



Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study

Amanda Mocroft, Jens D Lundgren, Michael Ross, Christoph A Fux, Peter Reiss, Olivier Moranne, Philippe Morlat, Antonella d'Arminio Monforte, Ole Kirk, Lene Ryom, for the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) Study*

Summary

Background Whether or not the association between some antiretrovirals used in HIV infection and chronic kidney disease is cumulative is a controversial topic, especially in patients with initially normal renal function. In this study, we aimed to investigate the association between duration of exposure to antiretrovirals and the development of chronic kidney disease in people with initially normal renal function, as measured by estimated glomerular filtration rate (eGFR).

Methods In this prospective international cohort study, HIV-positive adult participants (aged ≥ 16 years) from the D:A:D study (based in Europe, the USA, and Australia) with first eGFR greater than 90 mL/min per 1.73 m² were followed from baseline (first eGFR measurement after Jan 1, 2004) until the occurrence of one of the following: chronic kidney disease; last eGFR measurement; Feb 1, 2014; or final visit plus 6 months (whichever occurred first). Chronic kidney disease was defined as confirmed (>3 months apart) eGFR lower than 60 mL/min per 1.73 m². The primary outcome was the occurrence of chronic kidney disease. Poisson regression was used to estimate the incidence rate of chronic kidney disease associated with cumulative exposure to tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, ritonavir-boosted lopinavir, other ritonavir-boosted protease inhibitors, or abacavir.

Findings Between Jan 1, 2004, and July 26, 2013, 23 905 eligible individuals from the D:A:D study were included. Participants had a median baseline eGFR of 110 mL/min per 1.73 m² (IQR 100–125), a median age of 39 years (33–45), and median CD4 cell count of 441 cells per mm³ (294–628). During a median follow-up of 7.2 years (IQR 5.1–8.9), 285 (1%) of 23 905 people developed chronic kidney disease (incidence 1.76 per 1000 person-years of follow-up [95% CI 1.56–1.97]). After adjustment, we recorded a significant increase in chronic kidney disease associated with each additional year of exposure to tenofovir disoproxil fumarate (adjusted incidence rate ratio 1.14 [95% CI 1.10–1.19], $p < 0.0001$), ritonavir-boosted atazanavir (1.20 [1.13–1.26], $p < 0.0001$), and ritonavir-boosted lopinavir (1.11 [1.06–1.16], $p < 0.0001$), but not other ritonavir-boosted protease inhibitors or abacavir.

Interpretation In people with normal renal function, the annual incidence of chronic kidney disease increased for up to 6 years of exposure to tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir therapy. Although the absolute number of new cases of chronic kidney disease was modest, treatment with these antiretrovirals might result in an increasing and cumulative risk of chronic kidney disease. Patients on potentially nephrotoxic antiretrovirals or at high risk of chronic kidney disease should be closely monitored.

Funding The Highly Active Antiretroviral Therapy Oversight Committee.

Introduction

Following the widespread introduction of combination antiretroviral therapy (ART) and the rapid decline in mortality associated with HIV infection,¹ the focus of patient care has shifted to chronic diseases such as cardiovascular, liver, and renal disease, for which a complex association exists between immunodeficiency, chronic inflammation, ageing, and the long-term toxicities of antiretrovirals.² The prevalence of chronic kidney disease in HIV-positive individuals treated with combination ART varies greatly, ranging from 2% to more than 30%,³ depending on the prevalence of other

risk factors, including both HIV-related factors and more traditional risk factors for chronic kidney disease (eg, hypertension or diabetes).^{4,5} Several studies have focused on the role of antiretrovirals, including the D:A:D study.⁶ Tenofovir disoproxil fumarate has been widely shown to be associated with decreases in estimated glomerular filtration rate (eGFR) and progression to chronic kidney disease,⁷ and some studies have suggested similar associations with ritonavir-boosted atazanavir or lopinavir,⁸ together with reports of crystalluria, urolithiasis, and interstitial nephritis.^{9,10} Additionally, several antiretrovirals, including dolutegravir, ritonavir,

Lancet HIV 2015

Published Online
November 16, 2015
[http://dx.doi.org/10.1016/S2352-3018\(15\)00211-8](http://dx.doi.org/10.1016/S2352-3018(15)00211-8)

See Online/Comment
[http://dx.doi.org/10.1016/S2352-3018\(15\)00213-1](http://dx.doi.org/10.1016/S2352-3018(15)00213-1)

*D:A:D study investigators and participating cohorts are listed in the appendix

Department of Infection and Population Health, University College London, London, UK (Prof A Mocroft PhD); CHIP, Department of Infectious Diseases, Section 2100, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

(Prof J D Lundgren DMSc, O Kirk DMSc, L Ryom MD); Division of Nephrology, Icahn School of Medicine at Mount Sinai School, New York, NY, USA (M Ross MD); Clinic for Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Aarau, Switzerland (C A Fux MD); Academic Medical Center, Division of Infectious Diseases and Department of Global Health, University of Amsterdam, Amsterdam, Netherlands (Prof P Reiss MD); Stichting HIV Monitoring, Amsterdam, Netherlands (Prof P Reiss); Nephrology Unit, Carêmeau University Hospital, Nîmes, France (O Moranne MD); Biostatistics, Epidemiology and Public Health, Institut Universitaire de Recherche Clinique, University of Montpellier, Montpellier, France (O Moranne); Université de Bordeaux, INSERM U 897, CHU de Bordeaux, France (P Morlat MD); and Clinic of Infectious and Tropical Diseases, Department of

Health Sciences, University of
Milan, Milan, Italy
(Prof A d'Arminio Monforte MD)

Correspondence to:
Prof Amanda Mocroft,
Department of Infection and
Population Health, University
College London, Rowland Hill
Street, London NW3 2PF, UK
a.mocroft@ucl.ac.uk

See Online for appendix

Research in context

Evidence before this study

Some antiretrovirals that are used to treat HIV infection might be associated with an increased risk of chronic kidney disease or a decline in estimated glomerular filtration rate (eGFR). We did a review of the available literature on PubMed, in which we searched for clinical trials and observational (cohort) studies published from 2004 up to the search date (April 20, 2015) that reported changes in eGFR or chronic kidney disease and individual antiretroviral drugs. Our search terms were "gfr", "chronic kidney disease", "HIV", and "antiretrovirals", and we searched for articles published in English language only. Evidence from clinical trials, especially for tenofovir, suggests that any decreases in eGFR occur within the first few months of treatment, with little further change after this point. Evidence from observational studies has suggested a cumulative effect of antiretrovirals, including ritonavir-boosted atazanavir or lopinavir, and tenofovir, on chronic kidney disease. Clinical trials in HIV-positive individuals tend to be short in duration and might exclude those at a raised risk of chronic kidney disease, and therefore do not follow participants for long enough to record the occurrence of chronic kidney disease, whereas observational studies have not focused on people with an initially normal eGFR higher than 90 mL/min per 1.73 m², or have not used a confirmed eGFR lower than 60 mL/min per 1.73 m² to define chronic kidney disease.

