A Randomized, Pilot Trial to Evaluate Glomerular Filtration Rate by Creatinine or Cystatin C in Naive HIV-Infected Patients After Tenofovir/Emtricitabine in Combination With Atazanavir/Ritonavir or Efavirenz

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Background: Glomerular filtration rate (GFR) estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on creatinine or cystatin C may be more accurate methods especially in patients without chronic kidney disease. There is lack of data on GFR estimated by these methods in patients on highly active antiretroviral therapy.

Methods: Antiretroviral-naive HIV-infected patients were randomized to tenofovir/emtricitabine in association with atazanavir/ritonavir (ATV/r) or efavirenz (EFV) Patients had to have an actual creatinine clearance >50 mL/minute (24-hour urine collection) and were followed for 48 weeks.

Results: Ninety-one patients (48 ATV/r, 43 EFV) were recruited. Using the CKD-EPI creatinine formula, there was a significant decrease in GFR up to week 48 in patients receiving ATV/r (4.9 mL/minute/m², P = 0.02) compared with a not statistically significant increment in patients prescribed EFV. Using the cystatin C–based equation, we found greater decrease in GFR in both arms, although, in the EFV arm, the decrease was not statistically significant (5.8 mL/minute/m², P = 0.92). At multivariable analysis, ATV/r was a significant predictor of greater decrease in estimated glomerular filtration rate (eGFR) (P = 0.0046) only with CKD-EPI creatinine.

Conclusions: ATV/r plus tenofovir caused greater GFR decreases compared with EFV. The evaluation of eGFR by cystatin C confirmed this result, but this method seemed to be more stringent, probably precluding the possibility to detect a significant difference in the pattern of eGFR evolution between the two arms over time. More studies are needed to understand the clinical relevance of these alterations and whether cystatin C is a more appropriate method for monitoring GFR in clinical practice.

Key Words: antiretroviral therapy, creatinine, cystatin C, glomerular filtration rate, HIV

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INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has profoundly improved the outcome of HIV infection, leading to a dramatic decline in mortality and morbidity. The choice of the initial antiretroviral regimen is an extremely important decision in terms of managing HIV-infected patients. Treatment guidelines recommend the use of 2 nucleos(t)ide reverse transcriptase inhibitors, such as tenofovir (TDF) and emtricitabine (FTC) associated with a protease inhibitor boosted by ritonavir (PI/r), such as atazanavir (ATV)/r, or a nonnucleoside reverse transcriptase inhibitor (NNRTI), such as efavirenz (EFV).2

The efficacy and the overall safety of TDF as part of HAART regimens was demonstrated in several randomized controlled trials but cases of severe tubular dysfunction were described. Moreover, decrease in renal function was especially observed when TDF was associated with PI/r than with
NNRTI.\(^8,9\) Notably, even in antiretroviral-naive patients with an estimated glomerular filtration rate (eGFR) higher than 60 mL·min\(^{-1}\)·m\(^{-2}\), the coadministration of TDF and PI/r caused a greater median decline in eGFR compared with TDF + NNRTI.\(^10\) A possible reason for this finding is that PI/r slows down the renal clearance of TDF,\(^11\) increasing its bioavailability by 20%–30%.\(^12,13\) As a higher TDF plasma concentration was associated with greater decline in eGFR,\(^14\) the exposure to antiretroviral regimens based on TDF and PI/r may lead to a greater risk of nephrotoxicity. However, in similar patients with basal eGFR >60 mL/min, the ACTG A5202 trial demonstrated no significant changes in the eGFR among patients receiving ATV/r compared with a small but statistically significant increase in those receiving EFV.\(^15\) Noteworthy, in both studies\(^10,15\) GFR was estimated only using the Cockcroft–Gault formula,\(^16\) even if the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation proved to be more accurate in subjects with normal or mildly decreased kidney function (eGFR ≥60 mL·min\(^{-1}\)·m\(^{-2}\)).\(^17,18\) For this reason, the Italian guidelines for management of HIV-related problems have recommended to use CKD-EPI formula for monitoring eGFR.\(^19\)

