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Performance of Creatinine and Cystatin C GFR Estimating Equations in an HIV-positive population on Antiretrovirals

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Abstract

Objective—To evaluate the performance of CKD-EPI creatinine, cystatin C and creatinine-cystatin C estimating equations in HIV-positive patients.

Methods—We evaluated the performance of the MDRD Study and CKD-EPI creatinine 2009, CKD-EPI cystatin C 2012 and CKD-EPI creatinine-cystatin C 2012 glomerular filtration rate (GFR) estimating equations compared to GFR measured using plasma clearance of iohexol in 200 HIV-positive patients on stable antiretroviral therapy. Creatinine and cystatin C assays were standardized to certified reference materials.

Results—Of the 200 participants, median (IQR) CD4 count was 536 (421) and 61% had an undetectable HIV-viral load. Mean (SD) measured GFR (mGFR) was 87 (26) ml/min/1.73m². All CKD-EPI equations performed better than the MDRD Study equation. All three CKD-EPI equations had similar bias and precision. The cystatin C equation was not more accurate than the creatinine equation. The creatinine-cystatin C equation was significantly more accurate than the cystatin C equation and there was a trend toward greater accuracy than the creatinine equation. Accuracy was equal or better in most subgroups with the combined equation compared to either alone.

Conclusions—The CKD-EPI cystatin C equation does not appear to be more accurate than the CKD-EPI creatinine equation in patients who are HIV-positive, supporting the use of the CKD-EPI creatinine equation for routine clinical care for use in North American populations with HIV. The use of both filtration markers together as a confirmatory test for decreased estimated GFR based on creatinine in individuals who are HIV-positive requires further study.

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Conflicts of Interest:

The remaining authors declared no competing interests.

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Keywords

measured glomerular filtration rate; estimated glomerular filtration rate; Chronic Kidney Disease Epidemiology collaboration equation (CKD-EPI); Modification of Diet in Renal Disease Study equation (MDRD); creatinine; cystatin C

Introduction

Since the introduction of antiretroviral therapy (ART) in the mid-1990s, AIDS-related death and illnesses, including kidney failure, have declined in the United States and Europe¹⁻⁴. However, with improved survival and long-term ART, chronic diseases such as diabetes and hypertension are becoming more prevalent in the HIV-infected population^{2,5-7}. These chronic diseases as well as antiretrovirals themselves may cause acute and chronic kidney disease, leading to concern for an increase in End Stage Renal Disease (ESRD) in the future⁸⁻¹¹. An additional increase in the incidence of ESRD due to HIV-associated nephropathy (HIVAN) is projected due to the expansion of AIDS among the Black population¹². Detection of kidney disease at earlier stages will facilitate timely initiation of treatments to slow progression of kidney disease and prevent complications. In addition, medications including antiretrovirals must be appropriately dosed based on kidney function and clinical studies evaluating new medications or treatment regimens must be able to detect nephrotoxicity. These goals require accurate assessment of glomerular filtration rate (GFR).

More than 80% of clinical laboratories now report an estimated glomerular filtration rate (GFR) when serum creatinine is measured^{13,14} using the Modification of Diet in Renal Disease (MDRD) Study equation¹⁵ and the more recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation¹⁶. Despite standardization of serum creatinine assays, GFR estimates remain relatively imprecise, especially at the high range¹⁶, due to variation in non-GFR determinants of serum creatinine, particularly muscle mass and diet, which may be affected in acute and chronic illness¹⁷. Cystatin C is a newer filtration marker that has been proposed to be better than creatinine as its generation is thought not to be dependent upon muscle mass or diet, and CKD-EPI has now developed estimating equations based on cystatin C and on the combination of cystatin C and creatinine¹⁸. However, the factors that determine the level of cystatin C other than GFR are not well understood. Some studies have linked differences in generation of cystatin C to adipose tissue and higher or lower cell turnover, as is found in states of inflammation^{19,20}. The performance of estimating equations using creatinine or cystatin C has not been extensively tested in people with HIV. Given possible changes in muscle mass, adipose tissue and/or inflammation in people with HIV, it is possible that neither filtration marker performs well in this population. The purpose of this study is to evaluate the GFR estimating equations based on creatinine and cystatin C compared to GFR measured using iothexol clearance in the HIV population on stable ART.

