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Association Between Antiretroviral Exposure and Renal Impairment Among HIV-Positive Persons With Normal Baseline Renal Function: the D:A:D Study[a]

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(See the editorial commentary by Fine and Gallant on pages 1349–51.)

Background. Several antiretroviral agents (ARVs) are associated with chronic renal impairment, but the extent of such adverse events among human immunodeficiency virus (HIV)–positive persons with initially normal renal function is unknown.

Methods. D:A:D study participants with an estimated glomerular filtration rate (eGFR) of ≥90 mL/min after 1 January 2004 were followed until they had a confirmed eGFR of ≤70 mL/min (the threshold below which we hypothesized that renal interventions may begin to occur) or ≤60 mL/min (a value indicative of moderately severe chronic kidney disease [CKD]) or until the last eGFR measurement during follow-up. An eGFR was considered confirmed if it was detected at 2 consecutive measurements ≥3 months apart. Predictors and eGFR-related ARV discontinuations were identified using Poisson regression.

Results. Of 22 603 persons, 468 (2.1%) experienced a confirmed eGFR of ≤70 mL/min (incidence rate, 4.78 cases/1000 person-years of follow-up [95% confidence interval {CI}, 4.35–5.22]) and 131 (0.6%) experienced CKD (incidence rate, 1.33 cases/1000 person-years of follow-up [95% CI, 1.10–1.56]) during a median follow-up duration of 4.5 years (interquartile range [IQR], 2.7–6.1 years). A current eGFR of 60–70 mL/min caused significantly higher rates of discontinuation of tenofovir (adjusted incidence rate ratio [aIRR], 1.72 [95% CI, 1.38–2.14]) but not other ARVs compared with a current eGFR of ≥90 mL/min. Cumulative tenofovir use (aIRR, 1.18/year [95% CI, 1.12–1.25]) and ritonavir-boosted atazanavir use (aIRR, 1.19/year [95% CI, 1.09–1.32]) were independent predictors of a confirmed eGFR of ≤70 but were not significant predictors of CKD whereas ritonavir-boosted lopinavir use was a significant predictor for both end points (aIRR, 1.11/year [95% CI, 1.05–1.17] and 1.22/year [95% CI, 1.16–1.28], respectively). Associations were unaffected by censoring for concomitant ARV use but diminished after discontinuation of these ARVs.

Conclusions. Tenofovir, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir use were independent predictors of chronic renal impairment in HIV-positive persons without preexisting renal impairment. Increased tenofovir discontinuation rates with decreasing eGFR may have prevented further deteriorations. After discontinuation, the ARV-associated incidence rates decreased.

Keywords. HIV; eGFR; ART; tenofovir; atazanavir; lopinavir; chronic kidney disease; nephrotoxicity.

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The majority of human immunodeficiency virus (HIV)–positive persons have normal renal function, as defined by a normal estimated glomerular filtration rate (eGFR), with a relatively low overall risk of developing chronic renal impairment [1–4]. Exposure to several antiretroviral drugs (antiretrovirals [ARVs]), including tenofovir (TDF), ritonavir-boosted atazanavir (ATV/r), unboosted ATV, indinavir (IDV), ritonavir-boosted lopinavir (LPV/r), and other ritonavir-boosted protease inhibitors (other PI/r), may lead to chronic renal impairment in HIV-positive populations with varying degrees of preexisting impairment [1–4]. The extent of such adverse drug reactions in persons with normal baseline renal function is unknown but important to elucidate, given the numerous complications associated with chronic renal impairment [5]. Furthermore, the literature has not clarified the impact of clinicians' discontinuation of potentially nephrotoxic drugs. The aim of this analysis was to assess the possible independent contribution of potentially nephrotoxic ARVs relative to that of established risk factors for renal impairment, to the rate of progression from initially normal renal function to chronic impairment.

METHODS

The D:A:D study was established in 1999 and is a prospective cohort study including 49 734 HIV-positive persons from established cohorts in Europe, the United States, and Australia. Detailed information on predefined clinical events is collected in real time and centrally adjudicated. Information on treatment, laboratory values, demographic characteristics, and other variables is collected from the participating cohorts every 6 months. Study details have been published earlier [6].

The current analysis included persons who were undergoing active follow-up in the D:A:D study and had ≥3 serum creatinine measurements after 1 January 2004 (when systematic creatinine collection was first started) and a normal eGFR, defined according to the Kidney Disease Improving Global Outcomes as an eGFR of ≥90 mL/min [7]. Follow-up lasted from baseline, defined as the time of the first eGFR measurement after 1 January 2004, until development of a confirmed eGFR of ≤70 mL/min (the threshold below which we hypothesized that renal interventions may begin to occur) or ≤ 60 mL/min (a value indicative of moderately severe chronic kidney disease [CKD]) or until the last eGFR measurement during follow-up. An eGFR was considered confirmed if it was detected at 2 consecutive measurements ≥3 months apart. The Cockcroft-Gault equation [8], standardized for body surface area [9], was used to calculate eGFRs [10]. The Cockcroft-Gault equation was used because several cohorts had restrictions on the use of ethnicity data. For persons with frequent eGFR measurements, a 28-day average was calculated.

