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Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease

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Abstract

Objective—To examine the association between changes in glomerular filtration rates (GFR) and antiretroviral therapy (ART)-mediated suppression of plasma HIV-1 viremia.

Design—Observational, prospective, multicenter cohort study.

Intervention—ART regimens or treatment strategies in HIV-1-infected subjects were implemented through randomized clinical trials; 1776 ambulatory subjects from these trials also enrolled in this cohort study.

Method—The association between suppression of viremia and GFR changes from baseline was examined using the abbreviated Modification of Diet and Renal Disease equation in mixed effects linear models.

Results—GFR improvement was associated with ART-mediated suppression of plasma viremia in subjects with both chronic kidney disease stage ≥2 and low baseline CD4 cell counts (< 200 cells/μl). In this subset, viral suppression (by > 1.0 $\log_{10}$ copies/ml or to < 400 copies/ml) was associated with an average increase in GFR of 9.2 ml/min per 1.73 m^2 from baseline (95% confidence interval, 1.6–16.8; $P = 0.02$) over a median follow-up of 160 weeks. The magnitude of this association increased in subjects who had greater baseline impairment of renal function, and it did not depend on race or sex.

Conclusions—Viral suppression was associated with GFR improvements in those with both low CD4 cell counts and impaired baseline renal function, supporting an independent contribution of HIV-1 replication to chronic renal dysfunction in advanced HIV disease. GFR improvement not associated with viral suppression also was observed in subjects with higher CD4 cell counts.

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Keywords

antiretroviral therapy; chronic kidney disease; HIV-1 viremia; HIV-associated nephropathy

Introduction

HIV-1 infection is associated with a spectrum of kidney diseases that may result from direct infection of the kidneys, from coinfections or malignancies that are commonly associated with HIV-disease, or from toxicities of medications that are used to treat HIV-1 infection and its complications [1–3]. Although the incidence of end-stage renal disease has declined in HIV-1-infected persons in industrialized settings in association with the use of antiretroviral therapy (ART), the prevalence of chronic kidney disease (CKD) remains high in this population [4, 5]. In resource-limited settings, particularly sub-Saharan Africa, the recognition of end-stage kidney disease is likely to increase among HIV-1-infected persons with intensified laboratory monitoring and improved survival in association with the increasing availability of ART [6].

Direct HIV-1 infection of renal tubular and glomerular epithelial cells has been demonstrated in HIV-associated nephropathy (HIVAN), the most common, clinically significant nephropathological abnormality of HIV disease [2, 3, 7]. HIVAN is characterized histologically by a collapsing, focal segmental glomerulosclerosis, and clinically by nephrotic-range proteinuria with rapid progression to end-stage renal disease. HIVAN also is associated with low CD4 cell counts and is strongly, but not exclusively, associated with black race [8, 9]. A spectrum of other glomerulopathies has been described in persons with HIV, including immune-complex and membranoproliferative glomerulonephritis, membranous nephropathy, minimal change disease, IgA nephropathy, and amyloidoisis [10, 11]. Diabetes, hypertension and hepatitis C infection are also overrepresented in HIV-infected individuals and may also contribute importantly to CKD in this population [12].

Beneficial effects of ART on kidney function have been demonstrated in persons with HIVAN and also have been described in general in HIV-1-infected persons whose renal dysfunction may not have been limited to HIVAN [11, 13–20]. The extent of these renal benefits and their correlates remain incompletely understood. This study examined the hypothesis that ART-mediated suppression of HIV-1 replication may underlie these renal benefits by examining the association between changes in glomerular filtration rates (GFR) and corresponding reductions in plasma HIV-1 viremia, using mixed effects linear models.

Data were derived from subjects who were enrolled in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study, a large, multicenter, observational cohort study of HIV-1-infected persons who had previously enrolled into one of several parent ACTG randomized, controlled, clinical trials that tested ART regimens (see Appendix 1, available online). Other correlates of renal improvement were also explored using these models, including baseline immune and viral factors and comorbidities such as hypertension, diabetes, hepatitis B and hepatitis C.