Recently, cystatin C, a protein produced by all nucleated cells and cleared by glomerular filtration, emerged as a promising alternative to derive eGFR instead of creatinine, as the former is believed to be more sensitive and specific for the detection of early kidney impairment.\(^20,21\) In fact, creatinine levels can be influenced by several factors including the stage of liver disease and muscle mass,\(^22,23\) which are highly variable in HIV-infected populations.\(^24\) In contrast, cystatin C is less influenced by muscle mass\(^25\) or liver function than creatinine, and therefore, it is likely to be a more accurate index in HIV-infected patients.\(^26\)

Therefore, the goal of the present study was to evaluate whether the combination of TDF and ATV/r is associated with a different evolution of eGFR in comparison to TDF and EFV, when it is estimated by CKD-EPI cystatin C equations, methods that may be suitable in HIV-infected patients with GFR ≥50 mL·min\(^{-1}\)·m\(^{-2}\).

**METHODS**

**Participants and Study Design**

In this pilot study, patients were randomly assigned in a one-to-one ratio to receive ATV (300 mg, Reyataz 150 mg) plus ritonavir (100 mg, Norvir) once daily or EFV (600 mg, Sustiva) once daily, each being administered with TDF/FTC (300/200 mg, Truvada). HIV-infected patients were recruited from 4 centres in Italy (Brescia, Rome, Ferrara, Bari). A centralized randomization stratified by center and gender was performed by a computer-generated list. The patients' flow-chart is depicted in Figure 1.

The study was conducted in accordance with good clinical practice (ICH-E6).\(^27\) At each study site, the protocol and amendments were approved by the institutional review board/independent ethics committee, and patients provided written informed consent before screening. The enrollment period lasted from June 2007 to April 2009. The trial is registered with EudraCT number: 2007-007934-21.

Patients had to be of 18 years of age or older, naive to antiretroviral therapy, requiring antiretroviral therapy in accordance with official guidelines,\(^28\) and having no recent opportunistic infections. Patients with the following hematocrit alterations were excluded: hypertransaminasemia (aspartate aminotransferase, alanine aminotransferase ≥5·upper limit of normality), anemia (<8 mg/dL), hyperbilirubinemia (>1.5 mg/dL), neutropenia (<750/mm\(^3\)), and actual creatinine.

![FIGURE 1. Trial profile.](https://www.jaids.com)
clearance lower than 50 mL/min calculated from 24-hour urine collection. Genotypic resistance tests (Trugene HIV-1 genotyping Kit, Bayer, Milan, Italy) were performed to exclude patients infected by a virus with primary drug-resistant mutations associated with ineffective response to therapy.

Baseline evaluations included physical examination, CD4+ T-cell count, HIV RNA level (branched chain DNA-enhanced label amplification assay, Quantuplex 2-0; Chiron, with a 50 copies/mL cut-off), and chronic hepatitis coinfection serostatus. Follow-up lasted 48 weeks during which clinical examination, plasma HIV RNA, CD4+ T-cell counts, and laboratory tests were performed.

Evaluation of Kidney Function

Serum creatinine levels were measured at baseline and at weeks 4, 12, 24, 36, and 48 using the Roche enzymatic assay on a Roche/Hitachi P module automated analyzer (COBAS INTEGRA 400/700/800 Creatinine plus ver.2, Roche Diagnostics GmbH). Isotope dilution mass spectrometry was the reference standard method for the measurement of serum creatinine. Cystatin C was measured in frozen plasma samples (–70°C) stored at baseline, week 12, 24, and 48 using a particle-enhanced immunonephelometric assay (BN II nephelometer system). Values of GFR were estimated using the CKD-EPI creatinine equation. Cystatin C levels were used to estimate GFR using the CKD-EPI cystatin C equation (eGFR = 76.7 × CysC–1.193), corrected for body surface area by the DuBois method. According to the National Kidney Foundation recommendations, a mild reduction in eGFR was defined as a value ranging from 60 to 90 mL·min⁻² and moderate eGFR reduction as a value ranging from 30 to 59 mL·min⁻². Moreover, an abnormal decrease in eGFR was defined as a decrement >10 mL·min⁻² from baseline to week 48.