Methods

Study population

Participants were recruited from nephrology and infectious disease clinics at Mt Sinai Hospital and St Vincent's Medical Center in New York, Tufts Medical Center in Boston and University of Alabama at Birmingham, as well as from HIV community centers in Boston, Massachusetts. Eligible patients included those who were older than 18 years of age, on stable ART for at least three months, with confirmed HIV status and an HIV viral load and CD4 count within 6 months of recruitment. Patients were excluded if they were pregnant, had an allergy or other contraindication to use of iothexol or iodine, recent acute kidney

injury, had cognitive or physical impairments or were on cimetidine. Patients were recruited who were and who were not on tenofovir as well as those with higher levels of serum creatinine.

GFR Measurements

GFR was measured using protocols previously described^{21–23}. Subjects were asked to fast overnight and to discontinue medications that influence creatinine secretion for at least one week prior to the study visit (e.g. trimethoprim). Five milliliters of iohexol (Omnipaque™ 300, GE Healthcare) was administered through a intravenous line over a period of 30 seconds followed by 10 ml normal saline flush. The dose was calculated from the difference in the syringe weights before and after administration of the iohexol multiplied by the concentration of iohexol divided by the density at room temperature (1.345 g/cm³). Blood samples for plasma clearance measurements were taken from a separate intravenous line at approximately 10, 30, 120, and 240 minutes from the second intravenous line, with the exact times recorded. For participants with serum creatinine > 1.5 mg/dl, a sample at 360 minutes was drawn.

Laboratory methods

Concentration of iohexol was determined using high performance liquid chromatography at the University of Minnesota (CV 2.7% at 10 mg/dL and 2.4% at 50 mg/dL). Cystatin C was measured on the Siemens Pro-spec instrument particle-enhanced immuno-nephelometric assay (Siemens Healthcare Diagnostics, USA) at the University of Minnesota, traceable to the Institute for Reference Materials and Measurements (IRMM) certified reference material^{24–26}. Creatinine was measured at the University of Minnesota on the Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay (Hoffman-La Roche, Ltd., Basel, Switzerland), traceable to National Institute Standardized Technology (NIST) creatinine standard reference material 967^{27,28}.

Other variables

CKD risk factors include diabetes, hypertension and known cardiovascular disease. HIV status was determined by CD4 count and viral load in the past six months, and a list of all current ART medications was obtained. Inflammation was evaluated by level of C -reactive protein and serum albumin. Hepatitis B and C status were obtained either from a review of the patient's medical records or self-reported.

Statistical analyses

Plasma clearance of iohexol was calculated using the following equation: $I/(\exp A/\alpha + \exp B/\beta) \times 1.73/BSA$ where I is dose of the iohexol (mg), exp A is the intercept of the slow curve and α is its corresponding slope, exp B is the intercept of the fast curve and β is its corresponding slope²¹. The fast curve was determined from concentrations at 10 and 30 minutes. The slow curve was determined from concentrations at 120 and 300 minutes. GFR was corrected to 1.73 m² body surface area by the ratio of 1.73 m²/BSA.

GFR was estimated using the MDRD Study, CKD-EPI creatinine 2009, CKD-EPI cystatin C 2012 and CKD-EPI creatinine-cystatin C 2012 equations^{15,16,18} (herein referred to as creatinine, cystatin C and creatinine-cystatin C equations) (For equation formulae, see Supplemental Table 1). Comparisons were performed in the overall dataset and in subgroups defined by estimated GFR and clinical characteristics of age, sex, race, body mass index (BMI), presence of diabetes, tenofovir use, log transformed high sensitivity c-reactive protein, CD4 count (categorized by quartiles for initial regression analyses and by less than or greater than 350 cells/ul for graphic presentation), viral load (categorized as undetectable,

less or greater than 1000 copies/mL for regression analyses, and by less than or greater than 1000 copies/mL for graphic presentation).