Methods

Included in these analyses were HIV-1-infected subjects who enrolled into an ACTG parent study of ALLRT (in which they were randomized to an initial or a new ART regimen or a treatment strategy; see Appendix 1, available online) and who had a baseline HIV-1 viral load of ≥ 3.0 $\log_{10}$ copies/ml, a baseline plus at least one postbaseline measurement of serum creatinine, HIV-1 viral load and urine protein. Subjects could remain in the ALLRT

cohort study whether or not they changed or discontinued ART. All subjects gave informed consent to participate in the ALLRT cohort study, and this study was approved by the individual institutional review boards of each participating site.

Clinical and laboratory evaluations performed every 16 weeks in the ALLRT cohort included longitudinal serum creatinine levels, measured at each participating site; plasma HIV-1 viral load [measured with the Amplicor HIV-1 Monitor ultrasensitive assay with a lower sensitivity threshold of 50 copies/ml (Roche Molecular Systems, Branchburg, New Jersey, USA)]; and CD4 cell measurements, which were performed according to consensus methods [21]. Untimed urine specimens for protein and creatinine were collected annually. For the primary analysis, GFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation in which values > 200 ml/min per 1.73 m^2 were truncated to 200 ml/min per 1.73 m^2 [22]; for sensitivity analyses, GFR also was calculated using the Cockcoft–Gault equation. Subjects were categorized according to clinical practice guidelines for CKD using baseline GFR estimates and the earliest available urine protein measurement: normal, GFR ≥ 60 ml/min per 1.73 m^2 without proteinuria; stage 1, GFR ≥ 90 ml/min per 1.73 m^2 with proteinuria; stage 2, GFR 60–89 ml/min per 1.73 m^2 with proteinuria; and stage 3, GFR < 60 ml/min per 1.73 m^2. Proteinuria was defined as a urine protein to creatinine ratio > 200 mg/g [23]. Baseline characteristics were compared according to the CKD stage using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. All statistical analyses used SAS version 9.0 (SAS Institute, Cary, North Carolina, USA).

GFR slopes, and their 95% confidence intervals (CI), were estimated according to CKD stage, using mixed effects linear models of longitudinal GFR estimates that assumed a first-order autoregressive covariance structure. Differences in slope by CKD stage were assessed by testing interactions between the GFR slope and CKD stage, using $\alpha = 0.05$.

The primary analysis was to test the association between GFR changes from baseline and HIV-1 viral suppression (defined as a corresponding reduction in HIV-1 RNA by > 1.0 $\log_{10}$ copies/ml, or suppression to < 400 copies/ml), using mixed effects linear models that assumed a first-order autoregressive covariance structure. Models were adjusted for baseline values of HIV-1 viral load, CD4 cell counts, GFR, CKD stage, and GFR slope. History of prior ART, diabetes, active hepatitis B infection (determined by serum hepatitis B surface antigen), hepatitis C infection (determined by serum antibody to hepatitis C), and hypertension were included as possible explanatory variables. These models tested interactions between viral suppression and GFR slope, CKD stage, baseline CD4 cell counts, and both CKD stage and baseline CD4 cell counts. Age, sex, and race are included in the abbreviated MDRD equation, and so these variables were not included as main effects in the final model, but race and sex were both included in a separate, general model that tested the interaction between viral suppression and these variables. Final model selection used backward, stepwise selection at a significance of $P < 0.05$.

Simplified models tested the contribution of viral suppression to GFR changes from baseline in subjects with normal or CKD stage 1, versus CKD stage ≥ 2, that were stratified by baseline CD4 cell counts (as < 200 versus ≥ 200 cells/μl). These models also tested the interaction between viral suppression and GFR slope and used a first-order autoregressive covariance structure, with significance defined as $P < 0.05$. The association between the follow-up duration and either baseline GFR or GFR at the final observation was assessed in general linear models.

Results

Baseline measurements for the 1776 subjects included in this analysis were obtained between May 1997 and June 2004, at the time of enrollment into the ALLRT parent clinical trial. All postbaseline measurements were collected within the ALLRT cohort study between October 2002 and November 2004. The median duration of the first observation interval was 80 weeks [interquartile range (IQR), 32–192]; subsequent observation intervals were a median of 16 weeks in duration (IQR, 16–32). The first urine protein measurement was collected a median of 96 weeks after the baseline GFR (IQR, 32–224). Subjects in this analysis had a median of 5 postbaseline observations (IQR, 3–6), and a median follow-up duration of 176 weeks (IQR, 112–288 weeks); follow-up duration was not associated with either the baseline ($P = 0.52$) or the final ($P = 0.81$) GFR.

