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.[S1–S4] 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.[1,2] 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 (eGFR$_{Cr}$) in HIV-positive individuals.[1,2]

Until recently, the impact of active tubular secretion on eGFR$_{Cr}$ 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$_{Cr}$.[3,S5–S15] *In vitro* studies have demonstrated that cobicistat and dolutegravir interfere with the tubular secretion of creatinine by inhibiting specific tubular transporters.[4] 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 eGFR$_{Cr}$ 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.[4] 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 eGFR$_{Cr}$ 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 eGFR$_{Cr}$,[2,5,6] this could have implications both for epidemiologic research and for clinical practice. We sought to determine whether the performance of eGFR$_{Cr}$ 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.[7,8] Characteristics of the study population have been described previously.[7] 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

Table 1. Characteristics of the study population

Participant characteristics	Overall (n = 200)	PI/r (n = 87)	No PI/r (n = 113)
Median age, yr	48.0 (42.5, 53.0)	48.0 (43.0, 54.0)	47.0 (42.0, 52.0)
> 50 yr	68 (34)	36 (41)	32 (28)
Male	145 (73)	58 (67)	87 (77)
Black	104 (52)	51 (59)	53 (47)
Median weight, kg	77.0 (67.6, 87.7)	78.1 (69.1, 86.3)	75.6 (66.9, 88.6)
Median BMI, kg/m^2	26.1 (22.7, 29.1)	26.4 (23.1, 29.4)	25.7 (22.3, 28.7)
BMI <22 kg/m^2	35 (18)	13 (15)	22 (19)
BMI >30 kg/m^2	36 (18)	18 (21)	18 (16)
Hypertension	60 (30)	23 (26)	37 (33)
Diabetes mellitus	16 (8)	5 (6)	11 (10)
Hepatitis B–virus coinfection	22 (11)	11 (13)	11 (10)
Hepatitis C–virus coinfection	51 (26)	24 (28)	27 (24)
Ritonavir-boosted PI use			
Atazanavir/r	46 (23)	46 (53)	—
Darunavir/r	17 (9)	17 (20)	—
Lopinavir/r	15 (8)	15 (18)	—
Fosamprenavir/r	7 (4)	7 (8)	—
Saquinavir/r	2 (1)	2 (2)	—
Tipranavir/r	1 (1)	1 (1)	—
Unboosted PI use	20 (10)	—	20 (18)
Raltegravir use	23 (12)	9 (10)	14 (12)
Tenofovir (TDF) use	125 (63)	52 (60)	73 (65)
Undetectable HIV-RNA[a]	111 (61)	53 (68)	58 (56)
Median CD4+ cell count, cells/μl	536 (354, 775)	567 (312, 783)	505 (359, 770)
Median C-reactive protein, mg/l	1.6 (0.8, 4.8)	1.4 (0.8, 5.5)	1.6 (0.8, 4.4)
Median serum albumin, g/dl	3.8 (3.6, 4.1)	3.8 (3.6, 4.0)	3.8 (3.6, 4.1)
Median serum creatinine, mg/dl	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)
Median measured GFR, ml/min per 1.73 m^2	86 (69, 105)	82 (66, 100)	90 (73, 106)
< 60 ml/min per 1.73 m^2	28 (14)	14 (16)	14 (12)
Median estimated GFR, ml/min per 1.73 m^2			
CKD-EPI creatinine	81 (62, 100)	71 (55, 99)	83 (66, 100)
MDRD Study Equation	75 (57, 91)	67 (53, 91)	77 (62, 91)
Cockcroft-Gault CrCl	81 (63, 96)	77 (57, 93)	82 (67, 99)

BMI, body mass index; CKD-EPI, Chronic Kidney Disease–Epidemiology Collaboration; Cockcroft-Gault CrCl, calculated creatinine clearance indexed to 1.73 m^2 body surface area for consistency with measured GFR; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir disoproxil fumarate.
[a]Eighteen participants had missing data for viral load status.
Median values are expressed as median (25th percentile, 75th percentile). All other values are expressed as n (%).

(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 m^2 vs. 90 ml/min per 1.73 m^2, 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 m^2.

