwani V, Li Y, Grunfeld C, Choi AI, Shlipak MG. Risk factors for ESRD in HIV-infected individuals: traditional and HIV-related factors. Am J Kidney Dis **2012**; 59:628–35.
13. van Sighem A, Gras L, Kesselring A, et al. Human immunodeficiency virus (HIV) infection in the Netherlands. Monitoring report 2013. http://www.hiv-monitoring.nl/files/4013/8443/2702/SHM_MReport2013_Appendix.pdf. Accessed 22 July 2014.
14. Vrouenraets SM, Fux CA, Wit FW, et al. A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. Clin Nephrol **2012**; 77:311–20.
15. Mocroft A, Ryom L, Reiss P, et al. A comparison of estimated glomerular filtration rates using Cockcroft-Gault and the Chronic Kidney Disease Epidemiology Collaboration estimating equations in HIV infection. HIV Med **2014**; 15:144–52.
16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. chapter 1: definition and classification of CKD. Kidney Int Suppl **2013**; 3:19–62.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet **2007**; 370:1453–7.
18. Bansi L, Hughes A, Bhagani S, et al. Clinical epidemiology of HIV-associated end-stage renal failure in the UK. AIDS **2009**; 23:2517–21.
19. Ibrahim F, Hamzah L, Jones R, Nitsch D, Sabin C, Post FA. Baseline kidney function as predictor of mortality and kidney disease progression in HIV-positive patients. Am J Kidney Dis **2012**; 60:539–47.
20. Freedman BI, Soucie JM, Stone SM, Pegram S. Familial clustering of end-stage renal disease in blacks with HIV-associated nephropathy. Am J Kidney Dis **1999**; 34:254–8.
21. Papeta N, Kiryluk K, Patel A, et al. APOL1 variants increase risk for FSGS and HIVAN but not IgA nephropathy. J Am Soc Nephrol **2011**; 22:1991–6.
22. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol **2011**; 22:2129–37.
23. Alves TP, Hulgan T, Wu P, et al. Race, kidney disease progression, and mortality risk in HIV-infected persons. Clin J Am Soc Nephrol **2010**; 5:2269–75.
24. Ganesan A, Krantz EM, Huppler Hullsiek K, et al. Determinants of incident chronic kidney disease and progression in a cohort of HIV-infected persons with unrestricted access to health care. HIV Med **2013**; 14:65–76.
25. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis **2013**; 207:1359–69.
26. Mocroft A, Ryom L, Begovac J, et al. Deteriorating renal function and clinical outcomes in HIV-positive persons. AIDS **2014**; 28:727–37.
27. Stronks K, Kulu-Glasgow I, Agyemang C. The utility of 'country of birth' for the classification of ethnic groups in health research: the Dutch experience. Ethn Health **2009**; 14:255–69.