At enrolment into the parent clinical trial, 322 subjects (18.1%) had CKD stage ≥1, and 1362 of all subjects (76.7%) were previously naive to ART. Additional characteristics are summarized in Table 1, according to baseline CKD stage. Compared with those with normal renal function at baseline, subjects with CKD stage ≥ 1 were significantly older, were more likely to be female or to be black, were more likely to have previously received ART, and were more likely to have been diagnosed with diabetes or hypertension.

Changes in renal function over time

GFR for the entire cohort declined at an average annual rate of 0.3 ml/min per 1.73 m^2 ($P = 0.04$ for slope ≠ = 0) but GFR slopes differed significantly according to the baseline kidney function [Table 2 and Fig. 1]. Among subjects with normal baseline renal function, the average annual rate of GFR decline was 0.2 ml/min per 1.73 m^2 ($P = 0.38$ for slope ≠ = 0), while a GFR decline of 2.9 ml/min per 1.73 m^2 ($P < 0.001$ for slope ≠ = 0) was apparent in subjects with CKD stage 1. Significant renal function improvement was observed in subjects with CKD stage ≥ 2, however, in whom GFR increased at an average annual rate of 2.8 ml/min per 1.73 m^2 ($P < 0.001$ for slope ≠ = 0).

The final GFR measurement improved to > 90 ml/min per 1.73 m^2 in 33 subjects (28.0%) with CKD stage ≥ 2 at baseline, and GFR remained above 90 ml/min per 1.73 m^2 in 1184 subjects (81.4%) with normal baseline renal function or CKD stage 1. Of the 31 subjects with stage 3 at baseline, GFR improved to a final value > 60 ml/min per 1.73 m^2 in 24 (77.4%), including 5 subjects whose GFR improved to values > 90 ml/min per 1.73 m^2. GFR declined to < 60 ml/min per 1.73 m^2 in 19 subjects (1.3%) with normal baseline renal function, in 6 subjects (2.9%) with CKD stage 1, and in 9 subjects (10.3%) with CKD stage 2.

Correlates of renal function improvement

Viral suppression was associated with GFR improvement in mixed effects linear models, but this association depended on renal function and CD4 cell counts, as indicated by a significant three-way interaction between viral suppression, baseline CD4 cell counts and baseline CKD stage ($P = 0.03$). This general model also predicted greater average GFR improvement in association with a lower baseline GFR ($P < 0.001$), the absence of previous ART ($P < 0.001$), and hepatitis C coinfection ($P = 0.03$). To illustrate the complex interaction between viral suppression, CD4 cell counts and renal function, the contribution of viral suppression to GFR improvement was tested in simplified models among subjects with normal renal function or CKD stage 1 at baseline, versus CKD stage ≥2, who were stratified by baseline CD4 cell counts (as < 200 or ≥ 200 cells/μl). In these simplified models, viral suppression was associated with a 9.2 ml/min per 1.73 m^2 GFR improvement (95% CI, 1.6–16.8; $P = 0.02$) in subjects with CKD stage ≥ 2, who also had low CD4 cell

counts [Table 3]. The effect of viral suppression on GFR improvement was more pronounced in subjects with CKD stage 3 at baseline and low CD4 cell counts, in whom viral suppression was associated with a 32.0 ml/min per 1.73 m^2 average GFR increase (95% CI, 15.6–48.3; $P < 0.001$). Significant overall average GFR increases also were observed in subjects who had a CD4 cell count ≥ 200 cells/μl at baseline (9.5 and 1.7 ml/min per 1.73 m^2 increases above baseline in subjects with stage ≥ 2 or normal/stage 1, respectively; $P < 0.001$ and $P = 0.005$, respectively), but these improvements were not associated with viral suppression.

