Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients

Amanda Mocroft[a], Ole Kirk[b], Peter Reiss[c], Stephane De Wit[d], Dalibor Sedlacek[e], Marek Beniowski[f], Jose Gatell[g], Andrew N. Phillips[a], Bruno Ledergerber[h], Jens D. Lundgren[b,i], for the EuroSIDA Study Group

Objectives: Chronic kidney disease (CKD) in HIV-positive persons might be caused by both HIV and traditional or non-HIV-related factors. Our objective was to investigate long-term exposure to specific antiretroviral drugs and CKD.

Design: A cohort study including 6843 HIV-positive persons with at least three serum creatinine measurements and corresponding body weight measurements from 2004 onwards.

Methods: CKD was defined as either confirmed (two measurements $\geq$3 months apart) estimated glomerular filtration rate (eGFR) of 60 ml/min per 1.73 m^2 or below for persons with baseline eGFR of above 60 ml/min per 1.73 m^2 or confirmed 25% decline in eGFR for persons with baseline eGFR of 60 ml/min per 1.73 m^2 or less, using the Cockcroft–Gault formula. Poisson regression was used to determine factors associated with CKD.

Results: Two hundred and twenty-five (3.3%) persons progressed to CKD during 21 482 person-years follow-up, an incidence of 1.05 per 100 person-years follow-up [95% confidence interval (CI) 0.91–1.18]; median follow-up was 3.7 years (interquartile range 2.8–5.7). After adjustment for traditional factors associated with CKD and other confounding variables, increasing cumulative exposure to tenofovir [incidence rate ratio (IRR) per year 1.16, 95% CI 1.06–1.25, $P < 0.0001$), indinavir (IRR 1.12, 95% CI 1.06–1.18, $P < 0.0001$), atazanavir (IRR 1.21, 95% CI 1.09–1.34, $P = 0.0003$) and lopinavir/r (IRR 1.08, 95% CI 1.01–1.16, $P = 0.030$) were associated with a significantly increased rate of CKD. Consistent results were observed in wide-ranging sensitivity analyses, although of marginal statistical significance for lopinavir/r. No other antiretroviral dugs were associated with increased incidence of CKD.

Conclusion: In this nonrandomized large cohort, increasing exposure to tenofovir was associated with a higher incidence of CKD, as was true for indinavir and atazanavir, whereas the results for lopinavir/r were less clear.

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[a]HIV Epidemiology and Biostatistics Group, Research Department of Infection and Population Health, Division of Population Health, University College London Medical School, London, UK, [b]Copenhagen HIV Programme, Panum Institute, University of Copenhagen, Copenhagen, Denmark, [c]Academisch Medisch Centrum bij de Universiteit van Amsterdam, Center for Infection and Immunity Amsterdam and Center for Poverty Related Communicable Diseases, Amsterdam, The Netherlands, [d]St Pierre Hospital, Brussels, Belgium, [e]AIDS Centre, University Hospital, Medical Faculty, Charles University, Plzen, Czech Republic, [f]Department for AIDS Diagnostics and Therapy, Chorzow, Poland, [g]Hospital Clinic i Provincial, Barcelona, Spain, [h]University Hospital Zürich, University of Zürich, Zürich, Switzerland, and [i]Centre for Viral Disease KMA, Rigshospitalet, Copenhagen, Denmark.

Correspondence to Dr Amanda Mocroft, HIV Epidemiology and Biostatistics Group, Research Department of Infection and Population Health, Division of Population Health, University College London Medical School, Royal Free Campus, Rowland Hill St, London NW3 2PF, UK.

Tel: +44 20 7830 2239; fax: +44 20 7794 1224; e-mail: a.mocroft@ucl.ac.uk
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Introduction

HIV infection is associated with renal dysfunction, including HIV-associated nephropathy (HIVAN), immune complex kidney disease and acute renal failure [1,2], which may be associated with progression to AIDS and death [3,4]. There is increasing evidence that HIV infection of the kidneys is involved with HIVAN [5], whereas other disorders include nephropathy resulting from coinfection with hepatitis B, hepatitis C or syphilis [6,7]; diabetes or hypertension [8] and immune complex glomerulonephritis [9]. The incidence and occurrence of renal disease has decreased since the widespread introduction of combination antiretroviral therapy (cART) [10,11], with studies suggesting that cART reduces the incidence of HIVAN [12], possibly by slowing the decline in renal function [13,14]. Early stages of renal dysfunction are silent and only detectable through laboratory analyses; for example, the glomerular filtration rate (GFR) can be estimated using the Cockcroft–Gault or Modification of Diet in Renal Disease (MDRD) equations [15,16]. GFR correlates with the severity of kidney disease and typically decreases before the onset of symptoms of kidney failure [17–19]. Chronic kidney disease (CKD) is defined by the National Institute of Diabetes and Digestive and Kidney Diseases as an estimated GFR (eGFR) of below 60 ml/min per 1.73 m^2 measured over a period of at least 3 months. In HIV-positive persons, there is currently no consensus whether the Cockcroft–Gault or MDRD method for estimating GFR is more accurate compared with the gold standard [20–22].

The role of antiretroviral drugs in the development of CKD remains unclear. Nephrolithiasis was seen in up to 27% of patients treated with indinavir [23,24] and there are numerous studies [25–29] demonstrating that tenofovir is associated with impaired kidney function leading to a 'Dear Doctor' letter on the tenofovir package insert in 2006 [30]. There are few studies with long-term follow-up and sufficient statistical power, which have investigated the long-term relationship between specific antiretroviral drugs and the development of CKD using a rigorously defined endpoint. We aimed to describe the incidence of CKD in EuroSIDA, and to determine factors associated with the development of CKD, including the relationship with individual antiretroviral drugs.

Method

Patients

EuroSIDA is a prospective study, initiated in 1994, currently including 16 599 HIV-1-infected patients at 103 centres across Europe, Israel and Argentina; further details have been reported elsewhere [31]. Data are collected prospectively at clinical sites and is extracted and sent to the coordinating centre at 6 monthly intervals (see forms at www.cphiv.dk). These data include demographic and clinical information, a complete history of antiretroviral treatment and use of drugs for prophylaxis against opportunistic infections, as well as all CD4 cell counts and plasma HIV-RNA values measured. Data on serum creatinine have routinely been recorded since 1 January 2004. The current analysis includes follow-up to a median date of November 2008.

