

Changes in Proteinuria and Albuminuria With Initiation of Antiretroviral Therapy: Data From a Randomized Trial Comparing Tenofovir Disoproxil Fumarate/Emtricitabine Versus Abacavir/Lamivudine

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Background: Antiretroviral therapy (ART) is associated with improved kidney function; however, the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) has been associated with decreased kidney function and proteinuria.

Methods: We examined changes in urine protein:creatinine (UPCR) and urine albumin:creatinine (UACR) ratios in 245 ART-naïve participants in A5202 randomized in a substudy to blinded NRTI (abacavir/lamivudine, ABC/3TC, n = 124 or TDF/emtricitabine, TDF/FTC, n = 121) with open-label protease inhibitor (PI) atazanavir/ritonavir or nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz.

Results: At baseline, 18% of participants had clinically significant proteinuria (UPCR \geq 200 mg/g), and 11% had clinically significant albuminuria (UACR \geq 30 mg/g). The prevalence of clinically significant proteinuria and albuminuria decreased from baseline to week 96 in all treatment groups. In intention-to-treat analyses, there was a significant effect of NRTI component on

fold change in UPCR ($P = 0.011$) and UACR ($P = 0.018$) from baseline to week 96, with greater improvements in participants randomized to ABC/3TC. There was no significant effect of NNRTI/PI component on fold change in UPCR ($P = 0.23$) or UACR ($P = 0.88$), and no significant interactions between NRTI and NNRTI/PI components.

Conclusions: In this prespecified secondary analysis, ART initiation was associated with improvements in proteinuria and albuminuria, with significantly greater improvements in participants randomized to ABC/3TC versus TDF/FTC. These are the first data from a randomized trial to suggest that initiation of TDF/FTC may not be associated with the same degree of improvement in proteinuria and albuminuria that have been reported with other regimens. Future studies should consider the long-term clinical significance of these findings.

Key Words: HIV, antiretroviral therapy, kidney disease

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INTRODUCTION

HIV-infected individuals are at increased risk for chronic kidney disease (CKD), as indicated by a decrease in estimated glomerular filtration rate (eGFR) or an increase in urinary protein excretion, and the presence of CKD is associated with both AIDS and non-AIDS events.^{1–5} Higher urinary protein excretion, ranging from overt proteinuria to microalbuminuria, has been associated with increased risk of mortality in HIV-infected individuals, independent of eGFR.^{2–5} Although multiple studies have demonstrated improvements in eGFR or proteinuria with antiretroviral therapy (ART),^{6–8} in observational studies, cumulative exposure to the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) and the ritonavir-boosted protease inhibitors (PIs) atazanavir/ritonavir (ATV/r) and lopinavir/r have also been associated with low eGFR, and in the case of TDF, with increases in proteinuria.^{9–11} Randomized trials comparing TDF/emtricitabine (TDF/FTC) and abacavir/lamivudine (ABC/3TC) in ART-naïve adults have not demonstrated a higher risk of developing low eGFR among participants randomized to initiate ART containing TDF/FTC, and in the ASSERT study, the change in albuminuria was also similar between treatment arms over 48 weeks of therapy.^{12–14} We evaluated the effects of NRTI and nonnucleoside reverse transcriptase inhibitor (NNRTI)/PI components on changes in proteinuria and albuminuria over 96 weeks among ART-naïve participants in the metabolic substudy of a randomized HIV treatment trial.

METHODS

AIDS Clinical Trials Group (ACTG) Study A5202 randomized ART-naïve participants to a blinded NRTI component (ABC/3TC or TDF/FTC) and to an open-label PI or NNRTI component (ATV/r or efavirenz, EFV).¹⁴ Intention to enroll in the metabolic substudy A5224s was a stratification factor for randomization in the parent trial. A prespecified secondary objective of A5224s was to compare the change in proteinuria and albuminuria in participants randomized to TDF/FTC versus ABC/3TC, and in participants randomized to open-label ATV/r versus EFV.¹⁵

ACTG Studies A5202 and A5224s were supported by the National Institutes of Health. Abbott Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline provided the study medications. The decision to publish the article was solely that of the academic authors.

Study Participants

Inclusion criteria for the parent trial A5202 (n = 1858) included age ≥ 16 years, HIV-1 RNA > 1000 copies per milliliter, and Cockcroft–Gault creatinine clearance > 60 mL/min. The protocol did not initially exclude participants with hepatitis B virus (HBV) coinfection but was later amended to exclude participants with a positive HBV surface antigen within 6 months of study entry.¹⁴ Additional exclusion criteria for the metabolic substudy A5224s (n = 269) included endocrine disease (diabetes mellitus and Cushing syndrome), uncontrolled thyroid disease or hypogonadism, and use of

glucocorticoids, anabolic steroids, growth hormone, or osteoporosis medications. The institutional review board at each participating site approved the study protocol, and all participants provided written informed consent. The study is registered with ClinicalTrials.gov, number NCT00118898.