Added value of this study

23 905 study participants with first eGFR higher than 90 mL/min per 1.73 m² were included, of who 285 developed

chronic kidney disease. After adjustment for potential confounding variables (both HIV-associated and traditional risk factors for chronic kidney disease), we recorded a 14%, 20%, and 11% increase in chronic kidney disease associated with each additional year of exposure to tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir, respectively, but no increased incidence of chronic kidney disease associated with either abacavir or other ritonavir-boosted protease inhibitors.

Implications of all the available evidence

Our findings suggest that the annual incidence of chronic kidney disease was increasing for up to 6 years of follow-up after starting tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir treatment in HIV-positive individuals with an initially normal eGFR. Although the absolute number of chronic kidney disease events was modest, the incidence of the disease continued to increase with up to 5 or more years of exposure to the antiretrovirals; after 5 years, it was equivalent to an increased incidence of chronic kidney disease of 1.94-fold for tenofovir, 2.44-fold for ritonavir-boosted atazanavir, and 1.66-fold ritonavir-boosted lopinavir. The continued increase in risk of chronic kidney disease that we recorded with exposure suggests a cumulative toxic effect of these drugs. The benefits of potentially nephrotoxic antiretrovirals, even in individuals with an initially normal renal function, should be weighed against the risks in those patients at highest risk of chronic kidney disease.

and rilpivirine, can reduce creatinine clearance (thereby decreasing eGFR) without changing the actual glomerular filtration rate.¹¹

Results from some large cohort studies have shown that some antiretrovirals have nephrotoxic effects in people with both a normal and impaired eGFR at start of follow-up.^{6,8,12} Some clinical trials, mostly with short follow-up, have suggested that exposure to tenofovir disoproxil fumarate is associated with an initial decline in eGFR that does not continue with increasing exposure,^{13,14} whereas others have reported no initial decline in renal function.^{15,16} Despite the many studies of renal function in HIV, none so far has been adequately powered to formally assess the exact nature of the association between exposure to antiretrovirals and chronic kidney disease in people with an initially normal eGFR. Therefore, whether or not the so-called early-hit phenomenon remains true after extended exposure to antiretrovirals is unknown, especially in people with an initially normal renal function. Because treatment with combination ART can last for many years, to ascertain whether or not the risks of chronic kidney disease will be self-limiting is crucial, to help clinical decision making and monitoring of HIV-positive patients.

In this study, we aimed to investigate the association between duration of exposure to antiretrovirals and the development of chronic kidney disease in people with an initially normal eGFR.

Methods

Study design and participants

The Data Collection on Adverse events of Anti-HIV Drugs Study (D:A:D) is a prospective cohort collaboration established in 1999 with more than 49 000 HIV-1-positive people in Europe, the USA, and Australia; full details of the study have been published previously.¹⁷ Data for routine clinical care, including demographic factors, ART, laboratory values, cardiovascular risk factors, and AIDS events, are collected electronically at enrolment and annually thereafter. Serum creatinine measurements have been collected systematically in participating cohorts as required for clinical care since January, 2004.

Participants from the D:A:D study were eligible for this study if they were 16 years of age or older, had at least one eGFR measurement since Jan 1, 2004, and had a baseline eGFR greater than 90 mL/min per 1.73 m². Individuals were excluded if their baseline eGFR was less than 90 mL/min per 1.73 m², they had no CD4 cell count or

viral load measured within 6 months of baseline (closest before or, if not available, closest after), or less than 3 months follow-up after baseline.

All participating cohorts followed local national guidelines or regulations regarding patients' consent and ethics review. In particular, of the countries represented by the participating cohorts (in this study and in D:A:D overall), only Switzerland and Australia require specific ethics approval for D:A:D in addition to that required for their national cohorts (Swiss HIV Cohort Study and AHOD). Belgium, France, and Italy, do not require specific ethics approval over and above that needed for their individual cohorts (Nice/Aquitaine, Brussels St Pierre, and IcoNA, respectively), and the Netherlands do not require any specific ethics approval because data are provided as part of HIV care (ATHENA). For the EuroSIDA study (that includes the data from the BASS and Swedish cohorts), which encompasses participants from many European countries, each participating site has a contractual obligation to ensure that data collection and sharing is done in accordance with national legislation; each site's principal investigator either maintains appropriate documentation from an ethics committee (if required by law) or has a documented written statement to say that this is not needed.

Procedures

For this study, baseline was defined as the first eGFR measured during prospective follow-up after Jan 1, 2004; eGFRs were calculated by creatinine clearance by use of the Cockcroft-Gault formula and standardised for body surface area, with bodyweight measured within 1 year of serum creatinine. When more than one eGFR measurement was done within a 28-day period, the median of all measurements taken during that period was used and assigned to the median date. Combination ART was defined as three or more antiretrovirals from any drug class. Chronic kidney disease was defined as confirmed (>3 months apart) eGFR lower than 60 mL/min per 1.73 m². Follow-up for each individual was calculated until the occurrence of chronic kidney disease, last visit plus 6 months, last eGFR date plus 6 months, or Feb 1, 2014 (whichever occurred first), to allow for reporting delays. Exposure to tenofovir disoproxil fumarate, ritonavir-boosted lopinavir, ritonavir-boosted atazanavir, other ritonavir-boosted protease inhibitors (ie, all other ritonavir-boosted protease inhibitors except for lopinavir and atazanavir), and abacavir was investigated as cumulative exposure, as previously described and including exposure before baseline,¹⁷ and additionally as never exposed, exposed but off antiretroviral (including time since stopping), and currently exposed.

Statistical analysis

We used Poisson regression to model incidence rates of chronic kidney disease according to cumulative antiretroviral exposure, after adjustment for confounding