Statistical methods

Patients were selected for inclusion if they had at least three serum creatinine measurements measured after 1 January 2004, and a corresponding body weight measurement. When a patient had repeated creatinine measurements over 28 days, the median value was used and assigned to the mean date of measurement. Baseline for eligible patients was defined as the first eGFR at or after 1 January 2004. eGFR was calculated at each time point using the Cockcroft–Gault formula [16] standardized for body surface area [32]. CKD was defined as either confirmed ($\geq$3 months apart) eGFR of 60 ml/min per 1.73 m^2 or less for patients with baseline eGFR of above 60 ml/min per 1.73 m^2 or confirmed 25% decline in eGFR for patients with baseline eGFR of 60 ml/min per 1.73 m^2 or less. Patients were followed from baseline to either CKD (as defined above, patients were defined as having CKD at the confirmatory measurement) or the last eGFR measurement. In addition to demographic variables, cardiovascular disease (as evidenced by myocardial infarction, stroke, angioplasty, coronary artery bypass graft or carotic endarterectomy), diabetes (diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin at baseline) and hypertension (SBP $\geq$ 140 mmHg, DBP $\geq$ 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents) prior to or at baseline were described, as was smoking status and use of nonantiretroviral known nephrotoxic drugs (acyclovir, pentamidine, cidofovir, amphotericin B and foscarnet [25]).

Kaplan–Meier estimation was used to describe the cumulative probability of developing CKD. Incidence rates of CKD were compared between groups using Poisson regression. Initially, Poisson models were used to determine the factors associated with CKD, using demographic variables, current (time-updated) variables were used for hepatitis C antibody status, age, development of a new AIDS-defining illness or non-AIDS-defining malignancy, use of nephrotoxic drugs, hypertension, diabetes, smoking status, diagnosis of a cardiovascular event, HIV-RNA viral load and CD4 cell count. All demographic factors significant in univariate analyses ($P < 0.1$) were included in a multivariate model. Use of each antiretroviral was then included into this multivariate model as cumulative exposure time, recalculated on a monthly basis and included as continuous time-updated variables [33]. Those significant ($P < 0.1$) were included in

the final model. Cumulative exposure was also categorized in two alternative ways: never exposed, less than 12, 12–24, 24–36 and more than 36 months exposure and never exposed, exposed and currently on drug and exposed and currently off drug. In addition to including the individual antiretroviral drugs, use of cART was included as a categorical variable as any cART (yes/no) or type of cART (none, nonprotease inhibitor containing cART or protease inhibitor -containing cART; further classified as non-boosted or ritonavir boosted). The primary analyses were repeated using the MDRD [15] and improved MDRD formula [34]. An additional sensitivity analysis with greater specificity for CKD was used; confirmed decline in eGFR to 60 ml/min per 1.73 m^2 or less where baseline eGFR above 80 ml/min per 1.73 m^2 (i.e. 25% decline) or confirmed 25% decline in eGFR when baseline eGFR of 60 ml/min per 1.73 m^2 or less [International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), M. Ross, personal communication]. We performed additional analyses censoring patients at starting specific antiretroviral drugs such as tenofovir, atazanavir or a boosted-protease inhibitor-containing regimen. For example, censoring patients at initiation of starting a boosted-protease inhibitor-containing regimen allows investigation of the effect of, for example, tenofovir, when it is used without a boosted protease inhibitor.

All statistical analyses were performed using SAS version 9.1 (Statistical Analysis Software, Cary, North Carolina, USA).

Results

Out of 11 752 patients in EuroSIDA with follow-up after 1 January 2004, 2590 were excluded because they had less than three serum creatinine measurements and an additional 2319 patients were excluded because they did not have body weight, height or both measured in order to calculate eGFR using the Cockcroft–Gault formula. Patients excluded from the Cockcroft–Gault analysis because of missing information on weight, height or both were similar to those included in the primary analyses. Patients excluded due to having insufficient serum creatinine measurements were more likely to be men, be of white ethnic origin, infected with HIV through intravenous drug use, be coinfected with hepatitis C virus and be from Eastern Europe. They were also recruited to EuroSIDA later and were younger in age.

Six thousand, eight hundred and forty-three patients were included; the median number of eGFR measurements per patient was nine [interquartile range (IQR) 6–12] with a median time of 3.7 months (IQR 2.8–5.6) between measurements, and a median of 3.0 eGFR measurements per patient year of follow-up (IQR 2.3–3.6). The median date of baseline was July 2004 (IQR May 2004–August 2005). There was very little correlation between time between consecutive eGFR measurements and eGFR values (correlation coefficient 0.040, $P < 0.0001$), and the correlation was similar at low ($\leq$60 ml/min per 1.73 m^2; correlation coefficient 0.043) or high eGFR (>60 ml/min per 1.73 m^2; correlation coefficient 0.030). Two hundred and twenty-five patients (3.3%) progressed to CKD during 21 482 person-years of follow-up (PYFU), median follow-up was 3.7 years (IQR 2.8–5.7) giving an overall incidence of 1.05 per 100 PYFU [95% confidence interval (CI) 0.91–1.18]. At baseline, 278 patients (4.1%) had an eGFR of 60 ml/min per 1.73 m^2 or less and 4132 patients (60.4%) had an eGFR of above 90 ml/min per 1.73 m^2. Out of the 225 patients, 203 (90.2%) progressed due to a confirmed decline in eGFR to 60 ml/min per 1.73 m^2 or less and 150 (73.9%) progressed from an eGFR above 70 ml/min per 1.73 m^2 to 60 ml/min per 1.73 m^2 or less. Only 27 patients with a baseline eGFR above 90 ml/min per 1.73 m^2 progressed to CKD. Characteristics of the patients are shown in Table 1, together with a description of the patients stratified by whether they had, at baseline, ever been exposed to tenofovir, indinavir, atazanavir or lopinavir/r. There was little variation in the number of eGFR measurements per year of exposure to different antiretroviral drugs. For example, there was a median of 3.1 eGFR measurements per year while patients were treated with tenofovir (IQR 2.4–4.0) compared with 2.5 eGFR measurements per year for indinavir (IQR 2.0–3.3), 3.0 per year for atazanavir (IQR 2.3–4.0) and 2.9 per year for lopinavir/r (IQR 2.2–3.8).