Study Measurements and Definitions

In A5224s, fasting urine and serum samples were collected at study entry (baseline), week 24, week 48, and week 96; additional specimens were collected at 48-week intervals until 96 weeks after the last subject was enrolled in A5202. Urine protein, albumin, and creatinine were measured centrally at Quest Diagnostics. Urine protein and creatinine were measured using colorimetric assays (Pyragallol red and Jaffe, respectively), and urine albumin was measured using an immunoturbidimetric assay for calculation of the urine protein:creatinine (UPCR) and urine albumin:creatinine (UACR) ratios; all assays were performed on a Beckman Coulter/Olympus platform. Clinically significant proteinuria and albuminuria were defined based on clinical guidelines as a UPCR ≥ 200 mg/g or a UACR ≥ 30 mg/g.¹⁶ Dipstick urinalysis and fasting serum creatinine and glucose were measured locally. For the purposes of this analysis, the CKD Epidemiology Consortium (CKD-EPI) equation was used to recalculate eGFR from serum creatinine, to provide a more accurate estimate of this important potential confounder. The CKD-EPI eGFR equation has demonstrated the best overall performance in HIV-positive adults, as compared with a gold standard measure of GFR.^{17,18} Homeostasis model assessment–insulin resistance (HOMA-IR) was calculated from fasting insulin and glucose. HBV and hepatitis C virus (HCV) coinfections were defined by positive HBV surface antigen or HCV antibody, respectively.

Statistical Analysis

A prespecified secondary objective of A5224s was to compare changes in UPCR and UACR from baseline to week 96 between pooled, randomized NRTI components (TDF/FTC vs. ABC/3TC, with NRTI/PI components combined) and between NNRTI and PI components (ATV/r vs. EFV, with NRTIs combined). Primary analyses were performed using intent-to-treat principles based on randomized treatment assignment in which all available data were used and modifications to randomized treatment and missing values were ignored.

In February 2008, after a median follow-up of 97 weeks, the Data Safety and Monitoring Board (DSMB) recommended unblinding the NRTI component for A5202 participants with screening HIV-RNA $\geq 100,000$ copies per milliliter; participants receiving ABC/3TC were permitted to modify their regimen.¹⁴ To account for changes in therapy, supplemental as-treated analyses were performed in which values were censored after a change in the randomized NRTI component (when comparing NRTI components) or NNRTI/PI component (when comparing NNRTI/PI components). Post hoc sensitivity analyses included only participants who had achieved virologic suppression (HIV-RNA < 50 copies/mL) at week 96.

Because UPCR and UACR were not normally distributed, data were \log_{10} transformed before analysis. For ease of interpretation, the exponential of the estimated mean change in the transformed data was used to obtain the estimated mean fold change; a mean fold change = 1 would correspond to no change in mean UPCR or UACR from baseline, whereas a mean fold change <1 would correspond to a decrease in mean UPCR or UACR from baseline. The unadjusted analysis of the effects of NRTI component and NNRTI/PI component on changes in UPCR or UACR was evaluated separately using 2-sample *t* tests. Linear regression was used to initially test for interactions between NRTI and NNRTI/PI components. *P* values below 0.05 (<0.10 for interactions) were considered statistically significant. To assess baseline characteristics independently associated with changes in UPCR or UACR, multivariable linear regression models were constructed using backwards selection. Baseline characteristics considered for inclusion were age, sex, race/ethnicity, HIV-1 RNA, CD4 cell count (CD4), eGFR, presence of dipstick proteinuria, systolic, and diastolic blood pressure, HBV or HCV coinfection, HOMA-IR, and body mass index. All baseline variables with univariate *P* value <0.20 were considered for inclusion in the models, and variables with a *P* value <0.05 were retained; NRTI component and NNRTI/PI component were retained regardless of *P* value. Analyses were performed using SAS, version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Among 269 participants enrolled in the A5224s study, 245 participants with baseline UPCR and/or UACR contributed data to this analysis. Compared with excluded participants, included participants tended to be older and were less likely to be white, although these differences were not significant (*P* = 0.14 and 0.07, respectively). Included and excluded participants were not significantly different with respect to other baseline characteristics (all *P* > 0.3). One hundred eighty-one participants with available data for UPCR and/or UACR at the 96-week visit were included in the primary intention to treat analyses. These participants had marginally higher mean body weight and diastolic blood pressure (*P* = 0.066 and 0.052, respectively), but were not significantly different with respect to baseline characteristics from the 64 participants who did not contribute to the primary analysis (all other *P* > 0.12).

Baseline characteristics of included participants were well balanced across the treatment groups (Table 1). The mean age of included participants was 39 years, 85% were male, and 35% were of non-Hispanic black race. Only 19% had an eGFR <90 mL·min⁻¹·1.73 m⁻², including 2 participants who met entry criteria based on creatinine clearance >60 mL/min but who had CKD-EPI eGFR <60 mL·min⁻¹·1.73 m⁻². Dipstick proteinuria greater than or equal to trace was detected in 29% of participants and was balanced across the treatment groups. The median UPCR (95 mg/g) and UACR (4.75 mg/g) were within the normal range (<200 and <30 mg/g, respectively).