	All patients (n=23 905)	Patients who did not develop chronic kidney disease (n=23 620)	Patients who developed chronic kidney disease (n=285)
Sex			
Male	17 378 (73%)	17 175 (73%)	203 (71%)
Female	6527 (27%)	6445 (27%)	82 (29%)
Race			
White	10 939 (46%)	10 778 (46%)	161 (57%)
Black	1980 (8%)	1970 (8%)	10 (3%)
Other	543 (2%)	539 (2%)	4 (1%)
Unknown	10 443 (44%)	10 333 (44%)	110 (39%)
Risk factor			
Homosexual	10 710 (45%)	10 604 (45%)	106 (37%)
Injection drug user	3074 (13%)	2992 (13%)	82 (29%)
Heterosexual	8681 (36%)	8600 (36%)	81 (28%)
Other	1440 (6%)	1424 (6%)	16 (6%)
Hepatitis B status			
Negative	21 054 (88%)	20 803 (88%)	251 (88%)
Positive	1102 (5%)	1088 (5%)	14 (5%)
Unknown	1749 (7%)	1729 (7%)	20 (7%)
Hepatitis C status			
Negative	17 201 (72%)	17 050 (72%)	151 (53%)
Positive	4340 (18%)	4234 (18%)	106 (37%)
Unknown	2364 (10%)	2336 (10%)	28 (10%)
Antiretrovirals*			
Never used ART	6354 (27%)	6320 (27%)	34 (12%)
Ever started cART	17 151 (72%)	16 903 (72%)	248 (87%)
Smoking status			
Current	10 138 (42%)	9996 (42%)	142 (50%)
Previous	4247 (18%)	4183 (18%)	64 (22%)
Never	6625 (28%)	6566 (28%)	59 (21%)
Unknown	2895 (12%)	2875 (12%)	20 (7%)
Body-mass index (kg/m ²)			
<18	666 (3%)	641 (3%)	25 (9%)
18–26	16 576 (69%)	16 369 (69%)	207 (73%)
26–30	3867 (16%)	3833 (16%)	34 (12%)
>30	1493 (6%)	1479 (6%)	15 (5%)
Unknown	1303 (5%)	1298 (6%)	5 (2%)
Family history of cardiovascular disease			
No	15 327 (64%)	15 134 (64%)	193 (68%)
Yes	1737 (7%)	1710 (7%)	27 (10%)
Unknown	6841 (29%)	6776 (29%)	65 (23%)
Hypertension	1846 (8%)	1802 (8%)	44 (15%)
Previous cardiovascular disease	113 (1%)	109 (1%)	4 (1%)
AIDS	5305 (22%)	5204 (22%)	101 (35%)
Recent AIDS diagnosis (in previous 12 months)	1069 (5%)	1051 (5%)	18 (6%)
Diabetes	737 (3%)	707 (3%)	30 (11%)
Anaemia*	6047 (33%)	5935 (32%)	112 (46%)
Viral load <400 copies per mL	13 410 (56%)	13 225 (56%)	185 (65%)
Age (years)	39 (33–45)	39 (33–44)	47 (42–54)
CD4 cell count (cells per mm ³)	441 (294–628)	441 (294–629)	414 (259–585)
Nadir CD4 cell count (cells per mm ³)	240 (120–380)	240 (120–380)	161 (63–279)

(Table 1 continues on next page)

(Continued from previous page)

	All patients (n=23 905)	Patients who did not develop chronic kidney disease (n=23 620)	Patients who developed chronic kidney disease (n=285)
Baseline date	July, 2005 (June, 2004– March, 2007)	July, 2005 (June, 2004– April, 2007)	July, 2004 (March, 2004– September, 2015)
eGFR (mL/min per 1.73 m ²)	110 (100–125)	110 (100–125)	102 (95–113)

Data are n (%) or median (IQR) unless otherwise indicated. Baseline is defined as the first eGFR measured during prospective follow-up in D:A:D after Jan 1, 2004. ART=antiretroviral therapy. cART=combination antiretroviral therapy. eGFR=estimated glomerular filtration rate. *The numbers in this section do not add up to the total number of patients because some patients did not fall into either category: they might have been exposed to ART (ie, were not naive) but had not started cART. †Baseline haemoglobin known for 18 601 (78%) of 23 905 patients overall, 242 (85%) of 285 patients who developed chronic kidney disease, and 18 359 (78%) of 23 620 who did not develop chronic kidney disease.

Table 1: Baseline characteristics

variables (race, HIV exposure group, D:A:D enrolment cohort, D:A:D participating cohort, sex, nadir CD4, date of baseline, eGFR at baseline, hepatitis B and C serostatus, smoking status, hypertension, diabetes, previous cardiovascular disease, body-mass index, family history of cardiovascular disease, viral load, CD4 cell count, and a new AIDS diagnosis within the past 12 months, all as time-updated variables). Because indinavir is known to be associated with urolithiasis, but is not in widespread use, models were adjusted for previous cumulative exposure to indinavir but associations with indinavir are not explicitly presented.

We assumed a linear association between antiretroviral exposure and chronic kidney disease based on the crude incidence rates; this association can be modelled in different ways, including quadratic terms or categorical variables, but the continuous model provided the best statistical fit and could be interpreted easily. We included variables in multivariate analyses based on those routinely recorded in D:A:D and often adjusted for in D:A:D or in renal disease, and included all potential confounders, rather than those that were significant in univariate analyses. All variables were included as categorical in the first instance and then were included as the best fitting continuous variable (eg, age was included as a linear variable and CD4 cell count was included on a log₂ scale) when the categorical variables suggested the presence of a linear trend. We assessed goodness of fit by comparing the Akaike information criterion between different models and by adding and removing confounding variables to assess how their inclusion or exclusion changed the fit of the model and the variables remaining in the model.

We repeated the analyses with chronic renal impairment as an alternative endpoint to represent renal impairment and the point at which people with decreasing eGFR could be switched away from potentially nephrotoxic antiretrovirals.⁶ Chronic renal impairment was defined as confirmed (>3 months apart) eGFR lower than 70 mL/min per 1.73 m². The association between

ritonavir-boosted atazanavir and chronic kidney disease could be confounded by the use of tenofovir disoproxil fumarate because these antiretrovirals are often used together. The analysis was therefore repeated in individuals not exposed to tenofovir (ie, right censoring follow-up at start of treatment with this drug). An additional sensitivity analysis assessed the cumulative effect of antiretrovirals after excluding person-years of follow-up and events occurring in people not exposed to the antiretroviral of interest. This analysis was extended by also excluding person-years and follow-up in people currently off the antiretroviral in question, similar to an on-treatment type analysis.

SAS version 9.3 was used for all analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2004, and July 26, 2013, eligible individuals from the D:A:D study were enrolled. Of 37 022 individuals in the D:A:D study with at least one eGFR measurement since Jan 1, 2004, 25 933 had a baseline eGFR greater than 90 mL/min per 1.73 m². 1792 individuals were excluded because they did not have two additional eGFR measurements more than 3 months apart during follow-up, and 236 were excluded because of missing viral load or CD4 cell counts. These 2028 patients had a later baseline date, a higher eGFR, were older, had a lower baseline CD4 cell count, were less likely to be of white ethnic origin, and were more likely to have hepatitis C co-infection than were those who were included in these analyses. 9003 (38%) participants had their follow-up censored at final visit plus 6 months, 5607 (24%) at last eGFR measurement plus 6 months, and 9010 (38%) on Feb 1, 2014. 285 (1%) people developed chronic kidney disease during 161 628 person-years of follow-up (at a median of 7.2 years; IQR 5.1–8.9), giving an incidence of chronic kidney disease of 1.76 per 1000 person-years of follow-up (95% CI 1.56–1.97). 23 905 people were included (table 1). From Kaplan-Meier estimation, by 2 years 0.11% (95% CI 0.07–0.15) of participants had chronic kidney disease, increasing to 0.49% (0.39–0.57) by 5 years, and 1.46% (1.26–1.66) by 8 years. The analyses included 382 733 eGFR measurements, a median of 16 (IQR 9–22) measurements per person, with a median time between measurements of 3.9 months (IQR 2.9–5.8). Participants who developed chronic kidney disease were older, had lower eGFRs at baseline, had more cardiovascular risk factors (eg, smoking, hypertension, and diabetes), and were more likely to have started combination ART compared with those who did not develop chronic kidney disease.