Incidence rates of progression from an eGFR of ≥90 mL/min to eGFRs of ≤70 mL/min and CKD were calculated per 1000 person-years of follow-up. Poisson regression models were used to identify independent predictors for confirmed eGFR ≤70 and CKD from eGFR >90 and to assess discontinuation of included ARVs with respect to the current eGFR. Exposures to TDF, unboosted ATV, ATV/r, LPV/r, abacavir (ABC), and other PI/r (including darunavir, tipranavir, (fos)amprenavir, and other PIs, when boosted by ritonavir) were included a priori because of their documented or suspected relationship with renal function [1–5, 11, 12]. Because of limited IDV exposures after 2004, exposure to this drug was added only to account for possible confounding. In the primary analyses, ART exposure was assessed per additional year of exposure, as previously described [6]. Median exposure to each ARV drug was calculated until achievement of a confirmed eGFR of ≤70 mL/min or CKD or, for those not experiencing an event, until the last eGFR measurement.

Non-ARV variables statistically significant at an α level of 5% in univariate analysis were included in multivariate analysis. Excluded variables were tested to determine whether their inclusion improved the overall model fit. We included demographic variables, such as age, sex, and ethnicity; HIV-related variables, such as current and nadir $CD4^+$ T-cell count, HIV load, and prior AIDS-defining illness; hepatitis B virus (HBV) positivity (defined as detection of HBV surface antigen, detection of HBV e antigen, or detection of HBV DNA plus antibody to HBV e antigen); and hepatitis C virus (HCV) positivity (defined as detection of antibody to HCV plus detection or unknown presence of HCV RNA). Also included were established risk factors for renal impairment, such as hypertension (defined as a blood pressure of >150/>100 mmHg or use of antihypertensive drugs), diabetes (defined as initiation of antidiabetic treatment or verification of diabetes in a case report form), and cardiovascular disease (defined as verification of myocardial infarction, invasive cardiovascular procedure, or stroke in a case report form). More information about variables can be accessed at the Copenhagen HIV Program Web site (available at: http://www.cphiv.dk).

Various sensitivity analyses were performed. Because ethnicity data from a number of cohorts were not available, an analysis was performed that involved only individuals whose ethnicity was known. Analyses were also repeated for persons with current virologic suppression (ie, an HIV load of <400 copies/mL). In addition, ART exposure was assessed categorically (ie, never exposed and exposed for <1, 1–2, 2–3, and >3 years). Follow-up for the ARVs significant in multivariate analysis were censored for follow-up for concomitant exposure to each of the other ARVs included in the analysis (eg, follow-up on ATV exposure was censored for any TDF exposure and vice versa). Additional censoring was made for any ART

exposure prior to baseline by excluding all treatment-experienced persons. Another sensitivity analysis included only the baseline values of all covariates, to address possible time-related confounding. Finally, an analysis limited to patients with a confirmed eGFR of ≥90 mL/min at baseline rather than a single measurement was performed.

Analyses to investigate possible interactions were performed between ARVs significant in multivariate analysis for a confirmed eGFR of ≤ 70 mL/min and age, HCV positivity, HBV positivity, prior AIDS-defining illness, and current $CD4^+$ T-cell count. For a conservative approach and to account for multiple testing, we used a *P* value of .01 to assess statistical significance.

Possible selection bias and the generalizability of our findings were assessed by comparing patients included and those excluded from analysis, using logistic regression. Channeling bias for ABC was assessed by censoring follow-up for those initiating ABC at an eGFR of < 90 mL/min.

All statistical analyses were performed using SAS, version 9.2 (Statistical Analysis Software, Cary, NC).

RESULTS

Of 49 734 persons enrolled in the D:A:D study, 80% (39 629) had creatinine level data available. Of these, 83% (32 805) had ≥3 eGFR measurements, and 57% (22 603) had ≥3 eGFR measurements and a baseline eGFR of ≥ 90 mL/min. Excluded individuals were more likely to be of African ancestry, to be HCV or HBV positive, to be smokers, to have a prior AIDS-defining illness, to have cardiovascular disease, to have hypertension, and to have acquired HIV through injection drug use (IDU). Among the 22 603 included individuals, there were 283 040 eGFR measurements available, with a median of 12 measurements/person (interquartile range [IQR], 7–16 measurements/person) and a median interval of 3.7 months (IQR, 2.8–5.7 months) between measurements. Included persons were predominantly white, male, and infected through male-male sex, and with a median age of 39 years (IQR, 33–44 years; Table 1).

Sustained and Progressive Decline

A total of 468 persons (2.1%) progressed from an eGFR of ≥90 mL/min to a confirmed eGFR of ≤70 mL/min (incidence rate, 4.78 cases/1000 person-years of follow-up [95% confidence interval {CI}, 4.35–5.22]), and 131 (0.6%) progressed to CKD (incidence rate, 1.33 events/1000 person-years of follow-up [95% CI, 1.10–1.56]) during a median follow-up duration of 4.5 years (IQR, 2.7–6.1 years). Individuals reaching a confirmed eGFR of ≤70 mL/min therefore experienced an absolute eGFR decline of ≥20 mL/min during follow-up.