Figure 1 shows the Kaplan–Meier progression to CKD; at 24 months, 1.48% (95% CI 1.18–1.78) were estimated to have developed CKD rising to 2.97% (95% CI 2.51–3.43%) at 36 months after baseline. The crude (unadjusted) incidence of CKD stratified by years of exposure for commonly used antiretroviral drugs are shown in Fig. 2(a and b); a strong increasing incidence of CKD with increasing cumulative exposure to tenofovir, indinavir, atazanavir and lopinavir/r can be seen, which was less evident for efavirenz, abacavir, zidovudine or stavudine, although the test for trend was statistically significant. After adjustment (Table 2), a diagnosis of a new AIDS-defining event was associated with an increased incidence of CKD, as was female sex, older age, developing diabetes, being hypertensive and being hepatitis C antibody positive. In contrast, patients with a higher eGFR at baseline were less likely to develop CKD, as were patients with a higher HIV-RNA viral load. Each additional year of exposure to tenofovir was associated with a 16% increased incidence of CKD, lopinavir/r with an 8% increased incidence, indinavir with an 11% increased incidence and atazanavir with a 22% increased incidence ($P < 0.05$ for all). When atazanvir and tenofovir were used at the same time, there was a 41% increased incidence of CKD per year of additional exposure [incidence rate ratio (IRR) 1.41, 95% CI 1.24–1.61,

Table 1. Baseline characteristics of included patients.

				At/before baseline							
		All		Tenofovir		Indinavir		Atazanavir		Lopinavir/r	
		N	%	*N*	%	*N*	%	*N*	%	*N*	%
All		6843	100	1834	26.8	3156	46.1	644	9.4	1965	28.7
Sex	Male	5136	75.1	1470	77.4	2494	79.0	508	78.9	1528	77.8
Race	White	5851	85.5	1477	80.5	2694	85.4	511	79.4	1642	83.6
HIV	Homosexual	2931	42.8	810	44.2	1484	47.0	307	47.7	910	46.3
Exposure	IDU	1330	19.4	371	20.2	580	18.4	125	19.4	389	19.8
Group	Heterosexual	2045	29.9	480	26.2	840	26.6	155	24.1	500	25.5
	Other	537	7.9	173	9.4	252	8.0	57	8.8	166	8.4
Region	South/Argentina	1856	27.1	492	26.8	926	29.3	143	22.2	545	27.7
	Central	2069	30.2	745	40.6	1060	33.6	268	41.6	624	31.8
	North	1763	25.8	528	28.8	837	26.5	173	26.9	560	28.5
	East	1155	16.9	69	3.8	333	10.6	60	9.3	236	12.0
Prior AIDS		2138	31.2	699	38.1	1263	40.0	243	37.7	852	43.4
RNA < 500[a]		4880	73.7	1382	76.1	2375	76.2	482	75.8	1446	74.5
cART at/before baseline		6165	89.8	1828	99.7	3145	99.7	643	99.8	1955	99.5
Nephrotoxic drugs[b] at/before baseline		976	14.3	398	21.7	644	20.4	121	18.8	449	22.9
Any cardiovascular event[c]		216	3.2	79	4.3	132	4.2	38	5.9	77	3.9
Diabetes[d]		333	4.9	116	6.3	217	6.9	55	8.5	100	5.1
Hypertension[e]		1484	21.7	421	23.0	776	24.6	154	23.9	428	21.8
Smoking[f]	Current or past	2548	37.2	743	40.5	1383	43.8	246	38.2	812	41.3
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age		43	38–50	44	39–50	44	40–52	45	40–51	44	39–50
CD4 cell count		450	305–638	410	266–581	463	305–652	411	258–600	390	250–563
Nadir CD4 cell count		152	59–257	122	43–212	110	40–210	132	50–210	90	31–180
eGFR		96	82–111	92	78–108	91	78–106	93	78–107	94	81–110

Baseline was defined as the first eGFR at or after 1 January 2004. cART, combination antiretroviral therapy; eGFR, estimated glomerular filtration rate; IDU, intravenous drug user; IQR, interquartile range; PYFU, person-years of follow-up.

[a]Data available for $N = 6619$, 96.7% at baseline and for 99.0% of PYFU.

[b]Pentamidine, cidofovir, acyclovir, foscarnet or amphotericin B.

[c]Acute myocardial infarction, carotid endarterectomy, coronary artery bypass graft, angioplasty or stroke; data available for $N = 5982$, 87.4% at baseline and 90.4% of PYFU.

[d]Diagnosis of diabetes mellitus prior to baseline, or taking oral antidiabetic agents or insulin at baseline; data available for $N = 6104$, 89.2% at baseline and 89.8% of PYFU.

[e]Baseline SBP of at least 140 mm/Hg or baseline DBP of at least 90 mm/Hg or taking ACE inhibitors/antihypertensive agents at baseline; data available for $N = 5550$, 81.1% at baseline and 89.4% of PYFU.

[f]Data available for $N = 5255$, 76.8% at baseline and 90.7% of PYFU.

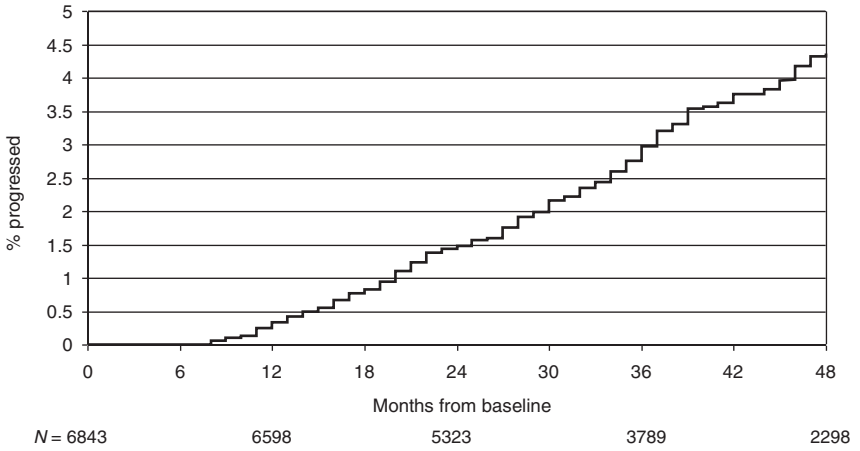

Fig. 1. Progression to chronic kidney disease. CKD defined as confirmed (persisting for ≥3 months) decrease to eGFR to 60 ml/min per 1.73 m^2 or less if eGFR at baseline above 60 ml/min per 1.73 m^2 or confirmed 25% decrease in eGFR if baseline eGFR 60 ml/min per 1.73 m^2 or less. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