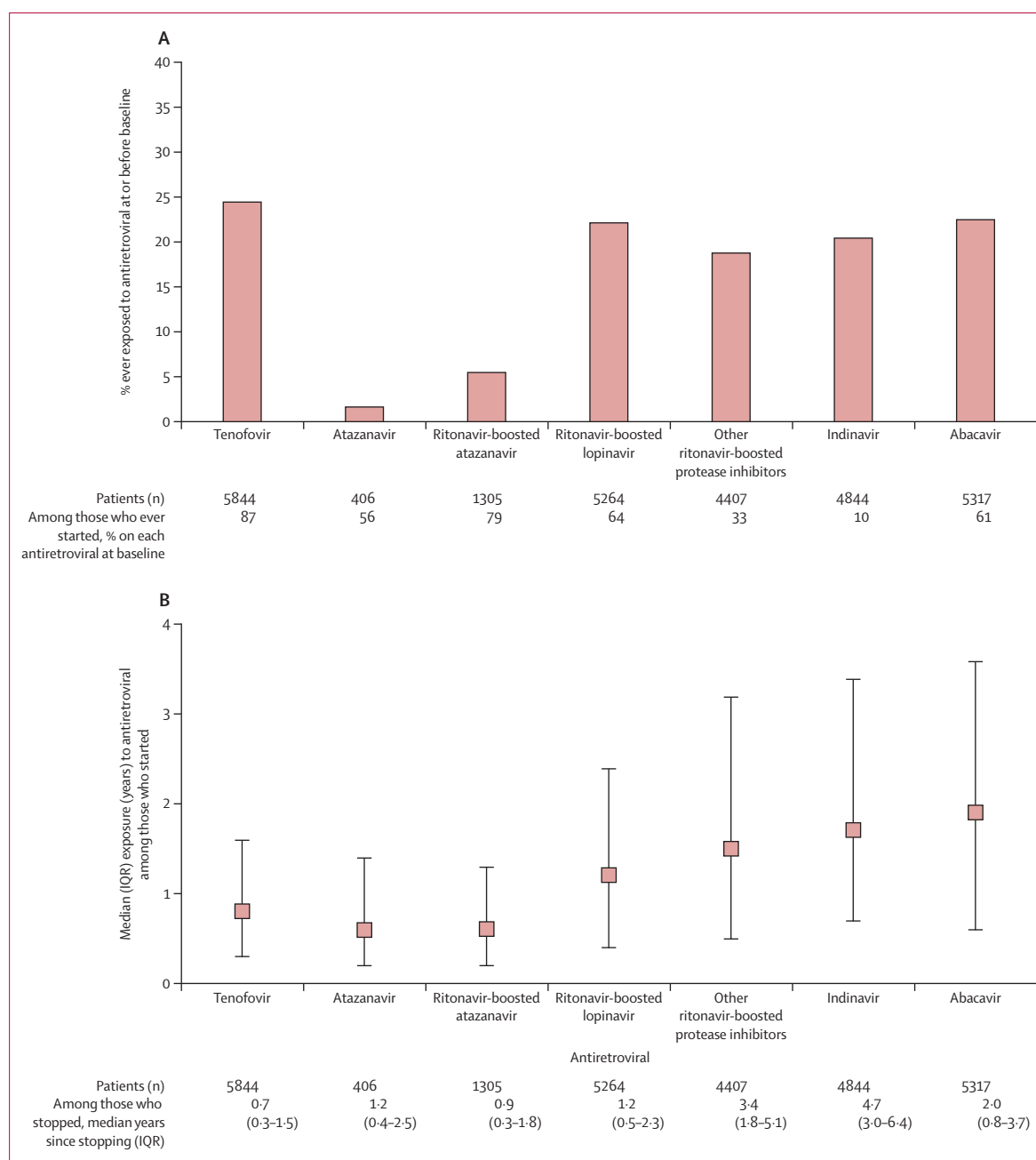


Figure 1: Use of potentially nephrotoxic antiretrovirals at baseline

(A) Exposure to antiretrovirals at or before baseline. (B) Median exposure to antiretrovirals in those who started. Baseline is the first estimated glomerular filtration rate measured during prospective follow-up in D:A:D after Jan 1, 2004.

5844 (25%) individuals had ever started tenofovir disoproxil fumarate at or before baseline, and 87% of these were taking this drug at baseline (figure 1A), with a median exposure of 0.8 years (IQR 0.3–1.6; figure 1B). Of the 761 (13%) of 5844 individuals who had stopped tenofovir before baseline, the median time since stopping was 0.7 years (0.3–1.5; figure 1B). Although a notable proportion of patients had ever used indinavir and other

ritonavir-boosted protease inhibitors, current use of either of these regimens was low at baseline (figure 1A). Furthermore, time since stopping other ritonavir-boosted protease inhibitors or indinavir was substantially longer than that for the other antiretrovirals (figure 1B).

For tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir, we recorded a clear trend of increasing incidence of chronic kidney

disease and chronic renal impairment as exposure to these antiretrovirals increased (figure 2). Insufficient data were available to consider atazanavir without ritonavir boosting. For example, in patients never exposed to tenofovir, the incidence of chronic kidney disease was 0·84 per 1000 person-years of follow-up (95% CI 0·62–1·06),