APPENDIX

STUDY GROUP MEMBERS

Clinical Centers

Academic Medical Centre of the University of Amsterdam: *HIV treating physicians:* J. M. Prins (site coordinating physician), T. W. Kuijpers, H. J. Scherpbier, J. T. M. van der Meer, F. W. M. N. Wit, M. H. Godfried, P. Reiss, T. van der Poll, F. J. B. Nellen, J. M. A. Lange (deceased), S. E. Geerlings, M. van Vugt, D. Pajkrt, J. C. Bos, W. J. Wiersinga, M. van der Valk, A. Goorhuis, J. W. Hovius. *HIV nurse consultants:* J. van Eden, A. Henderiks, A. M. H. van Hes, M. Mutschelknauss, H. E. Nobel, F. J. J. Pijnappel, A. M. Westerman. *HIV clinical virologists/chemists:* S. Jurriaans, N. K. T. Back, H. L. Zaaijer, B. Berkhout, M. T. E. Cornelissen, C. J. Schinkel, X. V. Thomas. **Admiraal De Ruyter Ziekenhuis, Vlissingen:** *HIV treating physicians:* M. van den Berge, A. Stegeman. *HIV nurse consultants:* S. Baas. *HIV clinical virologists/chemists:* L. Sabbe, J. Goudswaard. **Catharina Ziekenhuis, Eindhoven:** *HIV treating physicians:* M. J. H. Pronk (site coordinating physician), H. S. M. Ammerlaan. *HIV nurse consultants:* E. M. H. M. Korsten-Vorstermans, E. S. de Munnik. *HIV clinical virologists/chemists:* A. R. Jansz, J. Tjhie. **Emma Kinderziekenhuis:** *HIV nurse consultants:* A. van der Plas, A. M. Weijsenfeld. **Erasmus Medisch Centrum, Rotterdam:** *HIV treating physicians:* M. E. van der Ende (site coordinating physician), T. E. M. S. de Vries-Sluijs, E. C. M. van Gorp, C. A. M. Schurink, J. L. Nouwen, A. Verbon, B. J. A. Rijnders, H. I. Bax, R. J. Hassing, M. van der Feltz. *HIV nurse consultants:* N. Bassant, J. E. A. van Beek, M. Vriesde, L. M. van Zonneveld. *Data collection:* A. de Oude-Lubbers, H. J. van den Berg-Cameron, F. B. Bruinsma-Broekman, J. de Groot, M. de Zeeuw-de Man, M. J. Broekhoven-Kruijne. *HIV clinical virologists/chemists:* M. Schutten, A. D. M. E. Osterhaus, C. A. B. Boucher. **Erasmus**