Performance of the estimating equations was evaluated using standard metrics used in the evaluation of estimating equations^{29,30}. Bias was assessed as the median difference between the measured and estimated GFR, with positive values indicating an under-estimation of measured GFR. Precision was assessed as inter-quartile range (IQR) for the difference between measured and estimated GFR. Accuracy combines both bias and precision and was assessed as the percent of estimates within 30% of the measured GFR (P_{30}), with large errors indicated by $1-P_{30}$. In the overall dataset, the Wilcoxon signed rank test was used to test statistical significance of the difference for the median of errors for each equation and McNemar's test were used to determine statistical significance of differences of $1-P_{30}$. Significance testing was not performed in subgroups due to small sample size in some groups and concern about multiple testing. For the purpose of reporting, we defined clinically significant differences as differences greater than 2 mL/min per 1.73 m^2 for median difference and IQR, respectively, and differences greater than 4% of $1-P_{30}$. Overall and in subgroups, confidence intervals were calculated by bootstrap methods³¹ (2000 bootstraps) for median difference and IQR of the differences and by the binomial method for P_{30} . Analyses were performed using R (Version 2.9.2)³² and SAS (Version 9.2, Cary, NC).

Role of the Sponsor

The study was funded by Gilead Sciences Inc under an investigator-initiated protocol. Gilead Sciences was not required to approve publication of the finished manuscript. The project received IRB approval at all sites, and all participants provided written informed consent.

Results

Clinical characteristics of the participants are shown in Table 1. Of the 200 participants, 145 (73%) were male, 104 (52 %) were Blacks, 68 (34%) were older than 50 years. The mean (SD) measured GFR was 87 (26) mL/min/ 1.73 m^2 and ranged between 23 to 175 mL/min/ 1.73 m^2 , with 27 (14%) having measured GFR less than 60 mL/min per 1.73 m^2 , and 90 (45%) greater than 90 mL/min per 1.73 m^2 . Median (IQR) CD4 count was 536 (421) cells/ μL and 61% had undetectable viral loads. There were no significant differences in these descriptors between subjects taking tenofovir or not.

The CKD-EPI creatinine equation was less biased and more accurate than the MDRD study equation overall ($P < 0.0001$ for median difference and $p = 0.018$ for $1-P_{30}$) and across the range of GFR (Table 2). Overall, the CKD-EPI creatinine and cystatin C equations had similar bias [median difference (95% confidence intervals) of -5.4 (2.7 – 7.9) vs 4.3 (1.2 – 7.7) mL/min per 1.73 m^2 , $p = 0.048$], precision [IQR of the difference of 22.7 (18.3 – 26.3) vs 25.7 (20.6 – 28.8) mL/min per 1.73 m^2 , $p = 0.37$], and accuracy [$1-P_{30}$ of 15.0% (10.5, 20.0) vs 17.5% (12.5, 22.8), $p = 0.48$]. There appeared to be differences in performance across the range of GFR (Table 2). Compared to the creatinine equation, the cystatin C equation had greater bias at GFR less than 60 mL/min per 1.73 m^2 [13.1 (7.4 – 16.6) vs 7.4 (5.0 – 14.6) mL/min per 1.73 m^2] as well as at GFR greater than 90 mL/min per 1.73 m^2 [median difference of 5.4 (-10.9 – 0.5) vs 0.0 (-5.0 – 4.5) mL/min per 1.73 m^2]. The two equations had similar accuracy at GFR greater than 60 mL/min per 1.73 m^2 but the cystatin C equation was less accurate at GFR less than 60 mL/min per 1.73 m^2 [$1-P_{30}$ of 25.6% (12.8 – 38.7) vs 35.7% (21.4 – 50.0)].