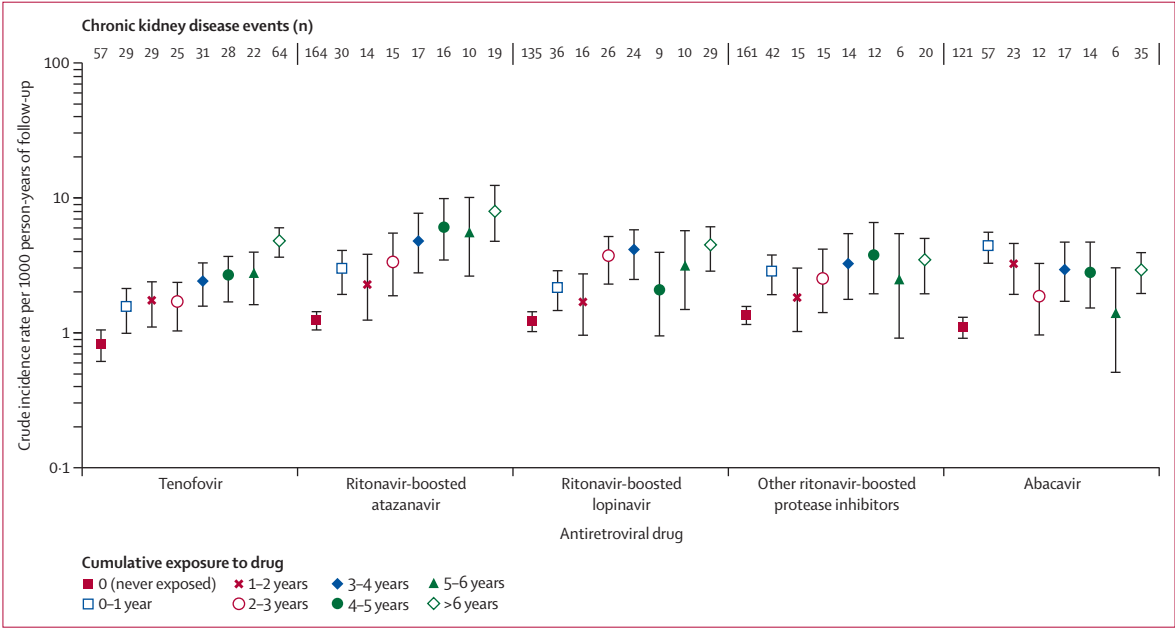


Figure 2: Crude incidence rates of chronic kidney disease and cumulative exposure to potentially nephrotoxic antiretrovirals
Error bars are 95% CIs. Chronic kidney disease is defined as confirmed (>3 months apart) estimated glomerular filtration rate <60 mL/min per 1·73 m².

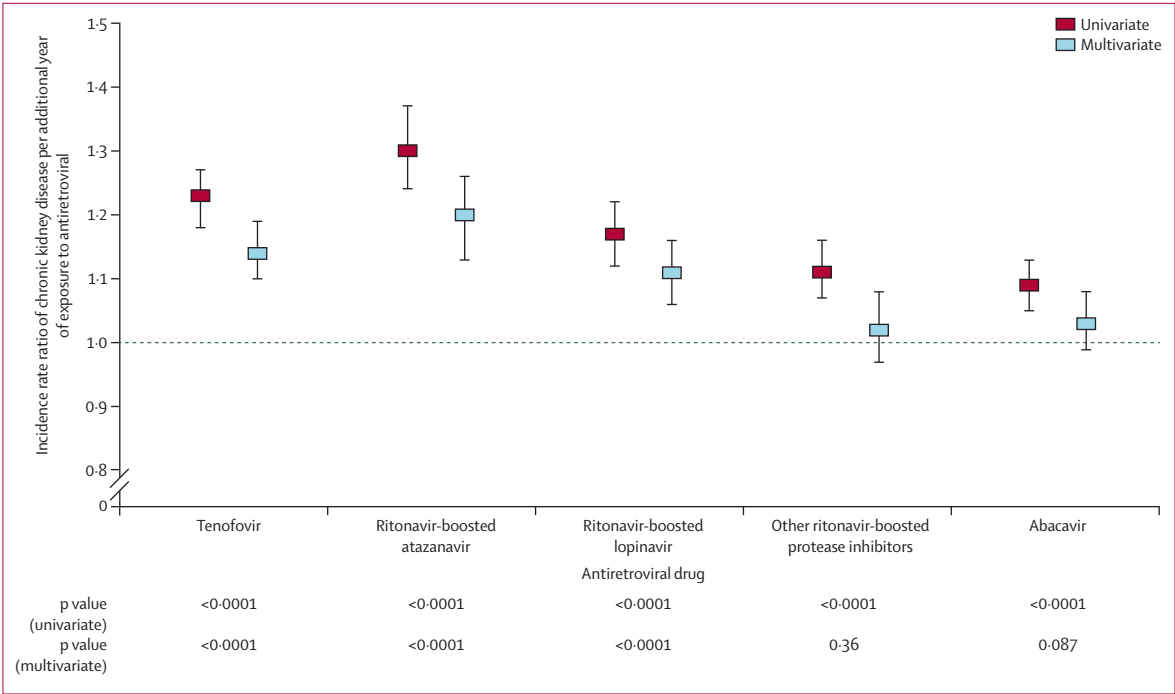


Figure 3: Unadjusted and adjusted incidence rates of chronic kidney disease per year of additional exposure to potentially nephrotoxic antiretrovirals
Error bars are 95% CIs. Chronic kidney disease is defined as confirmed (>3 months apart) estimated glomerular filtration rate <60 mL/min per 1·73 m². Multivariate models were adjusted for baseline date, sex, race, HIV exposure group, D:A:D enrolment cohort, previous cardiovascular disease, age, CD4 nadir, estimated glomerular filtration rate at baseline and hepatitis B/C serostatus, new AIDS diagnosis within previous 12 months, smoking status, body-mass index, family history of cardiovascular disease, CD4 cell count, viral load, anaemia, diabetes, hypertension, and combination ART (on/off) as time-updated variables. Models were also adjusted for cumulative exposure to indinavir.

	Tenofovir		Ritonavir-boosted atazanavir		Ritonavir-boosted lopinavir		Other ritonavir-boosted protease inhibitors		Abacavir	
	IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value
Chronic kidney disease*										
Model A: including all follow-up and events in all eligible patients (figure 3)										
Univariate (per year)	1.23 (1.18–1.27)	<0.0001	1.30 (1.24–1.37)	<0.0001	1.17 (1.12–1.22)	<0.0001	1.11 (1.07–1.16)	<0.0001	1.09 (1.05–1.13)	<0.0001
Multivariate (per year)	1.14 (1.10–1.19)	<0.0001	1.20 (1.13–1.26)	<0.0001	1.11 (1.06–1.16)	<0.0001	1.02 (0.97–1.08)	0.36	1.03 (0.99–1.08)	0.087
Multivariate (per 5 years)	1.94 (1.57–2.39)	<0.0001	2.44 (1.86–3.21)	<0.0001	1.66 (1.32–2.09)	<0.0001	NS	NS	NS	NS
Model B: censoring at start of tenofovir treatment										
Multivariate (per year)	1.22 (1.05–1.41)	0.0076	1.13 (1.02–1.25)	0.018	NS	NS	NS	NS
Multivariate (per 5 years)	2.71 (1.30–5.64)	0.0076	1.84 (1.11–3.03)	0.018	NS	NS	NS	NS
Model C: excluding those who never started antiretroviral therapy										
Multivariate (per year)	1.09 (1.04–1.15)	0.0009	1.13 (1.04–1.23)	0.0054	1.07 (1.00–1.14)	0.041	1.02 (0.96–1.09)	0.52	0.98 (0.93–1.03)	0.36
Multivariate (per 5 years)	1.55 (1.20–2.02)	0.0009	1.85 (1.20–2.84)	0.0054	1.40 (1.01–1.93)	0.041	NS	NS	NS	NS
Model D: patients on antiretroviral therapy, excluding those who never started antiretroviral therapy										
Multivariate (per year)	1.13 (1.06–1.21)	0.0002	NS	NS	NS	NS	NS	NS	NS	NS
Multivariate (per 5 years)	1.87 (1.34–2.61)	0.0002	NS	NS	NS	NS	NS	NS	NS	NS
Chronic renal impairment†										
Model A: including all follow-up and events										
Univariate (per year)	1.24 (1.22–1.27)	<0.0001	1.27 (1.23–1.30)	<0.0001	1.12 (1.09–1.15)	<0.0001	1.10 (1.07–1.13)	<0.0001	1.06 (1.04–1.08)	<0.0001
Multivariate (per year)	1.18 (1.15–1.22)	<0.0001	1.14 (1.10–1.17)	<0.0001	1.06 (1.03–1.09)	<0.0001	1.02 (0.99–1.05)	0.14	1.02 (0.99–1.05)	0.056
Multivariate (per 5 years)	2.27 (2.02–2.54)	<0.0001	1.91 (1.63–2.23)	<0.0001	1.32 (1.15–1.52)	<0.0001	NS	NS	NS	NS