$P < 0.0001$]. No other antiretroviral drugs or type of cART regimen was associated with CKD. For example, after adjustment, each additional year of exposure to abacavir was associated with a 4% increased incidence of CKD (IRR 1.04, 95% CI 0.98–1.09, $P = 0.16$), with efavirenz was 5% (IRR 1.05, 95% CI 0.98–1.10, $P = 0.12$), with zidovudine was 0% (IRR 1.00, 95% CI 0.96–1.04, $P = 0.97$) and with stavudine was 3% (IRR 1.03, 95% CI 0.98–1.08, $P = 0.28$).

When using the MDRD formula [15], 9162 patients were included in analyses and 277 developed CKD during 39 250.3 PYFU, an incidence of 0.95 per 100 PYFU (95% CI 0.84–1.06). Using the CKD Epidemiology Collaboration formula [34], there were 258 patients who developed CKD (incidence of 0.88 per 100 PYFU, 95% CI 0.77–0.99). There were 129 events (incidence of 0.60 per 100 PYFU, 95% CI 0.49–0.70) using the INSIGHT definition (confirmed 25% decline in eGFR to ≤60 ml/min per 1.73 m^2 or confirmed 25% decline in eGFR when baseline eGFR ≤60 ml/min per 1.73 m^2). In all cases, the results were completely consistent with each other (Fig. 3), as was CKD defined solely as confirmed eGFR of 60 ml/min per 1.73 m^2 or less when baseline eGFR above 60 ml/min per 1.73 m^2 (203 events).

Antiretroviral drugs are often taken together; therefore, we performed additional analyses censoring patient follow-up, using the Cockcroft–Gault formula (Fig. 3). Censoring patient follow-up at starting, atazanavir reduced the follow-up time by 19%. Figure 3 can then be interpreted as the adjusted IRR per additional year of exposure to tenofovir or lopinavir/r in patients who have not started atazanavir. The adjusted IRR per additional year of exposure to tenofovir and lopinavir/r were very similar, which suggests that the increased incidence of CKD in patients taking lopinavir/r or tenofovir cannot be explained by the fact that the patient was also treated with atazanavir. Similarly, the association with atazanavir and lopinavir/r was unaffected by censoring follow-up at starting tenofovir, although the marked reduction in power (40% of follow-up time was removed) reduced the statistical significance. Finally, the adjusted IRR for tenofovir per additional year of exposure was maintained when the analysis was censored at initiation of a boosted-protease inhibitor-containing regimen (60% of follow-up time was removed).

In addition to assessing the effect of continuous exposure to antiretroviral drugs for their possible association with CKD, other ways of assessing the effect of antiretroviral drugs was explored, as shown in Web Fig. 1(a) (Supplemental Digital Content 1, http://links.lww.com/QAD/A38, stratifying by years of exposure) and Web Fig. 1(b) (Supplemental Digital Content 1, http://links.lww.com/QAD/A39, current and previous use of antiretroviral drugs). Of note, the power of these analyses is reduced compared with our main analysis. After adjustment, there was an increasing trend of CKD associated with increasing exposure to atazanavir or indinavir (Web Fig. 1a); there was little additional increase in the incidence of CKD after 24 months exposure to tenofovir, whereas the increased incidence of CKD for lopinavir/r was only seen (with marginal significance) in patients with more than 36 months of exposure. Patients who had started atazanavir or lopinavir/r but were not currently taking the drug did not have an increased incidence of CKD compared with those who had never started the drug (Web Fig. 1b), whereas for indinavir and tenofovir, patients who had stopped the drug continued to have a significantly increased incidence of CKD. This was further investigated for tenofovir. After adjustment, compared with patients who had never started tenofovir, those who had started tenofovir but stopped within the last 12 months had a four-fold increased incidence of CKD (adjusted IRR 4.05, 95% CI 2.51–6.53, $P < 0.0001$). Patients who had stopped for