Effect of NRTI Assignment on Changes in UPCR and UACR

The effects of treatment assignment on the change in UPCR and UACR are summarized in Table 2. There were no significant interactions between the NRTI and NNRTI/PI components (*P* = 0.33 for analysis of change in UPCR, *P* = 0.91 for UACR). In the primary intention-to-treat analyses, there was significantly greater fold change in both UPCR and UACR in those randomized to ABC/3TC versus TDF/FTC (Figs. 1A, C). The mean fold change in UPCR from baseline to week 96 among 84 participants randomized to ABC/3TC was 0.80 [95% confidence interval (CI): 0.70 to 0.91], corresponding to a significant decrease in UPCR from baseline. Among 83 participants randomized to TDF/FTC, the mean fold change in UPCR was 1.02 (95% CI: 0.89 to 1.17), corresponding to no significant change in UPCR from baseline to week 96. Overall, there was a 21.7% difference (Δ) in mean fold change UPCR with ABC/3TC compared with TDF/FTC (*P* = 0.011), corresponding to a significantly greater decrease in UPCR from baseline to week 96 in participants randomized to ABC/3TC. Results were similar in as-treated analysis in which values were censored after a change in the randomized NRTI component.

In the primary intention-to-treat analysis for UACR, the mean fold change from baseline to week 96 among 92 participants randomized to ABC/3TC was 0.69 (95% CI: 0.57 to 0.84), corresponding to a significant decrease in UACR from baseline. Among 86 participants randomized to TDF/FTC, the mean fold change in UACR was 0.98 (95% CI: 0.80 to 1.19), corresponding to no significant change in UACR from baseline to week 96. Overall, there was a 28.8% difference in mean fold change UACR with ABC/3TC compared to TDF/FTC (*P* = 0.018), corresponding to a significantly greater decrease in UACR from baseline to week 96 in participants randomized to ABC/3TC. Results for the change in UACR were similar, although no longer statistically significant, in as-treated analysis in which values were censored after a change in the randomized NRTI component.

Although there were no significant interactions between the NRTI and NNRTI/PI components, prespecified intention-to-treat analyses of NRTI effect were performed within each NNRTI/PI arm for descriptive purposes. The results were qualitatively similar to the results of the primary intention-to-treat analyses, with greater mean fold changes in UPCR and UACR in participants randomized to ABC/3TC versus TDF/FTC, regardless of the NNRTI/PI component (Table 2).

There was no significant difference in mean fold change UPCR or UACR between participants with and without virologic suppression (HIV-RNA <50 copies/mL) at 96 weeks (data not shown; *P* > 0.8 for both). The proportion of included participants who achieved virologic suppression did not differ significantly between those randomized to ABC/3TC (78/93, 83.9%) versus TDF/FTC (79/88, 89.8%; Fisher exact *P* = 0.28). In post hoc sensitivity analyses, we evaluated the effect of treatment assignment on the changes in UPCR and UACR including only those participants who achieved virologic suppression at 96 weeks. In these analyses, the difference in mean fold change UPCR was similar in

TABLE 1. Baseline Characteristics of 245 Included A5224s Study Participants

Variable	TDF/FTC		ABC/3TC		Total n = 245
	ATV/r, n = 65	EFV, n = 56	ATV/r, n = 64	EFV, n = 60	
Age, yrs	40 (10)	38 (10)	39 (10)	38 (10)	39 (10)
Men	55 (84%)	48 (86%)	51 (80%)	54 (90%)	208 (85)
Race or ethnicity, n (%)					
Black, non-Hispanic	21 (32)	20 (36)	19 (30)	26 (43)	86 (35)
White, non-Hispanic	34 (52)	21 (38)	29 (45)	25 (42)	109 (44)
Hispanic	8 (12)	12 (21)	14 (22)	8 (13)	42 (17)
Other	2 (3)	3 (5)	2 (3)	1 (2)	8 (3)
Weight, kg	77 (16)	80 (18)	77 (15)	78 (15)	78 (16)
BMI, kg/m ²	24.8 (4.1)	26.1 (5.6)	25.6 (4.8)	25.5 (4.5)	25.5 (4.7)
CD4 cell count, cells/ μ L	248 (156)	220 (149)	230 (173)	233 (182)	233 (165)
HIV-RNA, log copies/mL*	4.6 (0.7)	4.7 (0.7)	4.6 (0.6)	4.7 (0.7)	4.6 (0.7)
<100,000 copies/mL, n (%)	52 (80)	44 (79)	53 (83)	45 (75)	194 (79)
Hepatitis B coinfection, n (%)	4 (6)	0 (0)	3 (5)	1 (2)	8 (3)
Hepatitis C coinfection, n (%)	5 (8)	2 (4)	8 (13)	7 (12)	22 (9)
Systolic blood pressure, mm Hg	120 (16)	120 (9)	123 (14)	120 (13)	121 (13)
Diastolic blood pressure, mm Hg	75 (9)	75 (7)	77 (10)	76 (11)	76 (9)
HOMA-IR	1.2 (1.7)	1.6 (2.2)	1.6 (1.5)	1.5 (1.5)	1.5 (1.7)
eGFR, mL·min ⁻¹ ·1.73 ⁻²	107.1 (15.0)	106.5 (21.4)	106.1 (19.5)	110.0 (16.4)	107.4 (18.1)
<90, n (%)†	9 (14)	15 (27)	15 (24)	7 (12)	46 (19)
Dipstick proteinuria, n (%)	16 (25)	18 (33)	21 (33)	16 (27)	71 (29)
UPCR, mg/g	(n = 63)	(n = 52)	(n = 64)	(n = 55)	(n = 234)
Median (IQR)	87 (67, 132)	86 (61, 156)	98 (70.50, 143.50)	101 (75, 170)	95 (67, 146)
\geq 200 mg/g, n (%)	10 (16)	10 (19)	11 (17)	12 (22)	43 (18)
UACR, mg/g	(n = 64)	(n = 54)	(n = 64)	(n = 60)	(n = 242)
Median (IQR)	4.60 (3.10–9.85)	4.65 (3.10–11.60)	4.90 (3.10–11.35)	4.80 (3.20–14.05)	4.75 (3.20–10.00)
\geq 30 mg/g, n (%)	6 (9)	6 (11)	5 (8)	10 (17)	27 (11)