IRR=incidence rate ratio. NS=not significant and therefore not presented. Multivariate models were adjusted for baseline date, sex, race, HIV exposure group, D:A:D enrolment cohort, D:A:D participating cohort, previous cardiovascular disease, age, CD4 nadir, eGFR at baseline, hepatitis B/C serostatus, new AIDS diagnosis within the previous 12 months, smoking status, body-mass index, family history of cardiovascular disease, CD4 cell count, viral load, anaemia, diabetes, hypertension, and combination antiretroviral therapy (on/off) as time-updated variables. Models were also adjusted for cumulative exposure to indinavir. A separate category was included for missing data when data were missing. Each multivariate model is also adjusted for cumulative exposure to all other potentially nephrotoxic antiretrovirals that are the not the focus of the model (eg, for tenofovir, the model is also adjusted for exposure to atazanavir, ritonavir-boosted atazanavir, ritonavir-boosted lopinavir, other ritonavir-boosted protease inhibitor regimens not already adjusted for, and abacavir). Model A is the main analysis, including all events and person-years of follow-up in all eligible patients. Model B is the same as model A but right censors individuals when they start tenofovir treatment. Model C considers the cumulative effect of antiretrovirals excluding people who had never started the antiretroviral of interest; a separate model is run for each antiretroviral (eg, for tenofovir, individuals are left censored at the point of starting tenofovir; person-years of follow-up and events occurring before starting tenofovir are excluded). Model D extends model C and considers the cumulative effect of antiretrovirals, excluding individuals who had never started the antiretroviral of interest and only includes patients who are currently taking the drug; a separate model is run for each antiretroviral. For example, for tenofovir, individuals are left censored at the point of starting tenofovir and right censored when they stop tenofovir; person-years of follow-up and events occurring before starting tenofovir are excluded, as are person-years of follow-up and events occurring while off tenofovir. *Chronic kidney disease defined as confirmed (>3 months apart) estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m². †Chronic renal impairment defined as confirmed (>3 months apart) eGFR <70 mL/min per 1.73 m².

Table 2: Incidence rates of chronic kidney disease and chronic renal impairment associated with increasing exposure to antiretrovirals

increasing steadily to 4.84 per 1000 person-years of follow-up (3.66–6.03) in individuals with more than 6 years of exposure to this drug. The rise in chronic kidney disease as exposure to other ritonavir-boosted protease inhibitors and abacavir increased was less clear. After adjustment, increasing exposure to tenofovir, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir was associated with an increased incidence of chronic kidney disease (figure 3). For example, in univariate analyses, each additional year of exposure to tenofovir disoproxil fumarate was associated with a 23% increased incidence of chronic kidney disease (table 2) and after adjustment (multivariate analyses), each additional year exposure to this drug was associated with a 14% increased incidence of chronic kidney disease (table 2). Cumulative exposure to other ritonavir-boosted protease inhibitors and abacavir was not associated with an increased incidence of chronic kidney disease after adjustment.

The increased incidence of chronic kidney disease per year of exposure to specific antiretrovirals (figure 3 and table 2; model A, chronic kidney disease) were all

quite modest in size, but antiretroviral treatment extends for many years. After 5 years of exposure to tenofovir disoproxil fumarate, there was almost a two-fold increased incidence of chronic kidney disease, with similar increases after 5 years of exposure to ritonavir-boosted atazanavir or lopinavir (see model A in table 2).

57 chronic kidney disease events occurred in 67971 person-years of follow-up after the exclusion of follow-up and events occurring after starting tenofovir disoproxil fumarate (model B, chronic kidney disease). This model assesses the relation between ritonavir-boosted atazanavir or lopinavir and chronic kidney disease in patients never exposed to or before starting tenofovir. The association between ritonavir-boosted atazanavir or ritonavir-boosted lopinavir and chronic kidney disease was similar to that in the main analysis (table 2), although with wider confidence intervals, indicating that there were significantly fewer events and person-years of follow-up, especially for ritonavir-boosted atazanavir. Additionally, we recorded a significant association between tenofovir and chronic kidney disease

in people never exposed to ritonavir-boosted atazanavir, lopinavir, or other protease inhibitors, including 55 events and 72 468 person-years of follow-up (adjusted incidence risk ratio 1.28 per year of exposure [95% CI 1.17–1.39]).

Participants who were not exposed to the antiretroviral of interest had substantially lower event rates than those who were exposed (figure 2), which could suggest a different underlying risk for chronic kidney disease in those who never started each antiretroviral compared with those who started. Exclusion of the events and person-years of follow-up in those never exposed to each of the antiretrovirals in turn (model C, chronic kidney disease, table 2) showed a weaker association between each antiretroviral and chronic kidney disease, but increasing exposure remained statistically significant (model C, chronic kidney disease; table 2). The final model for chronic kidney disease assesses the increased incidence of chronic kidney disease for those currently on the antiretroviral of interest, similar to an on-treatment analysis (model D, chronic kidney disease). The results from this analysis were consistent with the main analysis for tenofovir, but in this analysis, additional exposure to ritonavir-boosted atazanavir (adjusted incidence risk ratio per year of exposure 1.05, 95% CI 0.92–1.19) or ritonavir-boosted lopinavir (1.09, 0.98–1.21) was not associated with a significantly increased incidence of chronic kidney disease.