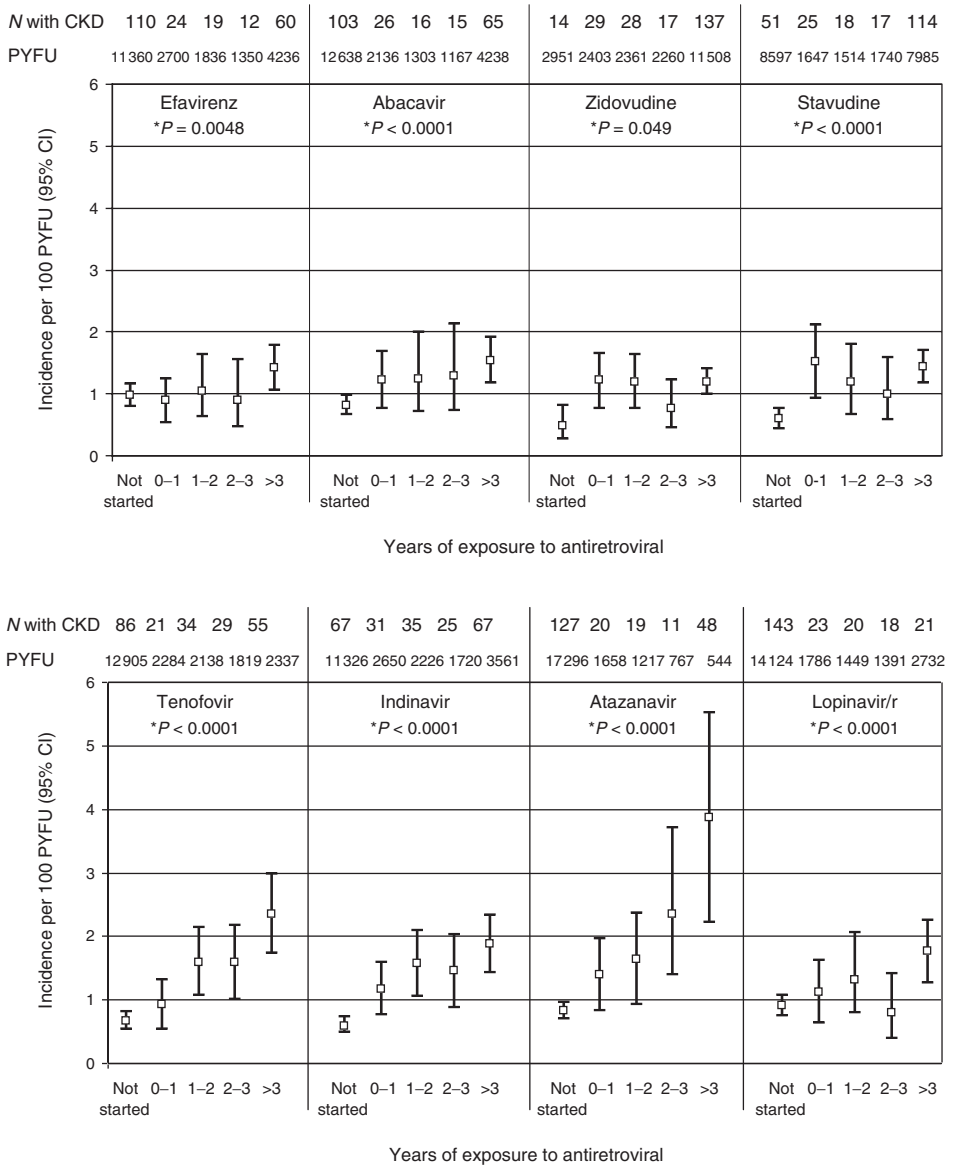

Fig. 2. Incidence of chronic kidney disease and increasing exposure to antiretroviral drugs. CKD defined as confirmed (persisting for ≥3 months) decrease in eGFR to 60 ml/min per 1.73 m^2 or less if eGFR at baseline above 60 ml/min per 1.73 m^2 or confirmed 25% decrease in eGFR if baseline eGFR 60 ml/min per 1.73 m^2 or less. *Test for trend from Poisson regression. CI, confidence interval; CKD, chronic kidney disease; PYFU, person-years of follow-up.

more than 12 months had a comparable incidence of CKD to those never starting the drug (IRR 1.12, 0.63–1.99, $P = 0.69$). Patients who were currently taking tenofovir had almost a two-fold increased incidence of CKD (IRR 1.94, 1.43–2.63, $P < 0.0001$).

There is limited follow-up in this study following CKD; there were 19 deaths during 327.8 PYFU, death rate 5.8 per 100 PYFU (95% CI 3.5–9.1 per 100 PYFU). Only one death was reported to be due to renal failure. Of the 225 patients diagnosed with CKD, 157 patients have at least two subsequent eGFR measurements (69.8%). Among these patients, the median follow-up after CKD was 14 months (IQR 8–21 months) and 56 patients resolved CKD (35.7%), that is, they had two consecutive (≥3 months apart) eGFR above 60 ml/min per 1.73 m^2 or two consecutive eGFR reversing the 25% decline. At 12 months after CKD, 23.3% were estimated to have resolved CKD (95% CI 16.1–30.5) using Kaplan–Meier estimation.

Discussion

This study has demonstrated a relatively low proportion of patients developing CKD and that in addition to the traditional risk factors for renal disease, increasing

Table 2. Progression to chronic kidney disease; univariate and multivariate analysis.

		Univariate			Multivariate		
		IRR	95% CI	*P*	RH	95% CI	*P*
eGFR at baseline	Per 5 ml/min per 1.73 m^2	0.75	0.73–0.78	<0.0001	0.84	0.80–0.87	<0.0001
AIDS at baseline	Yes vs. no	1.90	1.46–2.47	<0.0001	1.25	0.95–1.65	0.11
AIDS during follow-up[a]	Yes vs. no	2.78	1.48–5.25	0.0016	2.22	1.14–4.32	0.019
Nephrotoxic drugs[a]	Yes vs. no	1.81	1.33–2.46	0.0002	1.01	0.73–1.40	0.94
Current CD4 cell count[a]	Per doubling	0.85	0.75–0.95	0.0065	0.92	0.79–1.07	0.30
Current age[a]	Per 10 years older	2.57	2.30–2.87	<0.0001	1.54	1.31–1.80	<0.0001
Current HIV-RNA viral load[a]	Per $\log_{10}$ copies/ml higher	0.67	0.55–0.80	<0.0001	0.81	0.67–0.99	0.040
Any CVD event[a]	Yes vs. no/unknown	4.80	3.34–6.92	<0.0001	1.33	0.90–1.98	0.15
Hypertension[a]	Yes vs. no/unknown	3.19	2.45–4.16	<0.0001	1.69	1.26–2.27	0.0005
Diabetes[a]	Yes vs. no/unknown	3.82	2.73–5.31	<0.0001	1.50	1.05–2.16	0.028
Hepatitis C antibody positive[a]	Yes vs. no/unknown	1.23	0.82–1.65	0.17	1.98	1.44–2.71	<0.0001
Sex	Female vs. male	1.01	0.75–1.37	0.93	1.68	1.22–2.30	0.0013
Non-AIDS malignancy[a]	Yes vs. no	3.63	2.36–5.59	<0.0001	1.72	1.10–2.70	0.018
Cumulative	Tenofovir	1.32	1.21–1.41	<0.0001	1.16	1.06–1.25	<0.0001
Exposure[a]	Indinavir	1.18	1.13–1.24	<0.0001	1.12	1.06–1.18	<0.0001
	Atazanavir	1.48	1.35–1.62	<0.0001	1.21	1.09–1.34	0.0003
	Lopinavir/r	1.15	1.07–1.23	<0.0001	1.08	1.01–1.16	0.030