Urine protein: creatinine and albumin: creatinine ratios are presented as median (interquartile range, IQR). All other data are presented as mean (SD) or as n (%).

*HIV-1 RNA was measured at screening.

†Two participants who met entry criteria based on Cockcroft–Gault creatinine clearance >60 mL/min but who had a CKD-EPI eGFR <60 mL·min⁻¹·1.73 m⁻². Baseline data were missing for \leq 3 participants for the following characteristics: hepatitis B and C coinfection, eGFR, dipstick proteinuria, and UACR. Baseline data for UPCR were missing for 11 participants.

Hepatitis B coinfection, surface antigen positive; hepatitis C coinfection, antibody positive; urine dipstick proteinuria, any non-negative protein result on baseline urinalysis.

magnitude and direction to the primary analysis, but was not statistically significant. The difference in mean fold change UACR was marginally significant and similar in magnitude and direction to the primary analysis.

In a separate intention-to-treat analysis at week 48, the effect of NRTI component on mean fold change in UPCR was significant but smaller in magnitude than at week 96 ($P = 0.043$). The initial decline in UACR from baseline to week 24 seems to be similar in participants randomized to ABC/3TC versus TDF/FTC (Fig. 1C), and there was no statistically significant effect of NRTI component on the change in UACR at week 48 ($P = 0.74$).

Effect of NNRTI/PI Assignment on Changes in UPCR and UACR

There were no significant effects of open-label NNRTI/PI component on the change in UPCR or UACR from baseline to week 96 (Figs. 1B, D). The mean fold change in UPCR from baseline to week 96 among 79 participants randomized to ATV/r (0.85, 95% CI: 0.74 to 0.98) was not significantly

different than that observed among 88 participants randomized to EFV (0.96, 95% CI: 0.84 to 1.09; $P = 0.23$). The mean fold change in UACR among 88 participants randomized to ATV/r (0.81, 95% CI: 0.66 to 0.99) was not significantly different than that observed among 90 participants randomized to EFV (0.83, 95% CI: 0.68 to 1.01; $P = 0.88$).

Adjusted Analyses

In the multivariable intention-to-treat analyses, there remained a significantly greater fold change in UPCR (Table 3) and UACR (Table 4) at week 96 in participants randomized to ABC/3TC versus TDF/FTC. After adjusting for NRTI and NNRTI/PI components, higher eGFR and HOMA-IR were associated with a decrease in UPCR from baseline to week 96; higher baseline CD4 count and absence of dipstick proteinuria were associated with an increase in UPCR. In the multivariable analysis for change in UACR, screening HIV-RNA \geq 100,000 copies per milliliter and higher baseline eGFR and HOMA-IR were associated with a decrease in UACR from baseline to week 96; higher baseline CD4 and

TABLE 2. Treatment Assignment and Differences in Fold Change UPCR and UACR

NRTI Effect	UPCR, mg/g				UACR, mg/g			
	n	%	95% CI	P	n	%	95% CI	P
Intention-to-treat, week 0–96	167	–21.7	–35.1 to 5.5	0.011	178	–28.8	–46.2 to –5.8	0.018
As-treated, week 0–96	140	–20.7	–35.4 to –2.6	0.027	149	–24.8	–44.1 to 1.2	0.060
Stratified analysis, week 0–96								
ATV/r arm	79	–28.9	–45.8 to –6.6	—	88	–27.7	–51.6 to 8.1	—
EFV arm	88	–14.4	–33.9 to 10.8	—	90	–29.9	–52.9 to 4.1	—
Sensitivity analysis, week 0–96								
HIV-RNA <50 copies/mL*	144	–18.1	–33.4 to 0.7	0.058	154	–26.5	–46.0 to –0.1	0.049
Intention to treat, week 0–48	191	–16.5	–29.9 to –0.6	0.043	194	–4.4	–27.3 to 25.6	0.74