We repeated our analyses using chronic renal impairment as an endpoint (table 2). 923 people developed chronic renal impairment during 159 881 person-years of follow-up, to give an incidence of chronic renal impairment of 5.77 per 1000 person-years of follow-up (95% CI 5.40–6.15). Increasing exposure to tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir were all associated with an increased incidence of chronic renal impairment (table 2). Cumulative exposure to other ritonavir-boosted protease inhibitors or abacavir was not associated with an increased incidence of chronic renal impairment.

Discussion

This large study of almost 24 000 HIV-positive individuals with an initially normal eGFR clearly shows, for the first time, that the association between tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir and chronic kidney disease is cumulative in nature. This finding suggests that people starting treatment with these antiretrovirals have a small, but significantly rising, incidence of chronic kidney disease with increasing exposure to these drugs. The incidence of chronic kidney disease continued to increase with up to 5 years or more of exposure; after 5 years, it was equivalent to an increased incidence of chronic kidney disease of 1.94-times for tenofovir, 2.44-times for ritonavir-boosted atazanavir, and 1.66-times for ritonavir-boosted lopinavir. The continued rise in risk of chronic kidney disease that we

recorded with increased exposure suggests a cumulative toxic effect of these drugs.

The increased incidence of chronic kidney disease per year exposure to each of the antiretrovirals considered was consistent with previous data from EuroSIDA,⁸ one of the cohorts that contributed data to this analysis. This previous work did not focus on individuals with an initially normal eGFR, and was only able to show the cumulative effect of 2 years of antiretroviral exposure. Furthermore, this study adds to the earlier publication from D:A:D⁶ by focusing on chronic kidney disease alone, more than doubling the number of events, adding almost 3 years to median duration of follow-up, and considering the role of antiretrovirals in much greater detail (cumulative and current exposure). Treatment with combination ART can extend for many years, and, to our knowledge, ours is the first well-powered study to show the risks of chronic kidney disease were not self-limiting and extended up to 5 years of antiretroviral exposure. The relation between tenofovir disoproxil fumarate and chronic kidney disease was similar in people who were never exposed to any ritonavir-boosted protease inhibitor. Tenofovir disoproxil fumarate is widely recommended and used as first-line antiretroviral treatment in both developed and developing countries, and both ritonavir-boosted atazanavir and lopinavir are suggested as a suitable alternative first-line regimen for some individuals and are recommended as second-line therapy in developing countries.¹⁸ The so-called early hit phenomenon of tenofovir is largely a result of short-term clinical trials that suggested an early reduction in serum creatinine, with few changes after the first months of therapy.^{13,19–22} Preliminary data suggest that the risk of renal injury is lower with the novel tenofovir prodrug tenofovir alafenamide than tenofovir disoproxil fumarate,²³ but long-term follow-up will be necessary to confirm this.

Cumulative exposure to either ritonavir-boosted atazanavir or lopinavir was associated with an increased incidence of chronic kidney disease, independently of exposure to tenofovir disoproxil fumarate, and in patients not exposed to tenofovir. Tenofovir disoproxil fumarate has been associated with proximal renal tubular dysfunction related to mitochondrial toxicity²⁴ and both ritonavir-boosted lopinavir and atazanavir have been associated with interstitial nephritis, urolithiasis, and urinary stones,^{9,10} although the exact mechanism is unclear. Findings from other studies between ritonavir-boosted atazanavir, ritonavir-boosted lopinavir, and chronic kidney disease or other markers of renal function are contradictory^{7,12,25} and conflicting evidence exists regarding whether or not the precipitation of protease inhibitor crystals leads to interstitial nephritis and a decrease in eGFR.²⁶ Recent studies have shown that many antiretroviral drugs, including ritonavir, reduce tubular creatinine secretion¹¹ and declines in eGFR associated with antiretroviral medications might not be caused by renal toxicity itself. However, if changes in eGFR were merely a result of reduced tubular secretion,

one would expect a rapid decrease in eGFR after starting antiretroviral drugs without further changes in renal function. The association between chronic kidney disease and ritonavir-boosted atazanavir or lopinavir was somewhat weaker and not statistically significant when we restricted the analysis to those on treatment, in which, by definition, chronic kidney disease occurred only in those currently on ritonavir-boosted atazanavir or lopinavir, and chronic kidney disease events occurring after discontinuation of ritonavir-boosted atazanavir or lopinavir as eGFR declined were excluded. This finding could suggest some selection bias by clinicians of those thought to be at lower risk of chronic kidney disease to remain on their antiretroviral drugs as eGFR declined.

We found no evidence that other ritonavir-boosted protease inhibitors were associated with an increased incidence of chronic kidney disease, suggesting no large effect of ritonavir boosting on chronic kidney disease when not used to boost atazanavir or co-formulated as ritonavir-boosted lopinavir. The other ritonavir-boosted protease inhibitor group mainly comprised older boosted combinations. The number of people taking ritonavir-boosted tipranavir or darunavir either at baseline or during follow-up was low (<1000 person-years of follow-up and ten chronic kidney disease events for each of these antiretrovirals). Ritonavir-boosted darunavir was used more commonly during follow-up, with similar person-years of follow-up and chronic kidney disease events as atazanavir, but insufficient data were available to stratify the events according to duration of exposure. Further data are needed to explore the association between chronic kidney disease and newer or lesser used ritonavir-boosted protease inhibitor regimens such as tipranavir or darunavir, or other antiretroviral combinations such as elvitegravir boosted with cobicistat.

The increase in chronic kidney disease incidence per year of exposure to tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir was modest, and the risk-to-benefit ratio of any antiretroviral regimen should be considered for all patients initiating treatment. The effect of the association between tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir was cumulative and after 5 years of exposure the incidence of chronic kidney disease increased by two-to-three-fold. Notably, the effect per year of additional tenofovir exposure was smaller than previously reported in other studies,^{8,12} and was similar across various sensitivity analyses. This difference in effect size between studies could be explained by differences in baseline eGFR, HIV-independent risk factors, greater awareness of renal toxicities associated with tenofovir disoproxil fumarate with active selection of low-risk patients for treatment with this drug, and increased switching as eGFR declines before the development of chronic kidney disease. Importantly, the chronic kidney disease events in this study represented large and clinically important changes in eGFR. All participants started with

eGFR greater than 90 mL/min per 1.73 m²; those who developed chronic kidney disease lost a third or more of eGFR during follow-up and had a greater than 5 mL/min per 1.73 m² decline in eGFR, which is the threshold for rapid progression of chronic kidney disease.²⁷