The creatinine-cystatin C equation had a statistically, but not clinically significant larger bias compared to the creatinine equation [6.4 (3.1–9.3) vs 5.4 (2.7–7.9) $p = 0.013$] but a trend

towards better accuracy [1-P₃₀ of 10.0% (6.0 – 14.0) vs 15.0% (10.5 – 20.0), $p=0.059$ (Table 2). In contrast, the creatinine-cystatin C equation had similar bias to the cystatin C equation [6.4 (3.1–9.3) vs 4.3 (1.2–7.7) mL/min per 1.73 m², $p=0.24$], but better accuracy [1-P₃₀ of 10.0% (6.0 – 14.0) vs 17.5% (12.5–22.8) $p=0.0017$]. For both equations, results were consistent across the GFR range (Table 2). The performance of the average of the creatinine and cystatin C equations was approximately equivalent to the creatinine-cystatin C equation but differed minimally at the extremes of eGFR (data not shown).

Figures 1 and 2 shows the bias and accuracy across subgroups for the creatinine, cystatin C and creatinine-cystatin C equations. In general, there appeared to be no substantial differences in bias among the three equations for all subgroups defined by age, sex, race, BMI, diabetes status, HIV factors (CD4 count or viral load) or inflammation (c-reactive protein or serum albumin) (Figure 1). Accuracy appeared equal or better in most of these subgroups with the combined equation compared to equations with either marker alone (Figure 2). Compared to the creatinine and creatinine-cystatin C equations, the cystatin C equation appeared to have lower accuracy in the subgroup of participants with BMI less than 22 kg/m² [1-P₃₀ of 31.4 (16.5–47.1) vs 22.9 (9.4–37.1) or 22.9 (9.4–37.5), respectively], or who were on tenofovir [1-P₃₀ of 21.6 (14.5 to 28.9) vs 13.6 (7.8, 19.7) or 9.6 (4.8, 15.0), respectively]. Conversely, the creatinine equation appeared to be less accurate compared to the cystatin C as well as the creatinine-cystatin C equation in people with BMI greater than 30 kg/m² [1-P₃₀ of 13.9 vs 5.6 or 5.6, respectively].

Discussion

Here we report on the performance of GFR estimating equations using creatinine, cystatin C and the combination of the two markers in a population of HIV-positive patients on stable ART. Our results showed that similar to other populations, the CKD-EPI creatinine equation performs better than the MDRD study equation¹⁶. The creatinine-cystatin C based equation was significantly more accurate than the cystatin C equation and there was a trend toward greater accuracy than the creatinine equation¹⁸. These results have implications for clinical use of GFR estimating equations in the HIV-positive population.

The improved performance of the CKD-EPI creatinine equation compared to the MDRD Study equation is consistent with a recent systematic review that showed the CKD-EPI creatinine equation seems to be more accurate and less biased in studies with higher mean measured GFR across multiple clinical populations and research studies³³. In the recent paper evaluating the CKD-EPI 2012 cystatin C and creatinine-cystatin C equations in clinical and research populations without HIV, the creatinine-cystatin C equation was more precise and accurate than both creatinine and cystatin C equations. In the current study, we see some improvement in accuracy with the creatinine-cystatin C equation, however it is not as great as was observed in the non-HIV population¹⁸. This difference may be related to relatively small sample size or to greater imprecision of cystatin C in patients who are HIV-positive. Few studies have evaluated GFR estimating equations in an HIV population^{34–38}. Most studies have been small, did not use gold standard reference methods or did not consider differences among assays¹⁸. Similar to the current study, in a recent study of 22 HIV-positive patients, another combined creatinine-cystatin equation performed better than either creatinine or cystatin based equations, whereas the cystatin C equation had the worst performance³⁶. In contrast, in a recent study of 196 Thai HIV-positive patients, a different cystatin C equation than was used here had lesser bias than the creatinine equation, although had worse precision, and therefore had similar accuracy. Difference between these studies may be related to the differences in race and geographical region³⁹.