ARV Switches and eGFR

Assessment of discontinuation rates in relation to the current eGFR measurement showed that, after adjustment, persons with a current eGFR of 60–70 mL/min had a significantly higher rate of TDF discontinuation (adjusted incidence rate ratio [aIRR], 1.72 [95% CI, 1.38–2.14]) but not of other ARVs compared with persons with a current eGFR of ≥90 mL/min (Figure 1).

The nucleosides most commonly initiated after TDF discontinuation depended on the current eGFR level. At lower eGFR levels, significantly higher proportions of persons initiated ABC (eGFR <60:55%, eGFR 60–70:32% vs eGFR >90:11%) and lamivudine (3TC, eGFR <60:62%, eGFR 60–70:46% vs eGFR >90:27%). In contrast, at current eGFR >90 most (re) initiated TDF (78%) and emtricitabine (64%), *P*<0.0001 for all comparisons.

ARV Exposure

At baseline, 21% of persons were receiving TDF, 15% were receiving LPV/r, 14% were receiving ABC, and 5% were receiving any ATV regimen. Among those progressing to a confirmed eGFR of ≤ 70 mL/min, the longest median exposure was to ABC (1.7 years [IQR, 0.2–3.9, years]) and LPV/r (1.5 years [IQR, 0.2–3.4 years]), whereas one of the shortest median exposures was to ATV/r (0.2 years [IQR, 0–1.7 years]). Cumulative exposure to the investigated ARVs was similar among those developing a confirmed eGFR of ≤70 mL/min, CKD or neither end point.

In multivariate analysis, cumulative exposure to TDF (aIRR, 1.18/year [95% CI, 1.12–1.25]) and ATV/r (aIRR, 1.19/year [95% CI, 1.09–1.32]) but not to unboosted ATV were independently associated with increased rates of progression to a confirmed eGFR of ≤70 mL/min, whereas the association did not reach statistical significance for progression to CKD (aIRR, 1.08/year [95% CI, 0.97–1.21] for TDF and 1.14/year [95% CI, 0.93–1.39] for ATV/r). Cumulative LPV/r exposure was significantly associated with both end points (aIRR, 1.11/year [95% CI, 1.05–1.17] for a confirmed eGFR of ≤ 70 mL/min and 1.22/year [95% CI, 1.16–1.28] for CKD; Figure 2). Censoring for concomitant exposure to each of the other ARVs studied resulted in highly consistent estimates for a confirmed eGFR of ≤70 mL/min (aIRR, 1.23/year [95% CI, 1.10–1.38] for TDF, 1.11/year [95% CI, 0.95–1.29] for LPV/r, and 1.58/year [95% CI, 1.13–2.20] for ATV/r). These results were also unaffected by excluding persons receiving any ARVs prior to baseline (aIRR, 1.18 [95% CI, 0.97–1.44] for TDF, 1.22 [95% CI, 0.99–1.51] for LPV/r, and 1.40 [95% CI, 1.05–1.86] for ATV). Restriction of follow-up to those with current virologic suppression or the requirement of a confirmed eGFR of ≥ 90 mL/min at baseline did not alter our results (data not shown).

When ARV exposure was fitted into categories based on no history of exposure, duration of current use, and time since past use, those currently on TDF, ATV/r, and LPV/r experienced increasing rates of confirmed eGFR ≤70 from eGFR

Table 1. Demographic and Clinical Characteristics and Antiretroviral Therapy (ART) Use Among Participating Patients

Baseline[a] Characteristic	All Patients Included	Patients Progressing to a Confirmed[b] eGFR of ≤70 mL/min	Patients Progressing to a Confirmed[b] eGFR of ≤60 mL/min, CKD
All	22 603 (100)	468 (2)	131 (0.6)
Male sex	16 438 (73)	340 (73)	89 (68)
Ethnicity			
White	10 573 (47)	309 (66)	88 (67)
Unknown	9714 (43)	129 (28)	37 (28)
African ancestry	1806 (8)	20 (4)	4 (3)
Age, y	39 (33–44)	46 (41–52)	46 (40–51)
HIV transmission route			
Male-male sex	10 006 (44)	176 (38)	39 (30)
Injection drug use	3058 (14)	121 (26)	41 (31)
Heterosexual sex	8095 (36)	150 (32)	42 (32)
Prior AIDS-defining illness	4553 (20)	154 (33)	48 (37)
$CD4^+$ T-cell count, cells/mm^3	440 (290–624)	380 (217–568)	380 (221–585)
HIV RNA load, log_{10} copies/mL	2.1 (1.7–4.2)	1.8 (1.7–4.0)	2.3 (1.7–4.0)
Duration of HIV positivity, y	5.2 (1.2–11.1)	10.0 (5.3–14.9)	10.8 (4.5–15.5)
HBV positive[c]	2773 (12)	64 (14)	17 (13)
HCV positive[d]	2765 (12)	93 (20)	37 (28)
Hypertension	176 (8)	53 (11)	20 (15)
Diabetes	664 (3)	43 (9)	14 (11)
Prior cardiovascular event	336 (2)	17 (4)	6 (5)
Smoking	9548 (42)	239 (51)	71 (54)
cART exposure	14 263 (63)	346 (74)	94 (72)

ART use	All Patients, No.	ARV Exposure Duration: Cumulative, PYFU	ARV Exposure Duration: Median, y
TDF	5366	2015	0 (0–0.4)
LPV/r	4963	3358	0.1 (0–1.0)
ABC	4937	5613	0.3 (0–1.9)
ATV/r	1055	296	0 (0–0.2)
ATV	352	192	0.1 (0–0.6)
Other PI/r	2216	3669	1.1 (0.3–2.5)
IND	4567	9135	1.5 (0.6-3.0)

Data are no. (%) of subjects or mean value (interquartile range), unless otherwise indicated.