Phosphoremia was determined at baseline and every 4 weeks (Bayer ADVIA 2400 clinical analyzer, Siemens). The excretion rate of total protein (proteinuria) and microalbuminuria were analyzed in urine collected over 24 hours at baseline, week 24 and week 48.

Statistical Analysis and Power

Descriptive statistics were calculated for quantitative variables (mean, standard deviation, median, minimum, and maximum) and qualitative variables (absolute and percent frequencies). The 95% confidence intervals were calculated for appropriate cases. Treatment arms were compared using an unpaired Student t test (Wilcoxon rank sum test for variables that did not show Gaussian distribution) or χ² test (Fisher exact test) for quantitative or qualitative variables, respectively.

The primary analysis focused on the trend of eGFR over time, comparing patients who received ATV/r or EFV as part of their initial regimen. The temporal behavior of the main safety variable (eGFR) was compared between the 2 treatment arms using a mixed factorial random coefficient general linear model with an unstructured pattern of the variance–covariance matrix, selected from several models and several variance–covariance matrix patterns to take into account missing data due to drop-outs assumed as “missing at random” because no patients dropped out of the study for renal toxicity. Multiple comparisons were adjusted using the Sidak method. The relationship between the demographic, clinical, and laboratory variables and evolution of eGFR (by creatinine or cystatin C) from baseline to the last observation (week 48) was evaluated using correlation analysis. Variables with a statistically significant relationship were included in a multiple regression model with backward selection to obtain the set of the variables independently related. The secondary objectives (phosphoremia, proteinuria, and microalbuminuria) were analyzed using the mixed factorial analysis of variance for repeated measurements. Last observation carried forward method was applied for patients who had premature treatment discontinuation. Moreover, to evaluate the direct biological effect of receiving 1 of the 2 therapeutic regimens on eGFR, we also performed a “per protocol” analysis considering only the completer patients.

With the number of patients enrolled, we were able to demonstrate an effect size of 0.60 that implies 60% of the phenomenon variability corresponding to the standard deviation of the differences in GFR (mL·min⁻²) after 48 weeks of therapy; being this standard deviation about 25 mL·min⁻², as it has been shown by Goicoechea et al., we had a power of 0.80 to detect a difference of 15 mL·min⁻² in the GFR between the 2 arms after 48 weeks of therapy.

All analyses were carried out using the statistical software package SAS version 9.13. A P value <0.05 was considered to be statistically significant.

RESULTS

Patients at Baseline and Flow Along the Study

Ninety-one individuals were enrolled in the study; 48 patients were randomized into the ATV/r arm and 43 patients into the EFV arm (Table 1). Most patients were males and acquired HIV infection through sexual intercourse. Eighteen of 91 (19.8%) patients were severely immune suppressed (CD4+ <200 cells/mm³). No statistically significant differences were evident between the 2 treatment groups as far as baseline characteristics were concerned, with the exception of high-density lipoprotein cholesterol, which was greater in the ATV/r arm (P = 0.0156). Six patients were affected by hypertension (3 patients in each therapeutic arm), and 2 patients randomized to the ATV/r arm were affected by diabetes. At baseline, 8 and 10 patients took thrimetoprim/sulfametoxazole prophylaxis in the ATV/r and the EFV arm, respectively.