The contribution of viral suppression to GFR improvement did not depend on race or sex: interaction between viral suppression and race (black versus not-black: $P = 0.21$) and sex ($P = 0.24$). Comparable interactions between viral suppression, CD4 cell counts and baseline renal function also were evident when the analysis was restricted to subjects who were previously naive to ART, when GFR was calculated using the Cockcroft–Gault equation, when using a continuous variable for viral suppression (changes in HIV-1 RNA from baseline), or when baseline renal function was defined by GFR alone ($P = 0.01$, $P = 0.01$, $P = 0.02$, and $P < 0.001$ for these three-way interactions, respectively).

Discussion

We have demonstrated an independent association between ART-mediated suppression of HIV-1 replication and GFR improvement that was evident in subjects with impaired renal function who also had low CD4 cell counts at the start of therapy. Over a median follow-up of approximately 3 years, suppression of plasma HIV-1 viremia by > 1.0 $\log_{10}$ copies/ml or to < 400 copies/ml was associated with a 9.2 ml/min per 1.73 m^2 average GFR improvement from baseline in the subset of subjects with CKD stage ≥ 2 and CD4 cell count < 200 cells/μl. This association did not depend on race, the method that was used to estimate GFR, or a single definition of viral suppression. Greater GFR improvement also was evident in subjects who had greater baseline renal function impairment, who were previously naive to ART, or who were coinfected with hepatitis C. GFR improvement also was evident in subjects with a CD4 cell count ≥ 200 cells/μl at baseline, but this improvement was not associated with viral suppression.

The importance of viral replication in the pathogenesis of HIVAN is supported by transgenic mouse models, and by the demonstration of productive HIV-1 infection within glomerular and renal tubular cells [2, 3, 24]. The association between viral suppression and GFR improvement that we demonstrate supports an important role of viral replication in the pathogenesis of renal dysfunction in advanced HIV infection. Because this association did not depend on race, a general effect of HIV-1 replication on kidney function is implied, which may include other nephropathological processes in addition to HIVAN. While beneficial renal effects of ART have been demonstrated in persons with HIVAN [13–18, 20], they also have been documented in general HIV-1-infected populations, in which renal dysfunction may not have been limited to HIVAN [19, 25].

As in the present study, the beneficial effects of ART were accentuated in subjects with CD4 cell counts < 200 cells/μl in the multicenter HIV Outpatient Study [25]. Also consistent with the present study, greater renal benefits of ART were evident in association with greater baseline renal dysfunction in the randomized Development of Anti-Retroviral Therapy in Africa (DART) trial, which included symptomatic adults with a CD4 cell count < 200 cells/μl [26]. A beneficial renal effect of continuous ART also was demonstrated in the Strategies for Management of Antiretroviral Therapy (SMART) trial, in which subjects with a CD4 cell count > 350 cells/μl were randomized to either uninterrupted ART or to therapy that was interrupted when CD4 cells exceeded 350 cells/μl, to be reinitiated when counts fell to < 250

cells/μl [27]. Although the renal benefit that we observed in persons with CD4 cell counts ≥ 200 cells/μl was not associated with viral suppression, it is possible that mechanisms other than viral replication may have contributed to renal dysfunction in these subjects. Dysregulated activation of the transcription factor NF-κB in renal epithelial cells may contribute to the pathogenesis of HIVAN [28], and ART-associated reductions in immune activation, apart from their effects on viral replication, might have accounted for this renal benefit. Since all subjects in the present analysis were randomized to interventions that included continuous ART, we cannot determine whether renal benefits of ART also may extend to preserving normal kidney function.

Subjects were recruited to participate in the parent ACTG trials based on the absence of CKD; therefore, this cohort may not fully represent a general, HIV-1-infected population. The abbreviated MDRD equation underestimates GFR in adults without kidney disease; consequently, the GFR slope estimates in this cohort may not accurately reflect changes in renal function among subjects with a baseline GFR > 60 ml/min per 1.73 m^2 [29]. In this study, renal function was classified using urine protein measurements that were collected at later time points than the baseline GFR, thus introducing a potential source of classification error. The validity of the three-way interaction between baseline renal function, baseline CD4 cell counts and viral suppression, however, is supported by its demonstration in models where renal function was assessed using GFR alone. Although missing data could bias this longitudinal analysis, the absence of an association between the follow-up duration and GFR suggests that informative censoring did not importantly influence this analysis. Finally, subjects in this analysis were exposed to multiple ART regimens, and differences in renal function have been associated with specific medications, including indinavir and tenofovir [30–32]. Further study is warranted to determine the effects of specific ART regimens on renal function.