Abbreviations: ABC, abacavir; ATV, unboosted atazanavir; ATV/r, ritonavir-boosted atazanavir; cART, combination ART; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; IND, indinavir; IQR, interquartile range; LPV/r, ritonavir-boosted lopinavir; PI/r, ritonavir-boosted protease inhibitor; PYFU, person-years of follow-up; TDF, tenofovir.

[a] Baseline was defined as the defined as the time, during prospective follow-up, of the first eGFR measurement after 1 January 2004.

[b] An eGFR was considered confirmed if it was detected at 2 consecutive measurements ≥3 months apart.

[c] Defined as detection of HBV surface antigen, detection of HBV e antigen, or detection of HBV DNA plus antibody to HBV e antigen.

[d] Defined as detection of antibody to HCV plus detection or unknown presence of HCV RNA.

≥90 with increasing lengths of exposure. Whereas >12 months after adrug discontinuation, the incidence rates decreased toward 1 (Figure 3).

Channeling Bias

Inconsistent trends were seen for ABC exposure and the renal outcomes (Figures 2 and 3). We performed a number of exploratory analyses and found that a lower eGFR was associated with a higher ABC initiation rate. Right-censoring follow-up for initiation of ABC at eGFR of <90 mL/min did not, however, decrease the estimates for CKD in adjusted models (right censored CKD aIRR, 1.18/year [95% CI, 1.03–1.21]), compared with the primary analysis (aIRR, 1.08/year [95% CI, 1.00–1.17]). Because ABC and 3TC were the ARVs most