CKD defined as confirmed (persisting for ≥3 months) decrease in eGFR to 60 ml/min per 1.73 m^2 or less if eGFR at baseline above 60 ml/min per 1.73 m^2 or confirmed 25% decrease in eGFR if baseline eGFR <60 ml/min per 1.73 m^2 or less. CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; MI, myocardial infarction.
[a]Variable included as time updated. Any CVD event includes stroke, acute MI, bypass, angioplasty or carotid endarterectomy.
All demographic factors significant in univariate analyses ($P < 0.1$) were included in a multivariate model. Use of each antiretroviral was then included into this multivariate model as cumulative exposure time, recalculated on a monthly basis and included as continuous time-updated variables [33]. Those significant ($P < 0.1$) were included in the final model. No other antiretroviral drugs or cART strategies were associated with CKD.

exposure to tenofovir, indinavir, atazanavir and lopinavir was associated with an increased incidence of CKD. The prevalence and incidence of CKD within EuroSIDA was highly consistent with findings from other studies [35–37]. Well described risk factors such as older age, hypertension and diabetes for CKD in persons without HIV [38–41] were also independently associated with CKD in our study. The development of AIDS and non-AIDS malignancies could be associated with CKD possibly via a general deterioration in health, immune

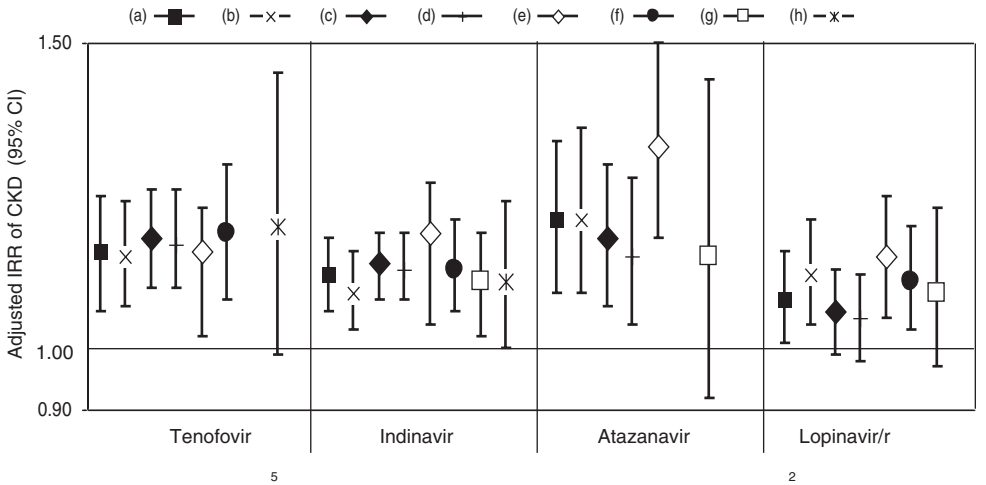

Fig. 3. Multivariate incidence rate ratios of chronic kidney disease associated with cumulative exposure (per year) to specific antiretroviral drugs. (a) From Table 2; From Cockcroft–Gault [5]. (b) Confirmed (≥3 months apart) eGFR of 60 ml/min per 1.73 m^2 or less for patients with baseline eGFR above 60 ml/min per 1.73 m^2; From Cockcroft–Gault [5]. (c) From MDRD [4]. (d) From CKD-EPI [23]. (e) INSIGHT definition; From Cockcroft–Gault [5]. Using Cockcroft–Gault [5], censored at starting (f) atazanavir (g) tenofovir (g) boosted protease inhibitor. CKD defined as confirmed (persisting for ≥3 months) decrease in eGFR to 60 ml/min per 1.73 m^2 or less if eGFR at baseline above 60 ml/min per 1.73 m^2 or confirmed 25% decrease in eGFR if baseline eGFR 60 ml/min per 1.73 m^2 or less. Adjusted for eGFR, sex (fixed at baseline) and AIDS, starting nephrotoxic drugs, CD4 cell count, age, HIV-RNA viral load, diabetes, hypertension, any CVD, non-AIDS malignancy and HCV serostatus (time-updated covariates). CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; MDRD, Modification of Diet in Renal Disease.

function or exposure to nephrotoxic drugs. Hepatitis C coinfection was also associated with CKD in agreement with a previous study [42].

Although the incidence and occurrence of renal disease has decreased since the widespread introduction of cART [10,11], we found that cumulative exposure to tenofovir was associated with an increased incidence of CKD. Previous studies have suggested that ART is associated with a decline in kidney function [43], which may be exacerbated in those taking tenofovir [35,44]. Results from clinical trials, with shorter follow-up and including patients with a lower risk of CKD, have shown no differences in changes in eGFR when comparing tenofovir with nucleoside reverse transcriptase inhibitors [45] and a mild but nonprogressive decline in eGFR [46–49]. Our study has a median follow-up of almost 4 years, includes approaching 7000 unselected patients, many of whom had preexisting risk factors for CKD, and has considerably more power than previous reports. There was, however, a relatively low proportion of patients with an eGFR at baseline of above 90 ml/min per 1.73 m^2 who progressed to CKD, and further follow-up in this patient group is required to more accurately determine long-term risk of CKD with exposure to antiretroviral drugs.

More detailed analyses of our data suggest that those with preexisting excess risk of CKD were more likely to develop tenofovir-associated CKD (Web Table 1, Supplemental Digital Content 1, http://links.lww.com/QAD/A37). Tenofovir may be associated with both glomerular and tubular dysfunction; the latter likely due to re-uptake of the drug via tubular cells [50]. There have been conflicting reports [25,51–53] that the effect of tenofovir on renal function is worse when coadministered with ritonavir-boosted protease inhibitor, and that deteriorating renal function was greater in boosted-protease inhibitor regimens than in nonnucleoside reverse transcriptase inhibitor regimens [54]. We found no effect of boosted protease inhibitors on CKD (data not shown); the association between CKD and atazanavir or lopinavir/r could not be explained by coadministration with tenofovir and the association between CKD and tenofovir could not be explained by concomitant use of boosted protease inhibitors.