NNRTI/PI Effect	Δ, ATV/r vs. EFV				Δ, ATV/r vs. EFV			
	n	%	95% CI	P	n	%	95% CI	P
Intention-to-treat, week 0–96	167	–11.0	–26.5 to 7.7	0.23	178	–2.2	–26.4 to 30.0	0.88
As-treated, week 0–96	143	–9.8	–26.7 to 10.9	0.32	154	–11.6	–34.5 to 19.4	0.42
Stratified analysis, week 0–96								
TDF/FTC	83	–2.2	–25.1 to 27.7	—	86	–2.7	–35.2 to 46.0	—
ABC/3TC	84	–18.7	–37.6 to 6.0	—	92	0.5	–32.1 to 48.7	—
Sensitivity analysis, week 0–96								
HIV-RNA <50 copies/mL*	144	–6.4	–24.0 to 15.4	0.54	154	0.8	–26.2 to 37.6	0.96
Intention to treat, week 0–48	191	–11.1	–25.5 to 5.9	0.19	194	–7.6	–29.6 to 21.5	0.57

In the as-treated analysis, participants were censored after a change in the assigned NRTI (for the analysis of NRTI effect) or NNRTI/PI (for the analysis of NNRTI/PI effect). Because of the limited sample size within strata, the results of the stratified analyses are provided for descriptive purposes only.

*Analyses in this table were planned a priori, with the exception of the sensitivity analyses including only participants who achieved HIV-RNA <50 copies per milliliter at week 96.

absence of dipstick proteinuria were associated with an increase in UACR. Traditional CKD risk factors, including older age, black race, and hepatitis coinfection, were not significantly associated with changes in UPCR or UACR from baseline to week 96.

Effect of Treatment Assignment in Participants With Significant Proteinuria or Albuminuria

At baseline, 18% of included participants had clinically significant proteinuria (UPCR ≥ 200 mg/g) and 11% had clinically significant albuminuria (UACR ≥ 30 mg/g) (Table 1). Only 4 participants had a baseline UPCR ≥ 1 g/g, consistent with overt proteinuria of more than 1 g/24 hours. These 4 participants and 1 additional participant had a baseline UACR ≥ 300 mg/g, signifying macroalbuminuria; by chance, all 5 of these participants with overt proteinuria and/or macroalbuminuria were randomized to open-label ATV/r. Overall, there was a decrease in the prevalence of clinically relevant proteinuria and albuminuria from baseline to week 96 in all treatment groups. Among participants with data available at baseline and at week 96, the prevalence of UPCR ≥ 200 mg/g decreased from 18.0% to 9.6%, and the prevalence of UACR ≥ 30 mg/g decreased from 11.2% to 5.1% (exact McNemar test $P = 0.013$ for both comparisons).

In 21 of 30 participants with baseline UPCR ≥ 200 mg/g, the week 96 UPCR was <200 mg/g. These 21 cases were balanced across the 4 treatment arms. New onset proteinuria

≥ 200 mg/g was observed in 7 of 137 participants with baseline UPCR <200 mg/g. Five of these participants were randomized to TDF/FTC (2 with EFV and 3 with ATV/r) and 2 were randomized to ABC/3TC (1 in each NNRTI/PI arm). In 14 of 20 participants with baseline UACR ≥ 30 mg/g, the week 96 UACR was normal. Five of these participants were randomized to TDF/FTC (4 with EFV and 1 with ATV/r) and 9 were randomized to ABC/3TC (3 with EFV and 6 with ATV/r). New onset albuminuria ≥ 30 mg/g was observed in 3 of 158 participants with normal baseline UACR, all of whom were randomized to TDF/FTC (2 with EFV and 1 with ATV/r). The numbers of participants with clinically significant proteinuria and albuminuria were too small to allow statistical comparisons.

DISCUSSION

In this prespecified secondary analysis of the metabolic substudy of a randomized clinical trial, we observed significantly greater improvements in proteinuria and albuminuria over 96 weeks among ART-naive adults randomized to ART containing ABC/3TC versus TDF/FTC. This effect remained significant after adjusting for potential imbalances in randomization. Assignment to open-label ATV/r versus EFV was not associated with a significant difference in proteinuria or albuminuria over 96 weeks of treatment.