We demonstrate a significant association between suppression of plasma HIV-1 viremia and renal function improvement among subjects with both low CD4 cell counts and renal function impairment at the start of therapy, supporting a direct role of HIV-1 viral replication in the renal dysfunction of advanced HIV infection. As this association was independent of race, a general effect of HIV-1 replication on kidney function also is suggested, which may not be limited to persons with HIVAN. GFR improvement not associated with viral suppression also was observed in subjects with higher baseline CD4 cell counts, suggesting that mechanisms other than HIV-1 viral replication also may contribute to renal dysfunction in HIV disease.

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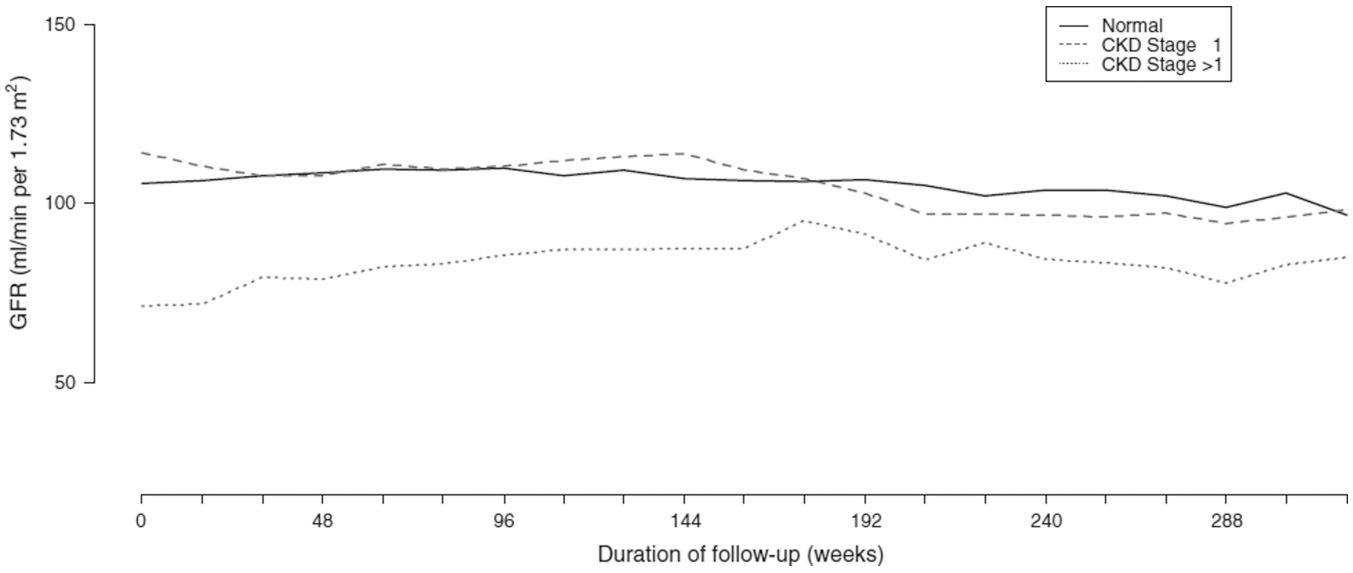

Fig. 1.

Mean glomerular filtration rate (GFR) according to the week after initiation of antiretroviral therapy, and the stage of chronic kidney disease: normal (upper broken line), stage 1 (solid line), stage ≥ 2 (lower broken line).

Table 1

Baseline characteristics according to baseline renal function.