In the current study, the cystatin C equation appears to be less accurate in people with lower levels of BMI, and the creatinine equation was less accurate in people with higher levels of BMI. This observation is opposite to the performance of these equations in non-HIV study populations, where the cystatin C equation was more accurate than either creatinine or creatinine-cystatin C equations in people with lower levels of BMI, and the three equations had similar performance at higher levels of BMI¹⁸. The results in the non-HIV population were hypothesized to be due to the fact that low BMI is an indication of low muscle mass, and the better performance of the cystatin C equation reflects the lesser association of cystatin C to muscle mass than creatinine. Our data suggests that this relationship may be more complex, and the relative contribution of adipose and muscle to BMI needs to be considered. In the Study of Fat Redistribution and Metabolic Change in HIV infection (FRAM); HIV-positive patients were shown to have lower levels of both adipose tissue and skeletal muscle compared to controls^{40,41}. In vitro studies have shown a relationship between pre-adipocyte cell cultures and cystatin C generation⁴². Variation in both muscle and adipose mass in HIV-positive patients vs HIV-negative patients may lead to changes in both creatinine and cystatin C independent of GFR, which in turn affects performance of both creatinine and cystatin C equations. Inflammation is thought by some to be another determinant of cystatin C independent of GFR^{19,43}. It is possible that people with lower levels of BMI have higher levels of inflammation and if so, this could also be a cause of the lower accuracy of the cystatin C equation in patients with low BMI. Previous studies have demonstrated higher levels of high c-reactive protein and fibrinogen levels in HIV-positive males compared to controls^{40,44}. However, we did not observe any associations of performance of the equations with c-reactive protein or serum albumin. We cannot fully explain the observation of the worse accuracy of the cystatin C equation in HIV-positive patients with low BMI, but it does caution use of cystatin C based equations in other population with low BMI on the assumption that creatinine based estimates are expected to be inaccurate. The more consistent performance of the combined creatinine-cystatin C equation across BMI is likely due to smaller influence of non GFR effects on each marker.

The performance of the creatinine and creatinine-cystatin C equations was similar for patients who were and were not on tenofovir, possibly supporting a lack of effect of tenofovir on creatinine handling by the kidney. The cystatin C equation appeared to be less accurate in patients on tenofovir. There were no apparent differences in clinical characteristics between patients on and not on tenofovir, which suggests that the greater inaccuracy may be due to a direct effect of tenofovir on the cystatin C assay, or on the generation, renal and/or extra-renal elimination of cystatin C. Given that both under and over estimation (i.e. no systematic bias) were observed, it is likely that there are several contributing factors or there is a variable effect of one factor. To our knowledge, no prior studies have suggested a possible mechanism for this effect, and as such this requires confirmation and further study. Differences in drug effects on creatinine vs cystatin C may also offer a potential explanation for the differences in GFR decline when GFR was estimated using creatinine or cystatin C in a trial comparing GFR decline in patients treated with tenofovir/emtricitabine in association with atazanavir/ritonavir or efavirenz⁴⁵

There are several implications to these findings. First, this is one of the first large scale studies evaluating GFR estimating equations in an HIV-positive population, and our results validate the use of CKD-EPI creatinine equation in this population. The better performance of the CKD-EPI equation compared to the MDRD Study equation reinforces recommendations by others and decisions by large laboratory service providers to report the CKD-EPI equation in place of the MDRD Study equation⁴⁶⁻⁴⁹. Accurate GFR estimates are particularly important in this population, due to the high prevalence of CKD, need to dose adjust multiple medications, and as such knowledge that the CKD-EPI creatinine equation is unbiased is informative for common clinical decision making in HIV-positive patients.

However, as in non-HIV populations, creatinine based GFR estimates were imprecise^{14,16}. The small sample size does not allow for definitive recommendations as to which patients are most likely to have an inaccurate estimate, but it would be prudent to be cautious in people at the extremes of BMI²². Clinicians should be cognizant of these limitations and should consider performing a confirmatory test, such as measured creatinine clearance from a 24 hour urine collection or measured GFR using an exogenous marker, especially when using medications with narrow therapeutic windows. Second, the lack of definitive improvement with the cystatin C based equations is in contrast to prior hypotheses as to the performance of cystatin C in HIV-positive patients. Further studies to confirm these findings as well as to explore the non GFR determinants of cystatin C in this population are required. Third this is one of the first indications of a possible difference in accuracy of cystatin C based equations by drug status. Since one of the major uses of GFR estimates in clinical practice is to adjust doses of medications, it is critical that the effect of drugs on the level of an endogenous marker is known, as is the case of the effect of cimetidine and trimethoprim on the level of serum creatinine.