These results are consistent with previous clinical trials demonstrating improvements in markers of CKD with the initiation of ART,^{6–8} even with regimens that include TDF, and it is reassuring that the prevalence of clinically significant

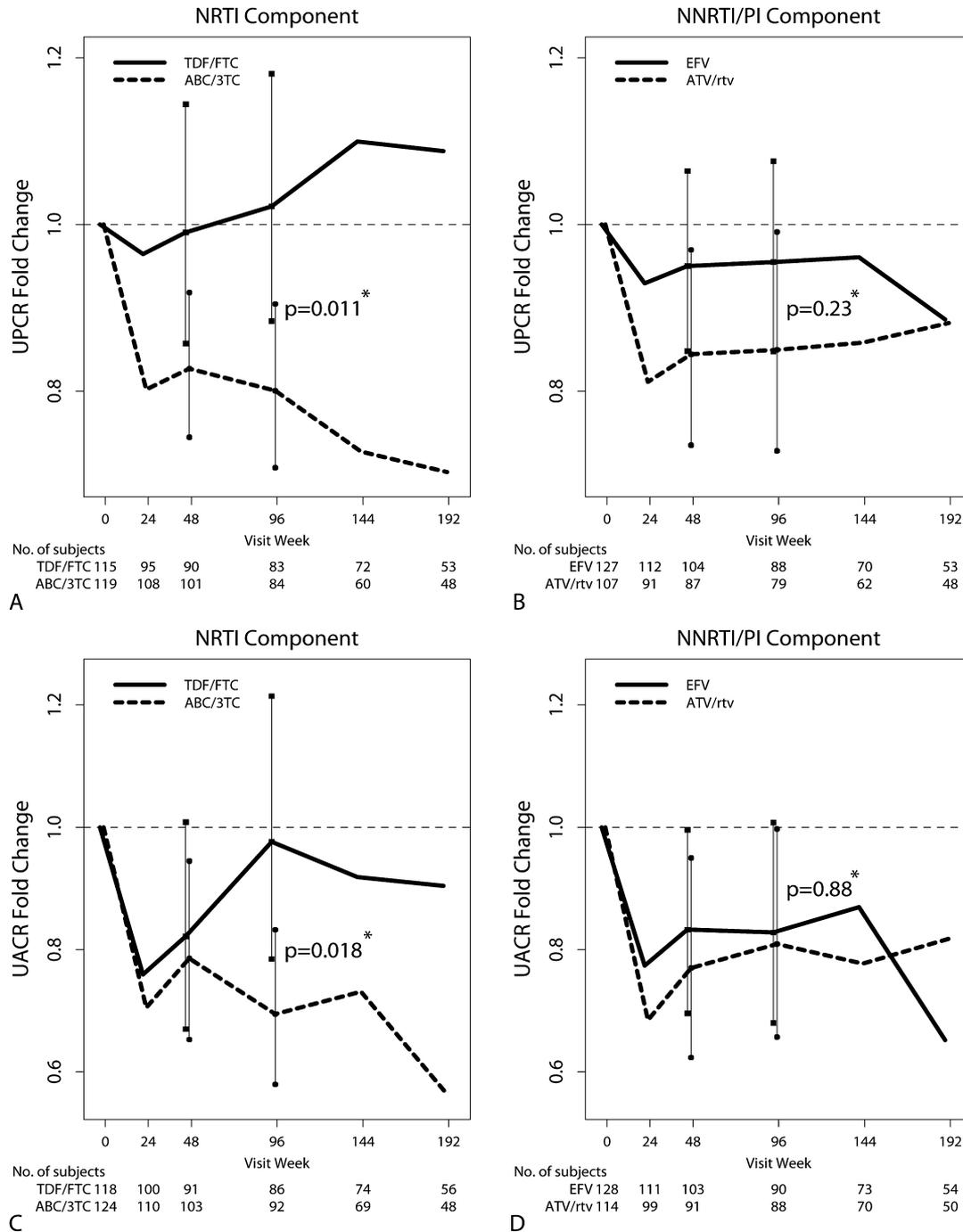


FIGURE 1. Mean fold change (95% CI) in UPCR (A and B) and UACR (C and D). Creatinine ratio (C and D) among 245 participants randomized to initiate ART in A5224s. Mean fold change in each ratio is compared between participants randomized to abacavir/lamivudine versus TDF/emtricitabine (A and C) and between participants randomized to open-label EFV versus ATV/ritonavir (B and D). Data are presented through week 192 for descriptive purposes; comparative statistics were performed at week 48 and week 96. *Two-sample *t* test.

proteinuria and albuminuria decreased in all treatment arms. Although observational studies have demonstrated an association between cumulative exposure to TDF and increased incidence of proteinuria,¹⁰ the change in albuminuria over 48 weeks did not differ significantly between participants

randomized to TDF/FTC versus ABC/3TC in the ASSERT study.¹³ Although we did not observe an increase in the prevalence or level of proteinuria or albuminuria over 96 weeks of therapy with TDF/FTC, the pattern of change in UACR suggests that an early improvement with ART initiation was

TABLE 3. Baseline Characteristics Associated With Change in Log₁₀-Transformed UPCR, Week 0 to Week 96