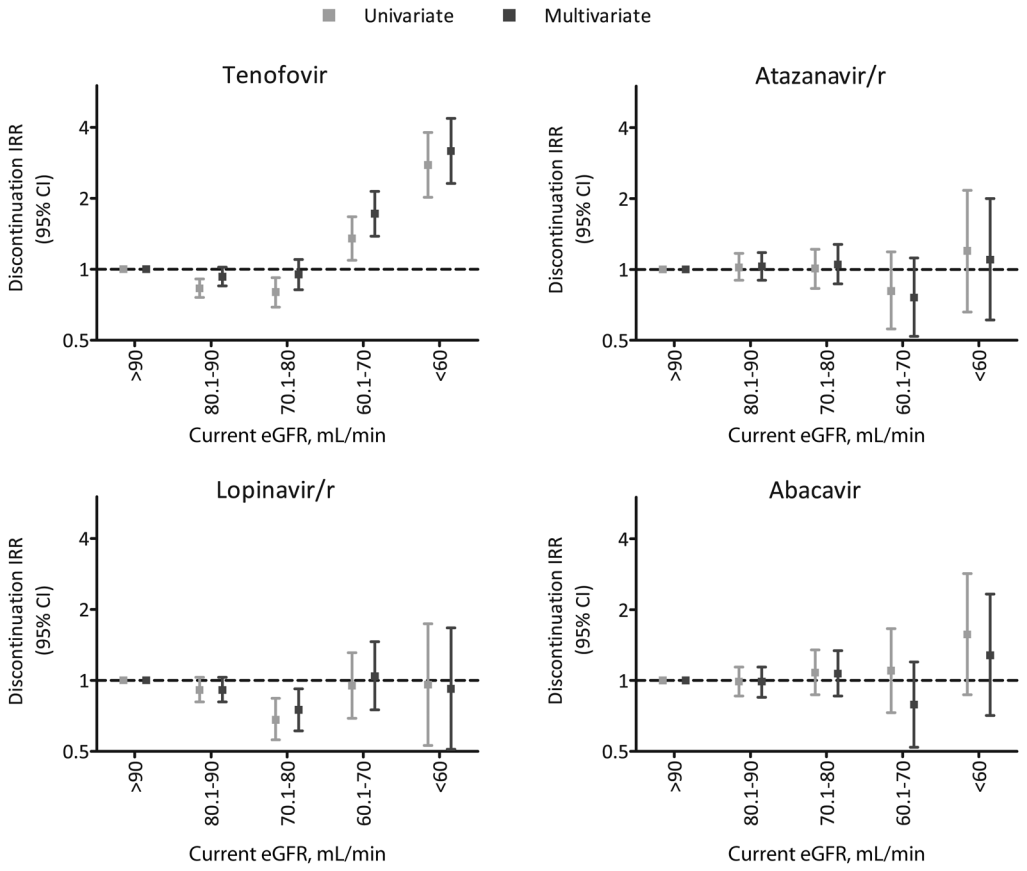

Figure 1. Antiretroviral discontinuation rates and current estimated glomerular filtration rates (eGFRs). Models adjusted for baseline eGFR (per 5-mL/min increase), age (per 10-year increase), sex, ethnicity (white, African ancestry, or unknown), mode of human immunodeficiency virus (HIV) transmission (male-male sex, heterosexual, injection drug use, unknown, or other), nadir $CD4^+$ T-cell count, enrollment cohort, prior AIDS-defining illness, and baseline date. Hepatitis B virus (HBV) positivity (defined as detection of HBV surface antigen, detection of HBV e antigen, or detection of HBV DNA plus antibody to HBV e antigen), hepatitis C virus (HCV) positivity (defined as detection of antibody to HCV plus detection or unknown presence of HCV RNA), current smoker, hypertension, diabetes, cardiovascular disease, $CD4^+$ T-cell count (per doubling), HIV load (per $\log_{10}$ copies/mL increase), and cumulative exposure (per year) to unboosted atazanavir, ritonavir-boosted atazanavir (atazanavir/r), ritonavir-boosted lopinavir (lopinavir/r), tenofovir, abacavir, indinavir, and other ritonavir-boosted protease inhibitors were included as time-updated variables. Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

commonly initiated at low eGFRs, we repeated our primary models with 3TC and observed a marginally increased rate of progression to both end points (data not shown).

Other Renal Predictors

In adjusted models, other significant predictors of progression to a confirmed eGFR of ≤70 mL/min included age (aIRR, 2.60 per 10-year increase [95% CI, 2.31–2.93]), female sex (aIRR, 1.57 [95% CI, 1.23–2.00]), diabetes (aIRR, 1.52 [95% CI, 1.05–2.21]), IDU (vs male-male sex) as mode of transmission (aIRR, 1.53 [95% CI, 1.07–2.19]), prior AIDS-defining illness (aIRR, 1.39 [95% CI, 1.13–1.70]), and current $CD4^+$ T-cell count (aIRR, 0.75 per doubling [95% CI, 0.69–0.82]); (Figure 4). Similar findings were observed for progression to CKD. Hypertension (aIRR, 0.93 [95% CI, 0.65–1.32]) and HBV positivity (aIRR, 0.89 [95% CI, 0.59–1.34]) were not associated with either end point, whereas a higher baseline eGFR and later calendar year were significantly associated with a lower rate of progression to a confirmed eGFR of ≤70 mL/min only. Sensitivity analyses that used baseline values of all non-ARV variables, rather than their time-updated values, did not alter our findings.

There were no significant interactions between ARV use and age, HCV positivity, HBV positivity, prior AIDS-defining illness, or $CD4^+$ T-cell count ($P > .01$ for all), indicating that the relationship between cumulative ART exposure and a confirmed eGFR of ≤70 mL/min was similar for younger and older patients; for patients with and those without HBV

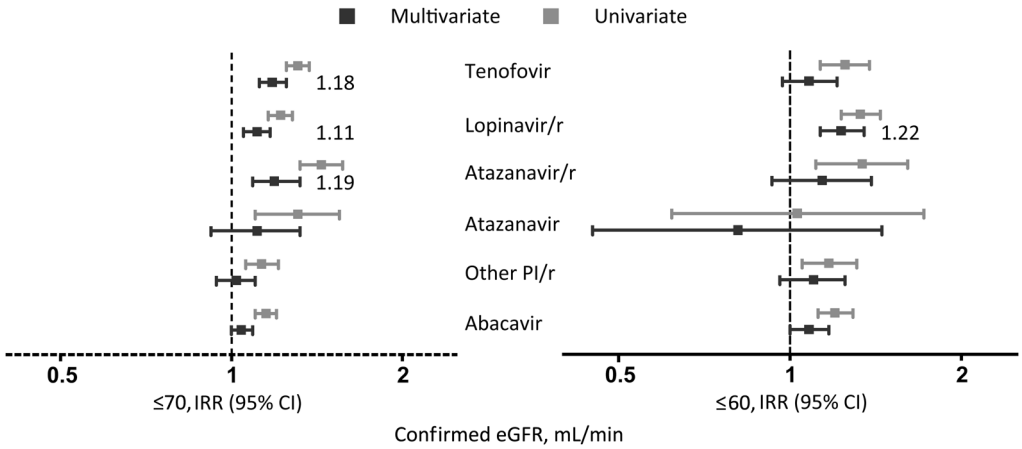

Figure 2. Antiretroviral exposure (per year) and incidence rate ratios of progression to confirmed estimated glomerular filtration rates (eGFRs) of ≤70 mL/min and CKD from an eGFR of ≥90 mL/min. Models adjusted for baseline eGFR (per 5-mL/min increase), age (per 10-year increase), sex, ethnicity (white, African ancestry, or unknown), mode of human immunodeficiency virus (HIV) transmission (male-male sex, heterosexual, injection drug use, unknown, or other), nadir $CD4^+$ T-cell count, enrollment cohort, prior AIDS-defining illness, and baseline date. Hepatitis B virus (HBV) positivity (defined as detection of HBV surface antigen, detection of HBV e antigen, or detection of HBV DNA plus antibody to HBV e antigen), hepatitis C virus (HCV) positivity (defined as detection of antibody to HCV plus detection or unknown presence of HCV RNA), current smoker, hypertension, diabetes, cardiovascular disease, $CD4^+$ T-cell count (per doubling), HIV load (per $\log_{10}$ copies/mL), and cumulative exposure (per year) to unboosted atazanavir, ritonavir-boosted atazanavir (atazanavir/r), ritonavir-boosted lopinavir (lopinavir/r), tenofovir, abacavir, indinavir, and other ritonavir-boosted protease inhibitors were included as time-updated variables. Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

infection, HCV infection, or a prior AIDS-defining illness; and according to level of immunosuppression.