	All subjects	Normal	CKD stage 1	CKD stage ≥ 2	*P*-value[a]
No. (%)[b]	1776	1454 (81.9)	204 (11.5)	118 (6.6)	
Median age [years (IQR)]	38 (33–45)	38 (32–44)	40 (33–46)	43 (38–49)	< 0.001
Male [No. (%)][c]	1455 (81.9)	1207 (83.0)	162 (79.4)	86 (72.9)	0.04
Black [No. (%)][c]	538 (30.3)	425 (29.2)	84 (41.2)	29 (24.6)	< 0.001
Median GFR [ml/min per 1.73 m^2 (IQR)]	100.9 (87.5–117.5)	101.5 (88.4–118.1)	110.4 (98.9–123.4)	72.3 (59.6–84.8)	< 0.001
Median CD4 cell count [cells/μl (IQR)]	214 (77–357)	219 (78–364)	192 (57–334)	198 (76–330)	0.12
Median HIV RNA [$\log_{10}$ copies/ml (IQR)]	4.8 (4.4–5.5)	4.8 (4.4–5.4)	4.8 (4.3–5.5)	5.0 (4.5–5.5)	0.21
ART naive [No. (%)][c]	1362 (76.7)	1141 (78.5)	140 (68.6)	81 (68.6)	< 0.001
Comorbidities [No. (%)][c]					
Hypertension	242 (13.6)	174 (12.0)	39 (19.1)	29 (24.6)	< 0.001
Diabetes	74 (4.2)	46 (3.2)	20 (9.8)	8 (6.8)	< 0.001
Hepatitis C	169 (9.5)	130 (8.9)	25 (12.2)	14 (11.9)	0.08
Hepatitis B	63 (3.5)	54 (3.7)	6 (2.9)	3 (2.5)	0.42

CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range (25th–75th percentiles); ART, antiretroviral therapy.

[a]Comparing normal with CKD stage ≥ 1 (χ^2 or Wilcoxon test).

[b]Among all subjects.

[c]Among subjects within each category, by CKD stage.

Table 2

Comparisons of average glomerular filtration rate slope estimates, according to baseline renal function.

	Annual GFR slope estimates [ml/min per 1.73 m^2 (95% CI)]	***P* value for slope ≠ 0**	***P* value for group differences**
All subjects	−0.3 (−0.02 to −0.6)	0.04	
Subjects by CKD stage			< 0.001
Normal	−0.2 (0.2 to −0.5)	0.38	
Stage 1	−2.9 (−3.7 to −2.0)	< 0.001	
Stage ≥ 2	2.8 (1.8–3.9)	< 0.001	

GFR, glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval.

Table 3

Average overall glomerular filtration rate changes from baseline and the independent contribution of viral suppression (as > 1.0 $\log_{10}$ copies/ml reduction or to < 400 copies/ml) to these changes that were predicted by simplified, mixed effects linear models applied separately to subsets of subjects who were defined according to baseline renal function and baseline CD4 cell counts.

Subsets	No.	Overall average GFR changes from baseline [ml/min per 1.73 m^2 (95% CI)]	Average GFR changes from baseline in association with viral suppression [ml/min per 1.73 m^2 (95% CI)]	*P* value[a]
CKD stage ≥ 2/< 200 cells/μl CD4 cells	59	14.4 (9.6–19.2)	9.2 (1.6–16.8)	0.02
CKD stage ≥ 2/≥ 200 cells/μl CD4 cells	59	9.5 (5.2–13.9) *	1.2 (−2.8–5.3)	0.56
CKD stage ≤ 1/< 200 cells/μl CD4 cells	777	−1.7 (−3.3, −0.1)	−1.2 (−4.1, 1.8)	0.44
CKD stage ≤ 1/≥ 200 cells/μl CD4 cells	881	1.7 (0.5–2.9) **	−0.1 (−2.1, 2.0)	0.93
CKD stage 3/< 200 cells/μl CD4 cells	18	21.6 (13.8–29.4)	32.0 (15.6–48.3)	< 0.001
GFR < 90 ml/min per/1.73 m^2/< 200 cells/μl CD4 cells	236	13.2 (10.9–15.4)	7.6 (3.2–12.0)	< 0.001

GFR, glomerular filtration rate; CKD, chronic kidney disease stage; CI, confidence interval.

[a]Significance for the association between plasma HIV-1 RNA suppression (by >1.0 $\log_{10}$ copies/ml or to < 400 copies/ml) and GFR changes from baseline.

*$P < 0.001$.

**$P = 0.005$.