Medisch Centrum–Sophia, Rotterdam: *HIV treating physicians:* G. J. A. Driessen, A. M. C. van Rossum. *HIV nurse consultants:* L. C. van der Knaap, E. Visser. **Flevoziekenhuis, Almere:** *HIV treating physicians:* J. Branger (site coordinating physician). *HIV nurse consultant and data collection:* C. J. H. M. Duijf-van de Ven. **HagaZiekenhuis, Den Haag:** *HIV treating physicians:* E. F. Schippers (site coordinating physician), C. van Nieuwkoop, R. W. Brimicombe. *HIV nurse consultants:* J. M. van IJperen. *Data collection:* G. van der Hut. *HIV clinical virologist/chemist:* P. F. H. Franck. **HIV Focus Centrum (DC Klinieken):** *HIV treating physicians:* A. van Eeden (site coordinating physician). *HIV nurse consultants:* W. Brokking, M. Groot. *HIV clinical virologists/chemists:* M. Damen, I. S. Kwa. **Isala Klinieken, Zwolle:** *HIV treating physicians:* P. H. P. Groeneveld (site coordinating physician), J. W. Bouwhuis. *HIV nurse consultants:* J. F. van den Berg, A. G. W. van Hulzen. *Data collection:* G. L. van der Bliek, P. C. J. Bor. *HIV clinical virologists/chemists:* P. Bloembergen, M. J. H. M. Wolfhagen, G. J. H. M. Ruijs. **Kennemer Gasthuis, Haarlem:** *HIV treating physicians:* R. W. ten Kate (site coordinating physician), R. Soetekouw. *HIV nurse consultants:* N. Hulshoff, L. M. M. van der Prijt, M. Schoemaker. *Data collection:* N. Bermon. *HIV clinical virologists/chemists:* W. A. van der Reijden, R. Jansen. **Leids Universitair Medisch Centrum, Leiden:** *HIV treating physicians:* F. P. Kroon (site coordinating physician), S. M. Arend, M. G. J. de Boer, M. P. Bauer, H. Jolink, A. M. Vollaard. *HIV nurse consultants:* W. Dorama, C. Moons. *HIV clinical virologists/chemists:* E. C. J. Claas, A. C. M. Kroes. **Maasstad Ziekenhuis, Rotterdam:** *HIV treating physicians:* J. G. den Hollander (site coordinating physician), K. Pogany. *HIV nurse consultants:* M. Kastelijns, J. V. Smit, E. Smit. *Data collection:* M. Bezemer, T. van Niekerk. *HIV clinical virologists/chemists:* O. Pontesilli. **Maastricht UMC+, Maastricht:** *HIV treating physicians:* S. H. Lowe (site coordinating physician), A. Oude Lashof, D. Posthouwer. *HIV nurse consultants:* R. P. Ackens, J. Schippers, R. Vergoossen. *Data collection:* B. Weijenberg Maes. *HIV clinical virologists/chemists:* P. H. M. Savelkoul, I. H. Loo. **MC Zuiderzee, Lelystad:** *HIV treating physicians:* S. Weijer (site coordinating physician), R. El Moussaoui. *HIV Nurse Consultant:* M. Heitmuller. *Data collection:* M. Heitmuller. **Medisch Centrum Alkmaar:** *HIV treating physicians:* W. Kortmann (site coordinating physician), G. van Twillert (site coordinating physician), J. W. T. Cohen Stuart, B. M. W. Diederen. *HIV nurse consultant and data collection:* D. Pronk, F. A. van Truijen-Oud. *HIV clinical virologists/chemists:* W. A. van der Reijden, R. Jansen. **Medisch Centrum Haaglanden, Den Haag:** *HIV treating physicians:* E. M. S. Leyten (site coordinating physician), L. B. S. Gelinck. *HIV nurse consultants:* A. van Hartingsveld, C. Meerkerk, G. S. Wildenbeest. *HIV clinical virologists/chemists:* J. A. E. M. Mutsaers, C. L. Jansen. **Medisch Centrum Leeuwarden, Leeuwarden:** *HIV treating physicians:* M. G. A. van Vonderen (site coordinating physician), D. P. F. van Houte. *HIV nurse consultants:* K. Dijkstra, S. Faber. *HIV clinical virologists/chemists:* J Weel. **Medisch Spectrum Twente, Enschede:** *HIV treating physicians:* G. J. Kootstra (site coordinating physician), C. E. Delsing. *HIV nurse consultants:* M. van der Burg-van de Plas, H. Heins. *Data collection:* E. Lucas. **Onze Lieve Vrouwe Gasthuis, Amsterdam:** *HIV treating physicians:* K. Brinkman (site coordinating physician), P. H. J. Frissen, W. L. Blok, W. E. M. Schouten. *HIV nurse consultants:* A. S. Bosma, C. J. Brouwer, G. F. Geerders, K. Hoeksema, M. J. Kleene, I. B. van der Meché, A. J. M. Toonen, S. Wijnands. *HIV clinical virologists/chemists:* M. L. van Ogtrop. **Radboud UMC, Nijmegen:** *HIV treating physicians:* P. P. Koopmans, M. Keuter, A. J. A. M. van der Ven, H. J. M. ter Hofstede, A. S. M. Dofferhoff, R. van Crevel. *HIV nurse consultants:* M. Albers, M. E. W. Bosch, K. J. T. Grintjes-Huisman, B. J. Zomer. *HIV clinical virologists/chemists:* F. F. Stelma. *HIV clinical pharmacology consultant:* D. Burger. **Rijnstate, Arnhem:** *HIV treating physicians:* C. Richter (site coordinating physician), J. P. van der Berg, E. H. Gisolf. *HIV nurse consultants:* G. ter Beest, P. H. M. van Bentum, N. Langebeek. *HIV clinical virologists/chemists:* R. Tiemessen, C. M. A. Swanink. **Sint Elisabeth Hospitaal, Willemstad, Curaçao:** *HIV treating physicians:* C. Winkel, A. Durand, F. Muskiet, R. Voigt. *HIV nurse consultants:* I. van der Meer. **Sint Lucas Andreas Ziekenhuis, Amsterdam:** *HIV treating physicians:* J. Veenstra (site coordinating physician), K. D. Lettinga. *HIV nurse consultants:* M. Spelbrink, H. Sulman. *Data collection:* M. Spelbrink, E. Witte. *HIV clinical virologists/chemists:* M. Damen, P. G. H. Peerbooms. **Slotervaartziekenhuis, Amsterdam:** *HIV treating physicians:* J. W. Mulder, S. M. E. Vrouenraets, F. N. Lauw. *HIV nurse consultants:* M. C. van Broekhuizen, H. Paap, D. J. Vlasblom. *Data collection:* E. Oudmaijer Sanders. *HIV clinical virologists/chemists:* P. H. M. Smits, A. W. Rosingh. **Stichting Medisch Centrum Jan van Goyen, Amsterdam:** *HIV treating physicians:* D. W. M. Verhagen. *HIV nurse consultants:* J. Geilings. **St Elisabeth Ziekenhuis, Tilburg:** *HIV treating physicians:* M. E. E. van Kasteren (site coordinating physician), A. E. Brouwer. *HIV nurse consultants and data collection:* B. A. F. M. de Kruijf-van de Wiel, M. Kuipers, R. M. W. J. Santegoets, B. van der Ven. *HIV clinical virologists/chemists:* J. H. Marcelis, A. G. M. Buiting, P. J. Kabel. **Universitair Medisch Centrum Groningen, Groningen:** *HIV treating physicians:* W. F. W. Bierman (site coordinating physician), H. G. Sprenger, E. H. Scholvinck, S. van Assen, K. R. Wilting, Y. Stienstra. *HIV nurse consultants:* H. de Groot-de Jonge, P. A. van der Meulen, D. A. de Weerd. *HIV clinical virologists/chemists:* H. G. M. Niesters, A. Riezebos-Brilman. **Universitair Medisch Centrum Utrecht, Utrecht:** *HIV treating physicians:* A. I. M. Hoepelman (site coordinating physician), M. M. E. Schneider, T. Mudrikova, P. M. Ellerbroek, J. J. Oosterheert, J. E. Arends, R. E. Barth, M. W. M. Wassenberg. *HIV nurse consultants:* D. H. M. van Elst-Laurijssen,