DISCUSSION

In this analysis, we investigated progression from normal renal function to 2 different levels of chronic renal impairment. Given the relatively short length of follow-up (<5 years), these declines were substantial as compared to the expected age-related decline of 1 mL/min per year [13, 14]. Such rapid deterioration in renal function is currently attracting much attention [3, 15] as a more dynamic measurement of renal impairment, and work is underway to further standardize this definition [16].

The primary findings of this analysis were that ongoing exposure to TDF, ATV/r, and LPV/r were each associated with an adverse chronic effect on renal function in persons without preexisting renal impairment. In contrast to other recent studies, this study further showed an independent effect of these ARVs rather than an effect only when coadministered with each other [4, 17, 18].

ATV may, similar to several other PIs, cause urolithiasis and crystalluria, but cases of interstitial nephritis have also been described [19–23]. In recent years, evidence has emerged that ATV may also be associated with chronic impairment and other renal outcomes, with or without coadministration of TDF [1, 4, 17, 20, 24–26]. We identified ATV/r, but not unboosted ATV use, as a predictor of chronic renal impairment, independently of TDF use and preexisting renal impairment. Importantly, only 25% of the ATV-treated persons received unboosted ATV, which may have reduced our power to demonstrate an effect of this drug without ritonavir. A recent study with similar follow-up also found an association between ATV use and rapid decline in renal function but no association with CKD [3]. It was unclear, however, whether ATV was boosted or unboosted in that study.

LPV/r is mainly metabolized in the liver, but approximately 10% is excreted in urine and may therefore also cause urolithiasis [27]. Prior evidence that LPV/r causes CKD is limited [1] and has been primarily described in cases when LPV/r was coadministered with TDF [17, 28, 29]. Our findings suggested an independent association between LPV/r use and progression to both renal end points from a normal eGFR.

The effect of the other PI/r group was not significant in the adjusted analysis. A recent study has found that darunavir is associated with asymptomatic crystalluria and that it may therefore be similar to other PIs in terms of its influence on renal function [30]. Use of darunavir was, however, limited in this study, which may explain why no association was observed. In the prescribing information for tipranavir and fos (amprenavir), renal damage possibly due to urolithiasis is mentioned [11, 12], but little is known about the nephrotoxic potential of these newer PIs. Because of their infrequent use, we are unable to comment specifically on the effects of tipranavir and fos(amprenavir), and the presence of PIs other than tipranavir and fos(amprenavir) in the other PI/r group may have diluted any possible effects of these 2 ARVs.

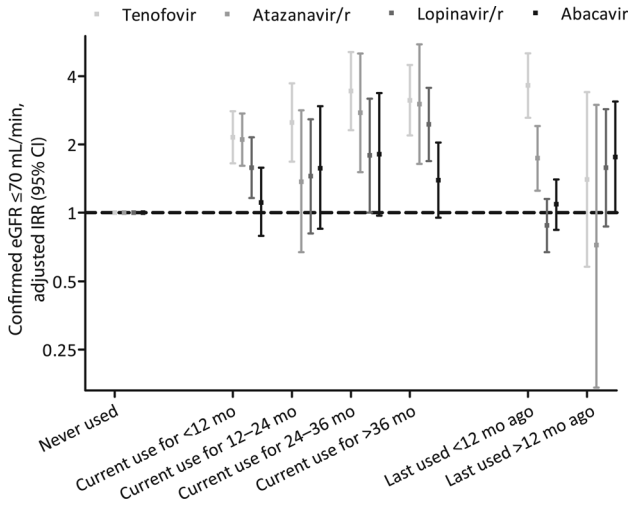

Figure 3. Antiretroviral exposure and rates of progression to a confirmed estimated glomerular filtration rate (eGFR) of ≤70 mL/min from an eGFR of ≥90 mL/min. Models adjusted for baseline eGFR (per 5-mL/min increase), age (per 10-year increase), sex, ethnicity (white, African ancestry, or unknown), mode of human immunodeficiency virus (HIV) transmission (male-male sex, heterosexual, injection drug use, unknown, or other), nadir $CD4^+$ T-cell count, enrollment cohort, prior AIDS-defining illness, and baseline date. Hepatitis B virus (HBV) positivity (defined as detection of HBV surface antigen, detection of HBV e antigen, or detection of HBV DNA plus antibody to HBV e antigen), hepatitis C virus (HCV) positivity (defined as detection of antibody to HCV plus detection or unknown presence of HCV RNA), current smoker, hypertension, diabetes, cardiovascular disease, $CD4^+$ T-cell count (per doubling), HIV load (per $\log_{10}$ copies/mL increase), and cumulative exposure (per year) to unboosted atazanavir, ritonavir-boosted atazanavir (atazanavir/r), ritonavir-boosted lopinavir (lopinavir/r), tenofovir, abacavir, indinavir, and other ritonavir-boosted protease inhibitors were included as time-updated variables. Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

In addition to mechanistic studies supporting a nephrotoxic potential of TDF [31–33], numerous other studies have investigated TDF nephrotoxicity, including case reports [25, 34, 35], cohort studies [1, 2, 36–38], and randomized controlled trials [39–43]. Most recently, a large US study found an independent association between TDF and 3 renal outcomes (proteinuria, CKD, and rapid eGFR decline) in treatment-naive persons [3]. Of note, follow-up in that study ended in 2007 and, thus, focused on TDF use fairly early after its introduction, when it was used predominantly in persons with acquired drug resistance. Our study extends these findings to a more contemporary cohort of HIV-positive persons, in whom TDF was used earlier during the course of treating HIV.