All patients achieved HIV RNA <50 copies per milliliter at week 24 and maintained virological success up to the end of the study. Treatment regimens were comparable in terms of mean CD4+ T cell increase from baseline to week 48 as follows: from 295.8 (standard deviation, SD: 126.2) cells per cubic millimeter to 472.8 (SD: 152.9) cells per cubic milliliter in the ATV/r arm and from 269.9 cells per cubic milliliter (SD: 114.4) to 480.3 (SD: 266.6) cells per cubic milliliter in the EFV arm. Seven of 48 (14.6%) individuals who received ATV/r and 10 of 43 (23.3%) who received EFV dropped out of the study before week 48; similar proportions of discontinuations were due to adverse events (6
TABLE 1. Baseline Characteristics of Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>Overall, N = 91</th>
<th>TDF/FTC + ATV/r, n = 48</th>
<th>TDF/FTC + EFV, n = 43</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualitative variables, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72 (79.1)</td>
<td>39 (81.3)</td>
<td>33 (76.7)</td>
<td>0.598</td>
</tr>
<tr>
<td>CD4+ T cell ≥ 200 (cells/mm³)</td>
<td>18 (19.8)</td>
<td>8 (16.7)</td>
<td>10 (23.3)</td>
<td>0.445</td>
</tr>
<tr>
<td>HIV RNA ≥ 100000 (copies/mL)</td>
<td>29 (31.9)</td>
<td>14 (29.2)</td>
<td>15 (34.9)</td>
<td>0.654</td>
</tr>
<tr>
<td>BMI &gt; 25</td>
<td>44 (48.9)</td>
<td>26 (55.3)</td>
<td>18 (41.9)</td>
<td>0.214</td>
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<td>Black race</td>
<td>1 (1.1)</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>0.405</td>
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<td>CDC classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>57 (67.06)</td>
<td>31 (67.39)</td>
<td>26 (66.67)</td>
<td>0.507</td>
</tr>
<tr>
<td>B</td>
<td>24 (28.24)</td>
<td>13 (28.26)</td>
<td>11 (28.21)</td>
<td>0.683</td>
</tr>
<tr>
<td>C</td>
<td>4 (4.71)</td>
<td>2 (4.35)</td>
<td>2 (5.13)</td>
<td>1.000</td>
</tr>
<tr>
<td>HIV risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>44 (48.35)</td>
<td>26 (54.16)</td>
<td>18 (41.86)</td>
<td>0.111</td>
</tr>
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<td>IVDU</td>
<td>8 (8.79)</td>
<td>4 (8.33)</td>
<td>4 (9.30)</td>
<td>0.871</td>
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<td>Homo/Bisexual</td>
<td>35 (38.46)</td>
<td>15 (31.25)</td>
<td>20 (46.51)</td>
<td>0.347</td>
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<tr>
<td>Other</td>
<td>1 (1.09)</td>
<td>0 (0.0)</td>
<td>1 (2.32)</td>
<td>0.293</td>
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<tr>
<td>Unknown</td>
<td>3 (3.30)</td>
<td>3 (6.25)</td>
<td>0 (0.00)</td>
<td>0.096</td>
</tr>
<tr>
<td>Chronic hepatitis coinfection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCVAb positive</td>
<td>10 (10.99)</td>
<td>5 (10.42)</td>
<td>5 (11.63)</td>
<td>0.854</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>3 (3.30)</td>
<td>1 (2.08)</td>
<td>2 (4.65)</td>
<td>0.493</td>
</tr>
<tr>
<td>Quantitative variables, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>43.66 (11.52)</td>
<td>45.44 (11.28)</td>
<td>41.68 (11.58)</td>
<td>0.1207</td>
</tr>
<tr>
<td>CD4+ T-cell (cells/mm³)</td>
<td>283.56 (119.46)</td>
<td>295.81 (126.18)</td>
<td>269.88 (111.36)</td>
<td>0.3039</td>
</tr>
<tr>
<td>Log HIV RNA (cps/mL)</td>
<td>4.64 (0.62)</td>
<td>4.59 (0.62)</td>
<td>4.69 (0.63)</td>
<td>0.4212</td>
</tr>
<tr>
<td>Actual CrCl 24 hours/urine (mL/min)</td>
<td>143.75 (45.67)</td>
<td>152.37 (48.03)</td>
<td>133.65 (41.06)</td>
<td>0.0535</td>
</tr>
<tr>
<td>eGFR by CKD-EPI creatinine (mL·min⁻²)</td>
<td>100.12 (19.7)</td>
<td>100.05 (27.2)</td>
<td>100.18 (28.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>eGFR by CKD-EPI cystatin C (mL·min⁻²)</td>
<td>109.64 (25.4)</td>
<td>110.21 (34.9)</td>
<td>109.06 (36.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Proteinuria (mg/24 hr)</td>
<td>122.17 (85.2)</td>
<td>121.04 (74.87)</td>
<td>123.58 (98.14)</td>
<td>0.8952</td>
</tr>
<tr>
<td>Microalbuminuria (mg/24 hr)</td>
<td>13.92 (13.6)</td>
<td>16.03 (18.5)</td>
<td>11.29 (7.6)</td>
<td>0.1525</td>
</tr>
<tr>
<td>Phosphoremia (mg/dL)</td>
<td>3.15 (0.6)</td>
<td>3.12 (0.6)</td>
<td>3.19 (0.7)</td>
<td>0.5972</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>164.39 (3.94)</td>
<td>172.81 (5.43)</td>
<td>155.98 (5.73)</td>
<td>0.4193</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>100.12 (3.36)</td>
<td>101.92 (4.50)</td>
<td>98.32 (5.00)</td>
<td>1.0000</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>38.67 (0.95)</td>
<td>41.89 (1.30)</td>
<td>35.46 (1.39)</td>
<td>0.0156</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>121.77 (61.87)</td>
<td>126.39 (63.92)</td>
<td>117.16 (59.87)</td>
<td>0.4937</td>
</tr>
</tbody>
</table>

BMI, body mass index; CDC, Centers for Disease Control and Prevention classification; CrCl, creatinine clearance; CKD-EPI creatinine, chronic kidney disease epidemiology collaboration equation based on creatinine; CKD-EPI cystatin C, chronic kidney disease epidemiology collaboration equation based on cystatin C; HCVAb, hepatitis C virus antibody; IVDU, intravenous drug use; HBsAg, hepatitis B surface antigen; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol.

in the ATV/r arm versus 8 in the EFV arm; P = 0.316) (Fig. 1). In particular, no one discontinued the trial due to an acute renal failure. Treatment discontinuations were more frequent in the EFV group, but the difference was not statistically significant (P = 0.345). Regarding the time distribution, among 7 patients who dropped out in the ATV/r arm, 5 did so before week 8, 1 at week 28, and 1 at week 32. Likewise, in the EFV arm, among 10 dropouts, 7 occurred before week 8, 1 at week 12, 1 at week 32, and the last 1 at week 44.

eGFR at Baseline

Four subjects had no available stored samples for cystatin C measurement, but all patients were assessed with the methods based on creatinine. Mean actual creatinine clearance calculated through urine collection over 24 hours was 143.7 (SD: 45.7) mL/min. Mean eGFRs were as follows: 100.1 (SD: 18.7) mL·min⁻¹·m⁻² using the CKD-EPI creatinine equation and 109.64 (SD: 25.5) mL·min⁻¹·m⁻² using the CKD-EPI cystatin C equation. Two patients had moderate renal dysfunction with eGFR <60 mL·min⁻¹·m⁻² using CKD-EPI creatinine formula and 1 patient using cystatin C-based equation. Patients with basal eGFR <90 mL·min⁻¹·m⁻² were as follows: 29 of 91 (31.9%) with the CKD-EPI creatinine and 20 of 87 (23%) with the CKD-EPI cystatin C equation (P = 0.371).

Evolution of Renal Function up to Week 48

Using the CKD-EPI creatinine equation, the ATV/r arm showed a significant decrease in eGFR from baseline to week 48 (4.9 mL·min⁻¹·m⁻², P = 0.02); whereas in the EFV arm, there was an increase, but it was not statistically significant.
(1.7 mL·min·m⁻², P = 0.99) (Fig. 2A). Therefore, using a general linear model, a different pattern in the eGFR trend between the 2 arms was found (P = 0.009). Likewise, using the cystatin C formula, a different trend in eGFR between the 2 treatment arms was detected (P = 0.02). In particular, there was a statistically significant decrement in the ATV/r arm (14.9 mL·min·m⁻², P < 0.0001). For the EFV arm, a decrease in eGFR was found at week 48 (5.8 mL·min·m⁻²), but it was not statistically significant (P = 0.92) (Fig. 2B). Consistent results were obtained through a “per protocol” analysis. For example, GFR estimated by the CKD-EPI creatinine formula showed a different pattern between the 2 arms (P = 0.0002), with a decrease of 4.8 mL·min·m⁻² in ATV/r (P = 0.045)—versus—an increase of 3 mL·min·m⁻² in EFV arm (P = 0.4780). Likewise, the cystatin C equation detected a significant change of eGFR over time (P = 0.0072), with a decrement both in the ATV/r arm (15.1 mL·min·m⁻²) and in the EFV arm (4.6 mL·min·m⁻²), although statistical significance was reached in the former (P = 0.0040) but not in the latter (P = 0.4297).

Afterwards, patients with eGFR decrease of ≥10 mL·min·m⁻² at week 48 were evaluated. Among 74 patients retained in the study with available creatinine values at week 48, sixty-two (83.8%) showed this decrement using the CKD-EPI creatinine formula, with a significant difference between the 2 arms 40/62 (64.5%) patients in ATV/r arm versus 22/62 (35.5%) in EFV arm (P = 0.0006). Among 70 patients with available cystatin C values, 57 (81.4%) patients showed this decrement (35 patients in ATV/r arm versus 22 in EFV arm, P = 0.045).

To obtain an overall picture of renal function, proteinuria, microalbuminuria, and phosphoremia were evaluated from baseline to week 48. A significant global increase in proteinuria was demonstrated from 122.2 (SD 85.2) mg/24 hr to 156.9 (SD 74.9) mg/24 hr at week 48 (P = 0.01), with a trend toward significant difference between the 2 arms [from 121.1 (SD 74.9) to 175.4 (SD 88.8) mg/24 hr in the ATV/r versus 123.6 (SD 98.1) to 133.8 (SD 57.5) mg/24 hr in the EFV arm, P = 0.06] (Fig. 2C). Microalbuminuria remained stable over time in both arms [from 13.9 (SD 13.6) mg/24 hr at baseline to 13.5 (SD 13.9) mg/24 hr at week 48, P = 0.95], as did phosphoremia [from 3.1 (SD 0.06) mg/dL at baseline to 3.2 (SD 0.04) mg/dL at week 48, P = 0.42].

**Predictors of eGFR Evolution**

Univariate and multivariable linear regressions were used to determine which factors were associated with an eGFR decline from baseline to week 48. The following covariates were included in the model: gender, age, hepatitis C virus coinfection, glycemia (≥110 mg/dL), hypophosphoremia (≥2.7 mg/dL), high systolic pressure (≥140 mmHg), CD4⁺ count (≤200 cells/mm³), viral load (≥100,000 copies/mL), body mass index, trimetoprim/sulfamethoxazole prophylaxis, and the randomized arm. With regard to GFR estimated using the CKD-EPI creatinine equation, the therapeutic arm emerged as the only parameter independently associated with a decrease in eGFR (P = 0.0046): indeed, the ATV/r arm was associated with a relative decrement in eGFR of 6.65 mL·min·m⁻² (SD: 2.27), although it accounted only for 16% in eGFR variability. By contrast, the therapeutic arm was not associated with a significant decrement in eGFR (P = 0.2506) using the CKD-EPI cystatin C formula.