Variable	Univariate Analyses		Multivariate Analyses	
	Estimated Mean Fold Change (95% CI)	P	Estimated Mean Fold Change (95% CI)	P
Assigned to ABC/3TC (vs. TDF/FTC)	0.78 (0.65 to 0.95)	0.011	0.76 (0.69 to 1.01)	0.001
Assigned to ATV/r (vs. EFV)	0.89 (0.74 to 1.08)	0.23	0.94 (0.80 to 1.12)	0.50
Age (per 1 yr)	1.00 (0.99 to 1.01)	0.78	—	—
Male sex	0.95 (0.72 to 1.25)	0.71	—	—
Race or ethnicity				
White, non-Hispanic	Reference	0.26	—	—
Black, non-Hispanic	0.84 (0.68 to 1.05)	—	—	—
Hispanic	0.87 (0.67 to 1.14)	—	—	—
BMI (per 1 kg/m ²)	1.00 (0.98 to 1.02)	0.87	—	—
CD4 cell count (per 50 cells/μL)	1.06 (1.02 to 1.09)	<0.001	1.06 (1.03 to 1.09)	<0.001
HIV-RNA (per 1 log₁₀ copies/mL)	0.86 (0.75 to 0.98)	0.028		
HIV-RNA ≥100,000 copies/mL*	0.84 (0.69 to 1.02)	0.074	—	—
Hepatitis B or C coinfection	0.77 (0.57 to 1.06)	0.11	—	—
Systolic blood pressure (per 10 mm Hg)	0.98 (0.91 to 1.06)	0.58	—	—
Diastolic blood pressure (per 10 mm Hg)	1.01 (0.91 to 1.12)	0.88	—	—
HOMA-IR (per unit higher)	0.94 (0.89 to 0.98)	0.010	0.94 (0.90 to 0.98)	0.006
eGFR (per 10 mL·min⁻¹·1.73 m⁻²)	0.96 (0.91 to 1.01)	0.092	0.94 (0.89 to 0.98)	0.004
Negative dipstick protein	1.57 (1.29 to 1.92)	<0.001	1.43 (1.19 to 1.72)	<0.001

*HIV-1 RNA was measured at screening. The estimated mean change in log₁₀-transformed UPCR was exponentiated to obtain the estimated mean fold change; values <1 correspond to a decrease in mean UPCR from baseline. Covariates with univariate *P* value <0.20 were considered for inclusion in the multivariate model, and variables with a *P* value <0.05 were retained; treatment assignment variables were retained regardless of *P* value.

Hepatitis B coinfection, surface antigen positive; hepatitis C coinfection, antibody positive.

followed by a rebound in albuminuria with longer exposure to TDF/FTC (Fig. 1C). This result is consistent with the previously reported association between cumulative exposure to TDF and increased incidence of proteinuria as assessed by

dipstick urinalysis, which largely detects albuminuria.¹⁰ Although it is possible that our results reflect an initial improvement in HIV-related kidney injury with virologic suppression, followed by the development of proximal tubular

TABLE 4. Baseline Characteristics Associated With Change in Log₁₀-Transformed UACR, Week 0 to Week 96

Variable	Univariate Analyses		Multivariate Analyses	
	Estimated Mean Fold Change (95% CI)	P	Estimated Mean Fold Change (95% CI)	P
Assigned to ABC/3TC (vs. TDF/FTC)	0.71 (0.54 to 0.94)	0.018	0.69 (0.54 to 0.88)	0.003
Assigned to ATV/r (vs. EFV)	0.98 (0.74 to 1.30)	0.88	1.04 (0.81 to 1.34)	0.74
Age (per 1 yr)	1.01 (1.00 to 1.03)	0.10	—	—
Male	0.87 (0.58 to 1.29)	0.48	—	—
Race or ethnicity				
White, non-Hispanic	Reference	0.37	—	—
Black, non-Hispanic	0.79 (0.57 to 1.10)	—	—	—
Hispanic	0.94 (0.63 to 1.40)	—	—	—
BMI (per 1 kg/m ²)	1.01 (0.98 to 1.04)	0.56	—	—
CD4 cell count (per 50 cells/μL)	1.08 (1.03 to 1.12)	0.001	1.07 (1.03 to 1.11)	0.001
HIV-RNA (per 1 log ₁₀ copies/mL)	0.78 (0.64 to 0.96)	0.017	—	—
HIV-RNA ≥100,000 copies/mL*	0.67 (0.51 to 0.90)	0.007	0.72 (0.56 to 0.93)	0.013
Hepatitis B or C coinfection	0.76 (0.48 to 1.20)	0.24	—	—
Systolic blood pressure (per 10 mm Hg)	0.96 (0.86 to 1.07)	0.46	—	—
Diastolic blood pressure (per 10 mm Hg)	1.03 (0.88 to 1.20)	0.74	—	—
HOMA-IR (per unit higher)	0.93 (0.86 to 1.00)	0.064	0.92 (0.86 to 0.98)	0.014
eGFR (per 10 mL·min ⁻¹ ·1.73 m ⁻²)	0.90 (0.83 to 0.97)	0.005	0.89 (0.83 to 0.95)	0.001
Negative dipstick protein	1.85 (1.38 to 2.48)	<0.001	1.67 (1.26 to 2.20)	<0.001

*HIV-1 RNA was measured at screening. The estimated mean change in log₁₀-transformed UACR was exponentiated to obtain the estimated mean fold change; values <1 correspond to a decrease in mean UACR from baseline. Covariates with univariate *P* value <0.20 were considered for inclusion in the multivariate model, and variables with a *P* value <0.05 were retained; treatment assignment variables were retained regardless of *P* value.