Several randomized trials have also investigated adverse renal events associated with TDF use among individuals with an initially normal renal function [39–43]. Many of these trials were, however, of insufficient size and follow-up to detect such rare events as chronic renal impairment, as was done in this analysis. Furthermore, the risk of renal impairment in the populations included in these trials was likely reduced because persons with comorbidities that confer a risk of renal impairment (which are often seen in the general population of HIV-positive individuals) are typically excluded from these trials [39, 40].

Our analysis revealed a clinician-driven switch away from TDF among persons experiencing a decline in renal function while receiving this drug. Because the nephrotoxic potential of TDF has been vigorously discussed [39, 40, 44], these proactive switches away from TDF are reassuring.

We found that LPV/r use was associated with an excess risk for both renal end points, whereas use of TDF and ATV/r were each significantly associated only with progression to a confirmed eGFR of ≤70 mL/min (although consistent nonsignificant trends were seen also for CKD). The proactive switch away from TDF in persons with deteriorating renal function may have limited our ability to fully address the potential association between TDF use and progression to CKD from an eGFR of ≥90 mL/min, since other parts of our analyses suggested that the TDF effect decreased after discontinuation. In relation to ATV/r, the drug was introduced much later into clinical care than LPV/r, and the duration of follow-up was therefore substantially shorter. This may have limited our ability to assess the full extent to which ATV/r may influence renal function. Once additional follow-up has accrued in the D:A:D study, we will reassess the association between ATV/r and the incidence of CKD.

The fact that the association between all 3 drugs and a confirmed eGFR of ≤70 mL/min was markedly decreased after their discontinuation suggests that the effect depends on ongoing exposure and that these associations were not just due to chance or confounding by indication. Importantly, these observed declines in IRR after the potential nephrotoxic drugs were discontinued (for whatever reason) does not reveal whether declining renal function is reversible, but rather suggests that, for persons who have not already reached this end point, the rate of experiencing the renal impairment end point was reduced after stopping the drug. A study with the specific aim of assessing the reversibility of declining renal function among persons experiencing chronic renal impairment during ART receipt is currently being designed. In this analysis, we were unable to address reversibility of renal function, because among individuals with initially normal renal function such analyses require longer follow-up after these still relatively rare renal events have occurred. In the meantime, this analysis highlights the need for continued and ongoing monitoring of renal function among HIV-positive persons and for an increased awareness of ARVs with an association with impaired renal function.

Initiation of ABC and 3TC was common at eGFR levels <70 mL/min, which may possibly explain the observed small and