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-EPI$_{Cr}$ equation had the smallest bias.[7] In the current study, we demonstrate that the bias, accuracy, and precision of the CKD-EPI$_{Cr}$ were similar regardless of PI/r use (Figure 1 and Table 2); for example, 1-P$_{30}$ 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.[9] We previously reported no difference in the performance of GFR estimates with the use of tenofovir disoproxil fumarate in this population,[7] 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
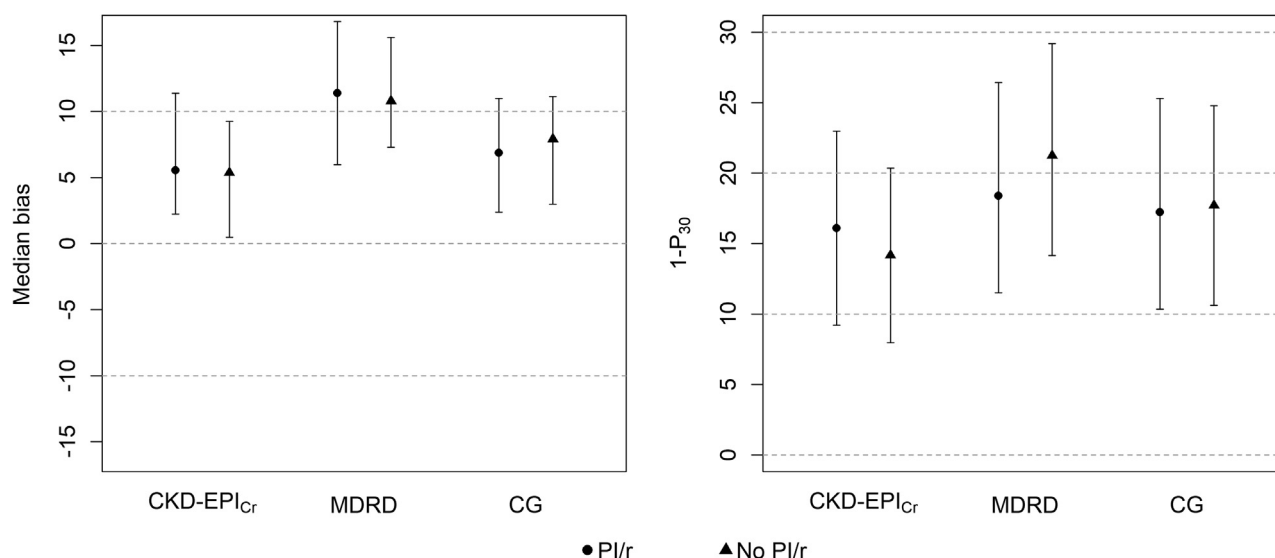
Figure 1. Performance of creatinine-based glomerular filtration rate (GFR) estimates stratified by ritonavir-boosted protease inhibitor use. Left: bias (median difference between measured and estimated GFR). Positive bias indicates an underestimation of measured GFR. Right: accuracy (percentage of estimates greater than 30% of measured GFR; 1-P_{30}). Error bars represent interquartile ranges. CG, creatinine clearance estimated by the Cockcroft-Gault equation indexed to 1.73 m^2 body surface area for comparison with the other equations; CKD-EPI$_{Cr}$, glomerular filtration rate estimated by the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation; MDRD, GFR estimated by the Modification of Diet in Renal Disease Study equation; PI/r, ritonavir-boosted protease inhibitor.

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.

Table 2. Performance of GFR estimating equations stratified by ritonavir-boosted protease inhibitor use ($n = 200$)

Equations	Boosted PI	Median bias (95% CI)	IQR (95% CI)	1-P_{30} (95% CI)
CKD-EPI$_{Cr}$	PI/r	5.5 (2.2–11.4)	21.9 (16.5–30.0)	16.1 (9.2–23.0)
	No PI/r	5.4 (0.5–9.3)	22.7 (17.3–30.5)	14.2 (8.0–20.4)
MDRD Study	PI/r	11.4 (6.0–16.8)	20.8 (16.8–26.9)	18.4 (11.5–26.4)
	No PI/r	10.8 (7.3–15.6)	22.4 (17.5–29.3)	21.2 (14.2–29.2)
Cockcroft-Gault	PI/r	6.9 (2.4–11.0)	22.6 (16.5–28.7)	17.2 (10.3–25.3)
	No PI/r	7.9 (3.0–11.1)	24.4 (19.4–29.7)	17.7 (10.6–24.8)

CI, confidence interval; CKD-EPI$_{Cr}$, glomerular filtration rate (GFR) estimated by the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation; Cockcroft-Gault, creatinine clearance estimated by the Cockcroft-Gault equation indexed to 1.73 m^2 body surface area; IQR, interquartile range; MDRD Study, GFR estimated by the MDRD Study equation; PI, protease inhibitor; P_{30}, accuracy indicated as percent of estimates within 30% of the measured GFR (mGFR), with large errors indicated by 1-P_{30}. Statistical significance of the difference for the median of errors for each equation was tested using the Wilcoxon 2-sample test with t-approximation and for differences of 1-P_{30} using the χ^2 test. None of the P values were less than alpha level of 0.05 and are, hence, not listed here. Bias (median difference between measured and estimated GFR). Positive numbers indicate an underestimate of mGFR and negative numbers indicate an overestimate of mGFR.

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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