Strengths of this study include its rigorous gold standard measure of GFR. Other studies have shown that accuracy of GFR estimating equations is not dependent upon the GFR measurement method³³. Recruitment of patients from three clinical sites allowed us to capture the broad spectrum of prevalent HIV patients on ART in current clinical practice. We recruited specifically for patients on and not on tenofovir, the most commonly used antiretroviral drug, and at low levels of GFR, to ensure that we captured the heterogeneity in clinical practice. Serum creatinine and cystatin C measurements were traceable to high level references materials for the respective assays and all equations are expressed use of such values.

Our study has limitations. First, the small numbers within subgroups do not allow us to make definitive conclusions about performance within subgroups. Second, the study population had a narrow age range, and also did not include a substantial number of patients at very low levels of GFR, but this is reflective of current clinical practice. Third, the population may not be representative of patients with markedly reduced muscle mass or malnutrition, in whom both creatinine and cystatin C might not be expected to perform well. Fourth, GFR is known to be measured with error, which may account for some of the observed imprecision^{22,50}.

In conclusion, the CKD-EPI cystatin C equation does not appear to be more accurate than the CKD-EPI creatinine equation in patients who are HIV-positive, supporting the use of the CKD-EPI creatinine equation for routine clinical care. Clinicians should consider confirmatory tests for some patients where estimated GFR based upon creatinine is expected to be inaccurate, especially those at the extremes of muscle mass²². The use of both filtration markers together as a confirmatory test for decreased estimated GFR based on creatinine in individuals who are HIV-positive requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Performance of estimating equations by clinical subgroups

Panel a: Bias: Median difference between measured and estimated GFR; Panel b: Accuracy: Percentage of estimates greater than 30% of measured GFR ($1 - P_{30}$). eGFR_{cr}, estimated GFR by the CKD-EPI equation¹⁶; eGFR_{cys}, estimated GFR by the CKD-EPI cystatin C equation¹⁸; eGFR_{cr,cys}, estimated GFR by the CKD-EPI creatinine-cystatin C equation¹⁸. The number of participants in each subgroup are age ≤ 50 (132), > 50 (68); female (55), male (145); Blacks (104), non Blacks (96); body mass index (kg/m²) <22 (35), 22–30 (129), >30 (36); diabetes yes (16), no (184).

Figure 2. Performance of estimating equations by tenofovir, CD4 and viral load subgroups

Panel a: Bias: Median difference between measured and estimated GFR; Panel b: Accuracy: Percentage of estimates greater than 30% of measured GFR (1-P₃₀) The number of participants in each subgroup are tenofovir status yes (125), no (75); CD4 count (cells/ul) <350 (56), ≥350 (144); Viral load (copies/mL) <1000 or undetected (168), ≥1000 (14); serum albumin (mg/dl) <3.6 (43), ≥3.6 (157); serum C- reactive protein (mg/L) <4.8 (150), ≥4.8 (50).

Table 1

Clinical Characteristics

Variable	Total N (%)
Number	200
Age (years), mean $\pm$ SD	48 $\pm$ 8
50 years	132 (66)
>50 years	68 (34)
Male	145 (73)
Blacks	104 (52)
Weight (kg), mean $\pm$ SD	79 $\pm$ 16
BMI (kg/m ²) mean $\pm$ SD	27 $\pm$ 6
<22 kg/m ²	35 (18)
22–30 kg/m ²	129 (65)
>30 kg/m ²	36 (18)
Hypertension	60 (31)
Diabetes	16 (8)
Source of HIV transmission	
Injection	24 (12)
Male-to-male contact	75 (38)
High-risk heterosexual contact	51 (26)
Unsure/Other/Missing	50 (43)
Tenofovir usage	125 (63)
Hepatitis B	22 (11)
Hepatitis C	51 (26)
CD4 (cells/ μ L), Median, IQR	536, 421
Viral load (copies/mL) *	
Undetected	111 (61)
<1000	57 (31)
1000	14 (8)
C- reactive protein (mg/L), Median, IQR	1.6, 4.0
Serum albumin (mg/dL), mean $\pm$ SD	3.8 $\pm$ 0.4
Kidney Function Measures	
Measured GFR (mL/min per 1.73 m ²), mean $\pm$ SD	87 $\pm$ 26
90 mL/min/1.73 m ²	90 (45)
60–89 mL/min/1.73 m ²	83 (41)
<60 mL/min/1.73 m ²	27 (14)
Standardized serum cystatin C (mg/L), mean $\pm$ SD	1.1 $\pm$ 0.4
Standardized serum creatinine (mg/dL), mean $\pm$ SD	1.2 $\pm$ 0.4
Estimated GFR, MDRD Study, (mL/min per 1.73m ²), mean $\pm$ SD	75 $\pm$ 23
Estimated GFR, CKD-EPI creatinine, (mL/min per 1.73m ²) mean $\pm$ SD	80 $\pm$ 24
Estimated GFR, CKD-EPI cystatin C, (mL/min per 1.73m ²) mean $\pm$ SD	83 $\pm$ 26