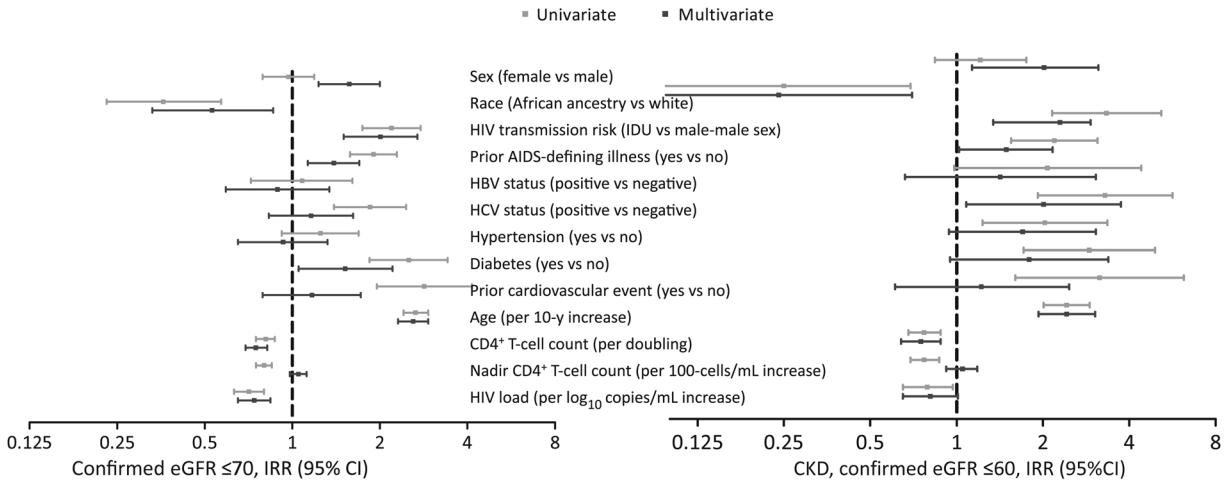

Figure 4. Other predictors of confirmed estimated glomerular filtration rates (eGFRs) of ≤ 70 mL/min and ≤60 mL/min, CKD, from an eGFR of ≥90 mL/min. Models adjusted for baseline eGFR (per 5-mL/min increase), age (per 10-year increase), sex, ethnicity (white, African ancestry, or unknown), mode of human immunodeficiency virus (HIV) transmission (male-male sex, heterosexual, injection drug use, unknown, or other), nadir $CD4^+$ T-cell count, enrollment cohort, prior AIDS-defining illness, and baseline date. Hepatitis B virus (HBV) positivity (defined as detection of HBV surface antigen, detection of HBV e antigen, or detection of HBV DNA plus antibody to HBV e antigen), hepatitis C virus (HCV) positivity (defined as detection of antibody to HCV plus detection or unknown presence of HCV RNA), current smoker, hypertension, diabetes, cardiovascular disease, $CD4^+$ T-cell count (per doubling), HIV load (per $\log_{10}$ copies/mL increase), and cumulative exposure (per year) to unboosted atazanavir (ATV), ritonavir-boosted ATV, ritonavir-boosted lopinavir, tenofovir, abacavir, indinavir, and other ritonavir-boosted protease inhibitors were included as time-updated variables. Abbreviations: CI, confidence interval; IDU, injection drug use; IRR, incidence rate ratio

borderline significant association of these drugs with both renal end points. However, we did not find evidence of channeling bias for ABC, after censoring for ABC initiation among persons with an impaired eGFR. To our knowledge, only 1 other study [2] has reported an association between CKD and ABC. Single cases of ABC-related Fanconi syndrome [45] and hypersensitivity related interstitial nephritis [46] have been described. However, because of the small effect size, the inconsistent trends in our analysis, and the tendency to start ABC at a lower eGFR, we urge caution in interpreting this finding. Further investigation for a possible biological mechanism is required.

Our analyses also identified and confirmed a variety of risk factors for renal impairment other than ARVs, which were the main focus. Importantly, the study focused on the development of renal impairment in HIV-positive persons with initially normal renal function, who currently compose the largest HIV-positive group seen in clinical practice. As a consequence, patients with prevalent comorbidities that are known to influence renal function were excluded because renal impairment (defined as an eGFR of <90 mL/min) had already developed. This likely affects our ability to identify other potential risk factors, such as hypertension and race, in this analysis.

Age is a traditional risk factor for renal impairment [25, 47, 48], and despite adjustment for this variable in the eGFR equation itself, age remained among the strongest predictors, along with diabetes [37] and $CD4^+$ T-cell count [1, 37], in this analysis. Prior AIDS-defining illness also represented an expected predictor [1] that may include infections and antimicrobial treatment harmful to the kidneys. Interestingly, nadir $CD4^+$ T-cell count was not a predictor after accounting for other HIV-related factors, and further investigations should examine the role of prior immune suppression on renal function in the modern combination ART era. Several illicit drugs have nephrotoxic potential and are associated with infections, which may explain the observed association with IDU as HIV transmission group. Neither prior CVD nor hypertension reached statistical significance, possibly because of the exclusion of a high proportion of patients with impaired renal function at baseline, inclusion of well-treated patients with hypertension, and missing hypertension values. HCV infection was associated with confirmed eGFRs of ≤70 mL/min and CKD in unadjusted analyses but only with CKD in adjusted analyses. However, both adjusted estimates were >1, suggesting a possible relation, which may be mediated both directly, by a HCV glomerulonephritis, and indirectly, by hepatorenal syndrome and factors associated with IDU. In the literature, there are conflicting reports on this association [49, 50].

African ancestry was not associated with chronic renal impairment in our analysis, but our power to detect such an association was low (<10% had African ancestry, and >40% had unavailable ethnicity information). Sensitivity analyses

including only persons with known ethnicity showed results entirely consistent with our main analysis.

Females generally have a lower eGFR than males, but after accounting for this in the eGFR equation, female sex was still associated with impaired renal function among persons with an initially normal eGFR. Women, however, only constituted 27% of included persons, which limited our ability to fully investigate the influence of sex.

There are several limitations to our study. Data on proteinuria, other urinary markers, serum phosphate level, biopsy findings, and family history of renal disease were not available within the study. Other potentially nephrotoxic non-ARV drugs may represent unmeasured confounding. The assessment of possible selection bias showed that persons with traditional and HIV-related risk factors were more likely to be excluded because of preexisting renal impairment and inadequate renal data. As a consequence the presented estimates of chronic renal impairment may be underestimated.

We were unable to use the Chronic Kidney Disease Epidemiology Collaboration/Modification of Diet in Renal Disease equation to calculate eGFR, because of restrictions on ethnicity information. Further imputation of ethnicity was not possible, as this information was not missing at random. Finally, the conclusions should be viewed in light of eGFR being a surrogate marker of renal function and the inability of any observational study to draw definitive conclusions about causality.

In conclusion, among HIV-positive persons with a normal eGFR, use of TDF, ATV/r, and LPV/r were independently associated with adverse chronic renal impairment, as were established renal- and HIV-related factors. The TDF discontinuation rates were increased among persons with a decreasing eGFR and may have prevented further deterioration to CKD. The incidence of chronic renal impairment associated with these ARVs decreased after their discontinuation.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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