L. M. Laan, E. E. B. van Oers-Hazelzet, J. Patist, S. Vervoort, *Data collection:* H. E. Nieuwenhuis, R. Frauenfelder. *HIV clinical virologists/chemists:* R. Schuurman, F. Verduyn-Lunel, A. M. J. Wensing. **VU Medisch Centrum, Amsterdam:** *HIV treating physicians:* E. J. G. Peters (site coordinating physician), M. A. van Agtmael, R. M. Perenboom, M. Bomers, J. de Vocht. *HIV nurse consultants:* L. J. M. Elsenburg. *HIV clinical virologists/chemists:* A. M. Pettersson, C. M. J. E. Vandenbroucke-Grauls, C. W. Ang. **Wilhelmina Kinderziekenhuis, UMCU, Utrecht:** *HIV treating physicians:* S. P. M. Geelen, T. F. W. Wolfs, L. J. Bont. *HIV nurse consultants:* N. Nauta.

Coordinating Center

Stichting HIV Monitoring *Director:* P. Reiss. *Data analysis:* D. O. Bezemer, L. A. J. Gras, A. I. van Sighem, C. Smit. *Data management and quality control:* S. Zaheri, M. Hillebregt, V. Kimmel, Y. Tong. *Data monitoring:* B. Lascaris, R. van den Boogaard, P. Hoekstra, A. de Lang, M. Berkhout, S. Grivell, A. Jansen. *Data collection:* L. de Groot, M. van den Akker, D. Bergsma, C. Lodewijk, R. Meijering, B. Peeck, M. Raethke, C. Ree, R. Regtop, Y. Ruijs, M. Schoorl, E. Tuijn, L. Veenenberg, T. Woudstra, Y. Bakker, A. de Jong, M. Broekhoven, E. Claessen. *Patient registration:* B. Tuk.