Variable	Total N (%)
Estimated GFR, CKD-EPI creatinine-cystatin C, (ml/min per 1.73m ²) mean ± SD	83 ± 24

MDRD, Modification of Diet in Renal Disease Study; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

*
18 patients had missing data for viral load status.

Table 2

Performance of creatinine and cystatin C equations overall and across the range of GFR

Equation	Overall	Estimated GFR <i>ml/min/1.73 m²</i>		
		<60	60–90	>90
Bias , Median Difference (95% confidence intervals), ml/min per 1.73 m ²				
MDRD Study	10.9 (8.0 – 14.0)	11.9 (7.9 – 18.7)	14.5 (11.2 – 17.1)	0.7 (–2.9 – 8.3)
CKD-EPI Creatinine	5.4 (2.7 – 7.9)	7.4 (5.0 – 14.6)	7.6 (3.5 – 13.0)	0.0 (–5.0 – 4.5)
CKD-EPI Cystatin C	4.3 (1.2 – 7.7)	13.1 (7.4 – 16.6)	6.5 (1.8 – 12.5)	–5.4 (–10.9 – 0.5)
CKD-EPI Creatinine-cystatin	6.4 (3.1 – 9.3)	8.8 (2.7 – 12.5)	8.8 (4.7 – 13.4)	0.4 (–7.0 – 8.0)
Precision , Interquartile range of the difference (95% confidence intervals), ml/min per 1.73 m ²				
MDRD Study	21.7 (18.6 – 25.8)	19.4 (14.3 – 25.7)	18.1 (13.9 – 27.2)	25.6 (15.6 – 34.8)
CKD-EPI Creatinine	22.7 (18.3 – 26.3)	18.1 (11.3 – 24.2)	23.1 (16.1 – 30.2)	22.8 (17.0 – 30.6)
CKD-EPI Cystatin C	25.7 (20.6 – 28.8)	17.2 (10.1 – 24.3)	22.9 (17.4 – 27.4)	24.6 (18.3 – 31.8)
CKD-EPI Creatinine-cystatin C	21.7 (18.1 – 24.4)	17.7 (9.5 – 20.2)	19.2 (14.4 – 24.2)	24.4 (20.1 – 30.4)
Accuracy , Percentage of estimates greater than 30% of measured GFR (95% confidence intervals), %				
MDRD Study	20.0 (14.5 – 26.0)	33.3 (20.4 – 45.9)	15.7 (8.2 – 23.6)	13.0 (4.5 – 22.5)
CKD-EPI Creatinine	15.0 (10.5 – 20.0)	25.6 (12.8 – 38.7)	12.0 (5.2 – 19.3)	12.2 (5.1 – 20.0)
CKD-EPI Cystatin C	17.5 (12.5 – 22.8)	35.7 (21.4 – 50.0)	11.3 (4.9 – 18.7)	14.1 (6.7 – 22.2)
CKD-EPI Creatinine-cystatin C	10.0 (6.0 – 14.0)	18.4 (6.5 – 30.8)	5.9 (1.2 – 11.5)	10.4 (3.9 – 17.8)

MDRD, Modification of Diet in Renal Disease Study; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration