Ritonavir-Boosted Protease Inhibitors Do Not Significantly Affect the Performance of Creatinine-Based Estimates of GFR

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Chronic kidney disease (CKD) is more common among HIV-positive individuals. Accurate estimation of glomerular filtration rate (GFR) is important for appropriate antiretroviral (ART) regimen selection and dose adjustment, and for the identification of patients with CKD who may benefit from more intensive modification of HIV-related and traditional CKD risk factors. Commonly used estimates of GFR are based on serum creatinine, a product of skeletal muscle metabolism that is primarily eliminated by glomerular filtration. The generation of creatinine by muscle, with substantial variability in muscle mass between and even within individuals over time, is well recognized as an important limitation of creatinine-based GFR estimates (eGFRCr) in HIV-positive individuals.

Until recently, the impact of active tubular secretion on eGFRCr has rarely been a clinically relevant concern. In early-phase clinical trials, the newer pharmacoenhancer cobicistat and the ART agents dolutegravir, raltegravir, and rilpivirine were observed to cause an early rise in serum creatinine and a corresponding decrease in eGFR Cr. In vitro studies have demonstrated that cobicistat and dolutegravir interfere with the tubular secretion of creatinine by inhibiting specific tubular transporters. As such, a small increase in serum creatinine is expected with the initiation of these agents and is not thought to reflect a decline in true kidney function. This can complicate the interpretation of eGFRCr or calculated creatinine clearance, particularly near dosing thresholds or in patients with or at risk for progressive CKD.

In the same series of in vitro experiments, ritonavir was also shown to inhibit the tubular transport of creatinine. Although the physiologic relevance is unknown, particularly with low-dose ritonavir used as a pharmacoenhancer, this raises the possibility that ritonavir-boosted protease inhibitors (PI/r) could also affect serum creatinine and eGFRCr independent of their effect on GFR. Because multiple prior studies have linked PI/r exposure to an increased risk of CKD as defined by decreased eGFRCr, this could have implications both for epidemiologic research and for clinical practice. We sought to determine whether the performance of eGFRCr is affected by the use of PI/r, using a direct measure of GFR by plasma iohexol clearance as the reference standard.

We conducted a secondary analysis of a published cross-sectional study that compared the performance of available GFR estimates in 200 HIV-positive individuals on stable ART therapy. Characteristics of the study population have been described previously. Briefly, 73% of participants were male, 52% were of self-reported black race, and 34% were older than 50 years (Table 1); 61% of participants had a suppressed HIV-RNA, and the median CD4+ cell count was 536 cells/µl. The ART regimen included a PI/r in 87 participants (44%), with the most common agents being atazanavir/r (n = 46), darunavir/r...
(n = 17), and lopinavir/r (n = 15). Among participants who were not taking a PI/r, 20 were taking an unboosted PI, most commonly atazanavir, and 23 were taking raltegravir. No participants were on cobicistat, dolutegravir, or rilpivirine. The most commonly used backbone was tenofovir disoproxil fumarate, in 63% of participants.

Overall, demographic and clinical characteristics were similar between participants on PI/r versus no PI/r regimens. The only statistically significant difference between groups was in measured GFR, which was lower in participants taking a PI/r versus no PI/r (median, 82 ml/min per 1.73 m² vs. 90 ml/min per 1.73 m², P = 0.04). Regardless of the GFR estimating equation used, eGFR also tended to be lower in participants taking a PI/r. Overall, 14% of participants had a measured GFR <60 ml/min per 1.73 m².

As we have previously reported, all 3 creatinine-based GFR estimating equations underestimated the measured GFR in the study population (positive bias), and the CKD-EPIcr equation had the smallest bias. In the current study, we demonstrate that the bias, accuracy, and precision of the CKD-EPIcr were similar regardless of PI/r use (Figure 1 and Table 2); for example, 1-P30 was 16.1 (95% confidence interval, 9.2–23.0) for participants on a PI/r and 14.2 (95% confidence interval, 8.0–20.4) for those not on a PI/r (P = 0.704). The results were qualitatively similar for the Modification of Diet in Renal Disease and Cockcroft-Gault equations (Figure 1 and Table 2) and in 2 sensitivity analyses: the first excluding participants with detectable plasma viral load or receiving an unboosted PI (Supplementary Table S1) and the second excluding participants on raltegravir (Supplementary Table S2).

Tubular secretion, estimated as the difference between measured creatinine clearance and measured GFR, was highly variable, with a similar distribution regardless of PI/r use.

In this study of HIV-positive adults on stable ART, the use of low-dose ritonavir as a pharmacoenhancer did not have a clinically or statistically significant impact on the performance of commonly used creatinine-based GFR estimates as compared with a direct measure of GFR. This finding is consistent with a more recent in vitro study suggesting that exposure of proximal tubular epithelial cells to ritonavir at low levels consistent with its use as a pharmacoenhancer does not inhibit the relevant tubular transporter for creatinine. We previously reported no difference in the performance of GFR estimates with the use of tenofovir disoproxil fumarate in this population, suggesting that the observed declines in eGFR with cumulative exposure to PI/r and tenofovir disoproxil fumarate alone or in combination likely reflect a true change in GFR rather than a change in tubular secretion of creatinine or other non-GFR effect.

Key strengths of the current analysis include use of a direct measure of GFR as the gold standard, use of a creatinine assay traceable to reference standards, and inclusion of a generalizable patient sample from 3 unique clinical sites, across a range of body composition, HIV disease control, and kidney function. Although we used a convenience sample with measured GFR available from a prior study, the sample included adequate numbers of participants receiving
PI/r and alternative third-agent ART regimens to allow for comparison between the groups. The relatively small sample of participants on PI/r did not allow for comparisons between specific PI/r, some of which have been more strongly linked to decreased eGFR. In addition, data on duration of ART exposure were not collected; however, all participants had been on a stable ART regimen for at least 3 months before enrollment. We were also unable to validate the reported impact of the newer pharmacoenhancer cobicistat or the antiretroviral agents dolutegravir and rilpivirine, as these agents were not approved for use at the time of the original study. Nonetheless, the absence of these agents simplifies the interpretation of our results. Sensitivity analyses excluding participants on raltegravir or an unboosted PI yielded similar results, suggesting that their inclusion did not influence the results. Finally, the original study was not specifically designed to evaluate differences in tubular creatinine secretion between groups. Creatinine clearance was measured using a short timed urine collection, and the resulting measure of estimated tubular secretion varied widely across the study population regardless of PI/r use.

Despite evidence that ritonavir interferes with the tubular secretion of creatinine in vitro, the results of the current study suggest that the use of low-dose ritonavir as a pharmacoenhancer does not have a clinically or statistically significant impact on the performance of creatinine-based GFR estimates.

### DISCLOSURE

All the authors declared no competing interests.

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**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

**Supplementary Methods.**

**Table S1.** Sensitivity analysis in participants with suppressed HIV-RNA, excluding participants on unboosted PIs ($n = 100^*$).

**Table S2.** Sensitivity analysis excluding participants on raltegravir ($n = 177^*$).

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