Indinavir, previously reported to be associated with a decline in renal function and crystalluria [24,55], was also associated with a higher incidence of CKD in our study, although this is of less clinical relevance, as indinavir is no longer a first-line recommended regimen [24,56]. We also found that cumulative exposure to atazanavir and lopinavir/r was associated with an increased incidence of CKD. There have been case reports of renal problems associated with atazanavir [57–62], possibly exacerbated in patients previously exposed to indinavir [58]. As with indinavir, atazanavir may cause crystalluria, crystal nephropathy and nephrolithiasis, perhaps due to concentrations of atazanavir sulphate increasing with acidity of the urine, which in turn may lead to intratubular crystal formation and renal injury [58]. Of note, 7% of atazanavir is excreted as unchanged drug in urine, substantially higher than, for example, lopinavir/r and saquinavir (<3 and 1%, respectively) [63–65]. As with tenofovir, the most plausible explanation for why this study detects these associations is better power and higher prevalence of CKD risk factors in the population studied. As opposed to the consistent results for atazanavir, those for lopinavir/r using different eGFR estimates were inconsistent and further research is warranted before a possible role in CKD can be determined.

The high risk of CKD in the group of people within 12 months of stopping tenofovir is likely in part due to patients with reduced eGFR stopping tenofovir. The elevated risk of CKD returned to that seen in patients not exposed to the drug 12 months after stopping tenofovir, whereas that associated with atanazavir and lopinavir/r reverted immediately. This observation suggests that the potential nephrotoxicity of these drugs is generally reversible. It is possible that potential tubular and glomerular toxicity due to tenofovir may take longer to revert, whereas continued drug crystallization in the kidneys (atazanavir and indinavir) requires ongoing exposure. When tenofovir exposure was categorized (Web Fig. 1, Supplemental Digital Content 1, http://links.lww.com/QAD/A38, http://links.lww.com/QAD/A39), after adjustment, the incidence of CKD did not continue to significantly increase after the initial 24 months of exposure, which may suggest a threshold with respect to the drug's glomerular toxicity. On the contrary, based on the current data, we cannot rule out that it will continue to increase. The decision to model exposure cumulatively was taken based on the crude incidence rates (Fig. 2) and further follow-up and data are required to establish whether the incidence of CKD continues to increase with time beyond 24 months exposure to tenofovir.

There are a number of limitations to this study. Although EuroSIDA is a well described, observational cohort study with long-term follow-up, patients have not been randomized to treatment and confounding by indication remains a possibility. There may be considerable variation in serum creatinine measurements between different laboratories using different techniques [66], although this is unlikely to bias the results for one specific antiretroviral drug compared with another. Patients taking different antiretroviral drugs had a similar frequency of eGFR measurements, and duration of follow-up was similar for patients exposed to different antiretroviral drugs (data not shown), both of which reduce potential bias. We have a median follow-up approaching 4 years and are neither able to say whether the risk of CKD will continue to increase with longer exposure nor can we describe the

relationship between CKD and antiretroviral drugs more recently introduced such as etravirine, darunavir, raltagravir or maraviroc. EuroSIDA has recently initiated data collection on tenofovir dosage in patients with CKD, wherein dose or dose interval adjustment may be necessary [30,56]; analyses of these data are ongoing. Patients lost to follow-up or who died before the study began collecting serum creatinine data were excluded from analysis and tended to be recruited to EuroSIDA later, were more likely to be coinfected with hepatitis C and were younger, which might suggest a lower incidence of CKD in excluded patients than in those included, whereas patients excluded from the Cockcroft–Gault analysis were very similar to those included in the larger MDRD sensitivity analysis. Patients with a minimal confirmed decrease in eGFR from 61 to 59 ml/min per 1.73 m^2 would be classified as having CKD according to our definition, although analyses which required a confirmed 25% drop in eGFR to 60 ml/min per 1.73 m^2 or less showed similar results.

To conclude, increasing exposure to tenofovir was associated with a higher incidence of CKD independently of other antiretroviral drugs and traditional CKD risk factors. The increase in risk of CKD was also true for indinavir and atazanavir, whereas the results for lopinavir/r were less clear. There may be some reversibility in CKD after discontinuation of the antiretroviral drugs, but this requires confirmation in larger studies with longer follow-up.

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A.M. contributed with discussions regarding study design and statistical analysis, performed all statistical analyses and wrote the manuscript. A.M. had full access to the dataset. O.K. contributed with discussions regarding study design, statistical analysis and provided significant input into the manuscript production. P.R., A.N.P. and B.L. provided input into study design, reviewed data and provided significant input into manuscript production. D.S., M.B. and J.G. coordinated national data collection and provided significant input into manuscript production. J.D.L. initiated the study, provided input into study design and statistical analyses, provided significant input into manuscript production and supervised the project.

The EuroSIDA study group (national coordinators) – Argentina: (M. Losso), C Elias, Hospital JM Ramos Mejia, Buenos Aires. Austria: (N. Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna; (R. Zangerle) Medical University Innsbruck, Innsbruck. Belarus: (I. Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk. Belgium: (N. Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; (L. Vandekerckhove) University Ziekenhuis Gent, Gent. Bosnia: (V. Hadziosmanovic) Klinicki Centar Univerziteta Sarajevo, Sarajevo. Bulgaria: (K. Kostov), Infectious Diseases Hospital, Sofia. Croatia: (J. Begovac), University Hospital of Infectious Diseases, Zagreb. Czech Republic: (L. Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; (D. Sedlacek), Charles University Hospital, Plzen. Denmark: (J. Nielsen, G. Kronborg, T. Benfield, M. Larsen), Hvidovre Hospital, Copenhagen; (J. Gerstoft, T. Katzenstein, A-B. E. Hansen, P. Skinhøj), Rigshospitalet, Copenhagen; (C. Pedersen), Odense University Hospital, Odense; (L. Oestergaard), Skejby Hospital, Aarhus. Estonia: (K. Zilmer) West-Tallinn Central Hospital, Tallinn, Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. Finland: (M.