Our study has several limitations. This is an observational study and unmeasured confounding cannot be ruled out and causality between antiretrovirals and chronic kidney disease cannot be proven. Because of limitations in collection of data regarding race in some European cohorts, we were limited to using the Cockcroft-Gault equation for creatinine clearance to estimate eGFR. Previous research has suggested that Cockcroft-Gault is similar to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for predicting chronic kidney disease in cohort studies.²⁸ The D:A:D study has no information about proteinuria, and we were not able to adjust for this as a risk factor for chronic kidney disease; however, studies adjusting for proteinuria have shown similar findings to ours.¹² We were also not able to adjust for concomitant medication, such as non-steroidal anti-inflammatory drugs. Participants in D:A:D contributing data to this study were from Europe and Australia, and although availability and access to antiretrovirals and serum creatinine measurements in different cohorts can be assumed to be similar after Jan 1, 2004, differences between cohorts in management of patients will remain. We adjusted for cohort to account for some of these differences, but unmeasured confounding might remain. We used a single measurement to categorise individuals as having a normal eGFR at baseline, but our results were consistent if we used a confirmed eGFR greater than 90 mL/min per 1.73 m² at baseline as an inclusion criterion, with significantly less power. We have shown an increased incidence of chronic kidney disease over 6 years of exposure, but even longer follow-up is needed to establish whether or not that increase will plateau with longer exposure to the antiretroviral drugs.

To conclude, the incidence of chronic kidney disease in HIV-positive individuals increases continuously with duration of exposure to specific antiretrovirals, with no evidence that the development of chronic kidney disease was limited to the first few months of starting antiretrovirals and no plateau in the increasing incidence after a median follow-up of more than 6 years. Our results were consistent across a range of sensitivity analyses and when we used chronic renal impairment as an alternative endpoint. Tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir are among the most widely used antiretrovirals used to treat HIV worldwide. The D:A:D study has previously published a risk score for chronic kidney disease, which is available online.²⁹ This online tool enables individuals to ascertain the risk of chronic kidney disease, and the risks and benefits of potentially nephrotoxic antiretrovirals should be weighed against the long-term risk of chronic kidney disease with extended exposure to antiretrovirals.

For the D:A:D study risk score
see <http://hivpv.org/Home/Tools/ChronicKidneyDiseaseTool.aspx>

Contributors

AM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AM, JDL, and LR proposed and developed the research question, and designed the statistical analyses. MR, CAF, PR, OM, PM, AdAM, and OK contributed ideas for study design and interpretation of the data. AM wrote the first draft of the report. All authors have seen and contributed to the final version of the report.

Declaration of interests

AM has received speaker fees, travel support, or honoraria from Gilead, Pfizer, Merck, BMS, BI, and Wragge LLC. CAF has received personal fees from Gilead, AbbVie, Janssen, and ViiV, outside the submitted work. OM has received honoraria, speaker fees, travel support, or honoraria from Gilead. PR has received grants from Gilead Sciences, ViiV Healthcare, Janssen, Bristol-Myers Squibb, and Merck, and personal fees, travel support and/or honoraria from Gilead Science, Janssen, and ViiV Healthcare, outside the submitted work. PM has received personal fees and non-financial support from ViiV Healthcare, Gilead, and BMS, and personal fees from Janssen and MSD, outside the submitted work. AdAM has received personal fees from AbbVie, Janssen, MSD, and ViiV Healthcare, and grants and personal fees from BMS and Gilead, outside the submitted work. The other authors declare no competing interests.

Acknowledgments

The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the funders of the D:A:D study. The D:A:D study was supported by the Highly Active Antiretroviral Therapy Oversight Committee, the European Agency for the Evaluation of Medicinal Products, the US Food and Drug Administration, the patient community, and the following pharmaceutical companies with licensed anti-HIV drugs in the European Union: AbbVie, Bristol-Myers Squibb, Gilead Sciences Inc, ViiV Healthcare, Merck & Co Inc, and Janssen Pharmaceuticals. Full funding acknowledgments are in the appendix.

References

- Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998; **352**: 1725–30.
- Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 2009; **338**: a3172.
- Winston JA. HIV and CKD epidemiology. *Adv Chronic Kidney Dis* 2010; **17**: 19–25.
- de Boer IH. Chronic kidney disease—a challenge for all ages. *JAMA* 2012; **308**: 2401–02.
- 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.
- 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.
- Yombi JC, Pozniak A, Boffito M, et al. Antiretrovirals and the kidney in current clinical practice: renal pharmacokinetics, alterations of renal function and renal toxicity. *AIDS* 2014; **28**: 621–32.
- 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.
- Brewster UC, Perazella MA. Acute interstitial nephritis associated with atazanavir, a new protease inhibitor. *Am J Kidney Dis* 2004; **44**: e81–84.
- Doco-Lecompte T, Garrec A, Thomas L, Trechot P, May T, Rabaud C. Lopinavir-ritonavir (Kaletra) and lithiasis: seven cases. *AIDS* 2004; **18**: 705–06.
- Lepist EI, Zhang X, Hao J, et al. Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicistat. *Kidney Int* 2014; **86**: 350–57.
- Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS* 2012; **26**: 867–75.
- Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *J Acquir Immune Defic Syndr* 2008; **47**: 74–78.
- Laprise C, Baril JG, Dufresne S, Trottier H. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 years of follow-up. *Clin Infect Dis* 2013; **56**: 567–75.
- Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naïve, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr* 2010; **55**: 49–57.
- Zolopa A, Sax PE, DeJesus E, et al. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr* 2013; **63**: 96–100.
- Friis-Møller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. *AIDS* 2003; **17**: 1179–93.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 2015. <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf> (accessed Feb 10, 2015).
- Cao Y, Han Y, Xie J, et al. Impact of a tenofovir disoproxil fumarate plus ritonavir-boosted protease inhibitor-based regimen on renal function in HIV-infected individuals: a prospective, multicenter study. *BMC Infect Dis* 2013; **13**: 301.
- Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005; **40**: 1194–98.
- Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004; **292**: 191–201.
- Winston A, Amin J, Mallon P, et al. Minor changes in calculated creatinine clearance and anion-gap are associated with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy. *HIV Med* 2006; **7**: 105–11.
- Sax PE, Zolopa A, Brar I, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr* 2014; **67**: 52–58.
- Kohler JJ, Hosseini SH, Green E, et al. Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters. *Lab Invest* 2011; **91**: 852–58.
- Albini L, Cesana BM, Motta D, et al. A randomized, pilot trial to evaluate glomerular filtration rate by creatinine or cystatin C in naïve HIV-infected patients after tenofovir/emtricitabine in combination with atazanavir/ritonavir or efavirenz. *J Acquir Immune Defic Syndr* 2012; **59**: 18–30.
- Harris M. Nephrotoxicity associated with antiretroviral therapy in HIV-infected patients. *Expert Opin Drug Saf* 2008; **7**: 389–400.
- Kidney Disease Improving Global Outcome Guidelines. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl* 2013; **3**: 19–62.
- 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.
- Mocroft A, Lundgren JD, Ross M, et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. *PLoS Med* 2015; **12**: e1001809.