**DISCUSSION**

Kidney function in HIV-positive patients who began 2 standard HAART regimens was monitored using the CKD-EPI formulae (either based on creatinine or cystatin C), as these are suggested for use in individuals without chronic kidney disease.35,36
Decrease in eGFR over time seemed to be greater when calculated using the CKD-EPI cystatin C equation than using the creatinine-based formula. Patients randomized to the EFV arm showed a decrease of eGFR using CKD-EPI cystatin C, but it was not statistically significant at week 48. Although there is no evaluation of GFR with a gold standard index because all eGFR formulae are imprecise at values >60 mL/min, 29,30,37–39 this study suggests that the CKD-EPI cystatin C equation is a more stringent tool than the CKD-EPI creatinine for early-onset reduction in eGFR. It has to be seen whether this alteration is clinically significant over prolonged follow-up.

The prevalence of patients who had a decrease in eGFR of ≥10 mL·min⁻¹·m⁻² (which predicted chronic kidney disease in certain populations 33,34) was significantly higher in the ATV/r arm (61.4%–64.5%) than in the EFV arm (35.5%–38.6%). Also, an increase in proteinuria occurred particularly in the ATV/r arm, though only a trend toward a statistical significance between the 2 arms was found. However, no patients developed severe renal diseases, and our findings may reflect only slight alterations whose long-term impact is uncertain. Furthermore, the clinical significance of increases in proteinuria within the normal range—which probably reflect minor changes in tubular function—remains unknown.

Interestingly, the cystatin C equation showed the highest decline in eGFR during the first 12 weeks, followed by a moderate but insignificant improvement in renal function. This trend could be explained by the early negative effect on kidney function due to the prescribed HAART regimens, and balanced by the subsequent renal benefit obtained by the suppression of HIV replication, as renal tubular and glomerular epithelial cells are directly infected by HIV. 40 Along the same line, there is evidence that cystatin C as a marker of renal function may be limited by the effects of inflammation. Indeed, higher levels of C-reactive protein and white blood cell count were associated with higher levels of cystatin C and lower levels of creatinine. 41–43 However, all patients obtained undetectable HIV RNA (the main driver of inflammation) upon HAART, so it is counterintuitive that inflammation (which could have indeed been decreased) may have contributed to cystatin C increase (and corresponding eGFR decrease) observed up to week 48. Noteworthy, several factors affect cystatin C levels besides GFR, such as serum albumin concentration, tubular reabsorption, so they may have influenced our results. 44,45

Although statistically significant differences between the 2 arms were demonstrated, the small sample size is a limitation of this study. Moreover, a small proportion of patients had concomitant alterations of renal function for the diagnosis of chronic kidney disease. 32 For example, only 20% patients had proteinuria >200 mg/24 hours. Therefore, we did not have enough power to stratify based on treatment group and abnormal protein excretion rate at baseline. This analysis would have been important to tease apart the benefit of antiretroviral therapy from the toxicity. For example, we even could have been able to find a beneficial effect of treatment on eGFR in patients with kidney damage (including abnormal proteinuria) due to HIV infection at baseline. Along the same line, it is important to highlight that our study was not intended to evaluate chronic kidney disease but only to assess the evolution of eGFR measured with 2 different methods in patients with preserved GFR at baseline.

In conclusion, this study provides further evidence that TDF associated with ATV/r results in an increased risk of eGFR decline compared with TDF in association with EFV. Cystatin C was able to detect a decrease in eGFR also after TDF in association with EFV, but this was not statistically significant at week 48. It has to be seen whether these preclinical conditions could have negative clinical implications over the long term. For instance, it should be investigated whether cystatin C is a more sensitive tool for predicting further deterioration in kidney function in patients on HAART. In addition, other factors that may impact on renal function—such as TDF pharmacogenomics, 46 TDF plasma, or intracellular concentrations, 14 or the degree of inflammation—need further investigation as possible explanations of our findings.

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