Ristola), Helsinki University Central Hospital, Helsinki. France: (C. Katlama) Hôpital de la Pitié-Salpétière, Paris; (J-P. Viard), Hôpital Necker-Enfants Malades, Paris; (P-M. Girard), Hospital Saint-Antoine, Paris; (J.M. Livrozet), Hôpital Edouard Herriot, Lyon; (P. Vanhems), University Claude Bernard, Lyon; (C. Pradier), Hôpital de l'Archet, Nice; (F. Dabis, D. Neau), Unité INSERM, Bordeaux. Germany: (J. Rockstroh), Universitäts Klinik Bonn; (R. Schmidt), Medizinische Hochschule Hannover; (J. van Lunzen, O. Degen), University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; (H.J. Stellbrink), IPM Study Center, Hamburg; (S. Staszewski), JW Goethe University Hospital, Frankfurt; (J. Bogner), Medizinische Poliklinik, Munich; (G. Fätkenheuer), Universität Köln, Cologne. Greece: (J. Kosmidis, P. Gargalianos, G. Xylomenos, J. Perdios, Athens General Hospital; (G. Panos, A. Filandras, E. Karabatsaki), 1st IKA Hospital; (H. Sambatakou), Ippokration Genereal Hospital, Athens. Hungary: (D. Banhegyi) Szent Lásló Hospital, Budapest. Ireland: (F. Mulcahy) St. James's Hospital, Dublin. Israel: (I. Yust, D. Turner, M. Burke), Ichilov Hospital, Tel Aviv; (S. Pollack, G. Hassoun), Rambam Medical Center, Haifa; (S. Maayan), Hadassah University Hospital, Jerusalem. Italy: (A. Chiesi) Istituto Superiore di Sanità, Rome; (R. Esposito, I. Mazeu, C. Mussini), Università Modena, Modena; (C. Arici), Ospedale Riuniti, Bergamo; (R. Pristera), Ospedale Generale Regionale, Bolzano; (F. Mazzotta, A. Gabbuti), Ospedale S Maria Annunziata, Firenze; (V. Vullo, M. Lichtner), University di Roma la Sapienza, Rome; (A. Chirianni, E. Montesarchio, M. Gargiulo), Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; (G. Antonucci, F. Iacomi, P. Narciso, C. Vlassi, M. Zaccarelli), Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; (A. Lazzarin, R. Finazzi), Ospedale San Raffaele, Milan; (M. Galli, A. Ridolfo), Osp. L. Sacco, Milan; (A. d'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan. Latvia: (B. Rozentale) P Aldins, Infectology Centre of Latvia, Riga. Lithuania: (S. Chaplinskas) Lithuanian AIDS Centre, Vilnius. Luxembourg: (R. Hemmer, T. Staub), Centre Hospitalier, Luxembourg. The Netherlands: (P. Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway: (J. Bruun, A. Maeland, V. Ormaasen), Ullevål Hospital, Oslo. Poland: (B. Knysz, J. Gasiorowski), Medical University, Wroclaw; (A. Horban, E. Bakowska), Centrum Diagnostyki i Terapii AIDS, Warsaw; (D. Prokopowicz, R. Flisiak), Medical University, Bialystok; (A. Boron-Kaczmarska, M. Pynka), Medical Univesity, Szczecin; (M. Beniowski, E. Mularska), Osrodek Diagnostyki i Terapii AIDS, Chorzow; (H. Trocha), Medical University, Gdansk; (E. Jablonowska, E. Malolepsza, K. Wojcik), Wojewodzki Szpital Specjalistyczny, Lodz. Portugal: (F. Antunes, E. Valadas), Hospital Santa Maria, Lisbon; (K. Mansinho), Hospital de Egas Moniz, Lisbon; (F. Maltez), Hospital Curry Cabral, Lisbon. Romania: (D. Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr Victor Babes, Bucarest. Russia: (A. Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; (E. Vinogradova), St Petersburg AIDS Centre, St Peterburg; (S. Buzunova), Novgorod Centre for AIDS, Novgorod. Serbia: (D. Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovakia: (M. Mokráš, D. Staneková), Dérer Hospital, Bratislava. Slovenia: (J. Tomazic) University Clinical Centre Ljubljana, Ljubljana. Spain: (J. González-Lahoz, V. Soriano, L. Martin-Carbonero, P. Labarga), Hospital Carlos III, Madrid; (S. Moreno) Hospital Ramon y Cajal, Madrid; (B. Clotet, A. Jou, R. Paredes, C. Tural, J. Puig, I. Bravo), Hospital Germans Trias i Pujol, Badalona; (J.M. Gatell, J.M. Miró), Hospital Clinic i Provincial, Barcelona; (P. Domingo, M. Gutierrez, G. Mateo, M.A. Sambeat), Hospital Sant Pau, Barcelona. Sweden: (A. Karlsson), Karolinska University Hospital, Stockholm; (P.O. Persson), Karolinska University Hospital, Huddinge; (L. Flamholc), Malmö University Hospital, Malmö. Switzerland: (B. Ledergerber, R. Weber), University Hospital, Zürich; (P. Francioli, M. Cavassini), Centre Hospitalier Universitaire Vaudois, Lausanne; (B. Hirschel, E. Boffi), Hospital Cantonal Universitaire de Geneve, Geneve; (H. Furrer), Inselspital Bern, Bern; (M. Battegay, L. Elzi), University Hospital Basel. Ukraine: (E. Kravchenko, N. Chentsova), Kiev Centre for AIDS, Kiev; (G. Kutsyna) Luhansk AIDS Center, Luhansk; (S. Servitskiy), Odessa Region AIDS Center, Odessa; (S. Antoniak) Kiev; (M. Krasnov) Kharkov State Medical University, Kharkov. United Kingdom: (S. Barton) St Stephen's Clinic, Chelsea and Westminster Hospital, London; (A.M. Johnson, D. Mercey), Royal Free and University College London Medical School, London (University College Campus); (A. Phillips, M.A. Johnson, A. Mocroft), Royal Free and University College Medical School, London (Royal Free Campus); (M. Murphy), Medical College of Saint Bartholomew's Hospital, London; (J. Weber, G. Scullard), Imperial College School of Medicine at St Mary's, London; (M. Fisher), Royal Sussex County Hospital, Brighton; (C. Leen), Western General Hospital, Edinburgh.

Virology group: B. Clotet, R. Paredes (Central Coordinators) along with ad-hoc virologists from participating sites in the EuroSIDA Study.

Steering Committee: F. Antunes, B. Clotet, D. Duiculescu, J. Gatell, B. Gazzard, A. Horban, A. Karlsson, C. Katlama, B. Ledergerber (Chair), A. D'Arminio Montforte, A. Phillips, A. Rakhmanova, P. Reiss (Vice-Chair), J. Rockstroh.

Coordinating Centre Staff: J. Lundgren (project leader), O. Kirk, A. Mocroft, N. Friis-Møller, A. Cozzi-Lepri, W. Bannister, M. Ellefson, A. Borch, D. Podlekareva, J. Kjær, L. Peters, J. Reekie, J. Kowalska.

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