Hepatitis B coinfection, surface antigen positive; Hepatitis C coinfection, antibody positive.

injury or dysfunction in the setting of TDF/FTC, the current study was not designed to evaluate potential mechanisms. Similarly, we cannot explain the apparent differences in pattern and magnitude of change in proteinuria and albuminuria, which may indicate different types of kidney injury. Future studies should include additional biomarkers that can help to distinguish between HIV-related and ART-related kidney injury. Finally, it is notable that clinically significant proteinuria and albuminuria were observed in fewer than 20% of participants at baseline. Nonetheless, even small elevations in proteinuria and albuminuria, such as those observed in this study, have been associated with clinically significant differences in cardiovascular disease and all-cause mortality.²⁻⁵

Although recent studies have suggested that cumulative exposure to ATV/r is associated with decreased eGFR,⁹⁻¹¹ we did not observe a differential effect of ATV/r versus EFV on changes in proteinuria or albuminuria, other indicators of CKD. It is possible that this lack of difference reflects a deleterious effect of EFV, consistent with a previously reported association between NNRTI use and higher albuminuria.¹⁹ Of note, by chance, all subjects with high levels of proteinuria and albuminuria were randomized to the ATV/r arm. We have previously reported greater improvements in albuminuria in individuals with higher baseline levels.²⁰ It is possible that imbalance in baseline proteinuria and albuminuria could have masked a true benefit of EFV over ATV/r. Nonetheless, the number of participants with high levels of proteinuria or albuminuria was small, and the effect of outliers should be minimized by the log transformation of UPCR and UACR data. Of note, the distribution of proteinuria and albuminuria was similar between the NRTI treatment arms, the primary focus of this analysis.

Although this is the first study to demonstrate differential effects of TDF/FTC and ABC/3TC on proteinuria and albuminuria using data from a randomized trial, several additional limitations should be acknowledged. First, although UPCR and UACR measurements were centralized, our analysis was based on a single measurement of proteinuria and albuminuria at each time point. It is reassuring that the observed effects of NRTI component were in the same direction, albeit less significant, at 48 weeks. Second, the study was not specifically powered for this secondary analysis, and missing data at week 96 further limited our sample size for the primary intention-to-treat analyses. Although there were no statistically significant differences with respect to baseline characteristics, it is also possible that participants with missing data at week 96 differed from participants who were included in the primary analysis. Third, our analysis was complicated by the unblinding of the NRTI component and switches from ABC/3TC to TDF/FTC in participants with high screening HIV-RNA following the DSMB report in February 2008. Results of the as-treated analyses with data censored after a change in NRTI were qualitatively similar, although the differences in albuminuria reduction were no longer statistically significant. Fourth, although it is reassuring that proteinuria and albuminuria did not worsen in participants randomized to TDF/FTC, our results are short term when viewed in the context of lifelong ART. By design, follow-up of study participants ended when the last enrolled participant

reached week 96; as a result, there is a decreasing sample size on visits after this time point. Particularly, given the low baseline prevalence of clinically significant proteinuria/albuminuria or decreased eGFR, these short-term results do not exclude the possibility of worsening proteinuria or albuminuria with more prolonged exposure. We did observe a more significant effect of NRTI assignment at week 96 than at week 48, which could suggest a cumulative effect of treatment; unfortunately, the small sample size after week 96 did not allow us to explore this further. Fifth, although we did not detect a significant interaction between NRTI and NNRTI/PI component, the current analysis likely only had adequate power to detect large treatment interactions. Finally, our results may not be generalizable to patients with baseline creatinine clearance <60 mL/minute or with uncontrolled diabetes, who were excluded from the current study and who are at greatest risk for adverse renal and cardiovascular outcomes. In contrast, more than one-third of participants were of self-reported black race, another important risk factor for CKD. There were no significant interactions between NRTI component and race, age, or blood pressure, suggesting that the observed NRTI effects were not significantly influenced by these traditional CKD risk factors.

Our data are consistent with previous studies demonstrating improvements in proteinuria or albuminuria after the initiation of ART.⁶⁻⁸ These are the first data from a randomized clinical trial to suggest that the initiation of TDF/FTC in ART-naive individuals may not be associated with the same degree of improvements in proteinuria and albuminuria that are observed with ABC/3TC. Future studies should consider the long-term clinical significance of these differences, particularly among individuals with pre-existing CKD or CKD risk factors.

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