Estimating Glomerular Filtration Rate in Patients With HIV Infection

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Summary: Accurate markers of glomerular filtration rate in human immunodeficiency virus (HIV)-infected persons would be useful for early diagnosis of HIV-associated nephropathy and other glomerular diseases, and for identifying patients at high risk for subsequent declines in kidney function who also may develop cardiovascular disease or renal complications from antiretroviral agents or other therapies. Creatinine-based estimates of glomerular filtration rate have not been tested rigorously in HIV-infected persons. Their accuracy has been questioned in malnourished patients, with or without a wasting syndrome, and in those treated with anabolic steroids. Cystatin C level is increased in HIV, but more studies are needed to determine its association with kidney function, inflammation, and long-term outcomes.
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The most widely used estimates of glomerular filtration rate (GFR), the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations, have neither been validated in people with normal kidney function nor rigorously tested in special populations, such as in persons with human immunodeficiency virus (HIV) infection. Their accuracy and reliability in HIV infection has been questioned because the relationships between muscle mass and creatinine generation derived from other populations may not hold true in patients with extremes of muscle mass as seen in malnutrition, chronic wasting, or anabolic steroid use. In addition, the relationship between serum creatinine and GFR may be altered by the effect of antiretroviral agents and other medications on renal tubule function, or by prior nephrotoxic or ischemic insults. In the absence of studies that validate these formulae, their ability to detect small changes in kidney function when the GFR is well above 60 mL/min/1.73 m^2 is unclear.

The spectrum, prevalence, and risk factors for kidney disease in HIV infection are reasonably well established. There is a disproportionate kidney disease burden in black people, a high prevalence of hypertension and diabetes in patients with HIV, an important association between HIV infection and HIV-associated nephropathy, a high prevalence of hepatitis C virus co-infection and injection drug use, and repeated exposure to potential nephrotoxins.[1-4] Guidelines to screen for chronic kidney disease (CKD) recommend annual testing for proteinuria and estimated GFR (eGFR), using either Cockcroft-Gault or MDRD equations, in patients with any of these risk factors.[5] Early CKD detection could alter medical decision making and improve outcomes. Especially important is the opportunity to make a timely diagnosis of HIV-associated nephropathy, which would lower the threshold for initiating antiretroviral therapy in a subset of drug-naive patients with CD4 cell counts greater than 350 cells/mm^3, the current recommended threshold for initiating treatment.[6] Other benefits include identification of those at high risk for future declines in GFR, which would be particularly helpful in risk-stratifying for complications from drugs such as tenofovir, nonsteroidal anti-inflammatory drugs, or even angiotensin-converting enzyme inhibitors.[7]

Several studies designed to examine long-term renal safety issues with tenofovir have

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shown that GFR decreases over time in many patients with HIV, irrespective of antiretroviral regimen.[8-10] A better understanding of the clinical significance of seemingly minor increases in the serum creatinine level when GFR is greater than the current CKD threshold of 60 mL/min/1.73 m^2 has a real potential to improve clinical outcomes. The precision of the MDRD equation decreases and bias increases at GFR levels at or above 60 mL/min/1.73 m^2.[11] Patients with borderline GFR often are misclassified, and small changes in eGFR above 60 mL/min/1.73 m^2 are difficult to interpret. GFR estimating equations must be validated in a large cross-section of HIV-infected persons, and long-term outcomes related to changes in GFR must be tracked. Renal disease was an important secondary end point in the Strategies for Management of Antiretroviral Therapy trial comparing episodic with continuous antiretroviral therapy; however, the analysis was limited to dialysis dependency or life-threatening increases in serum creatinine (grade 4 adverse events).[12,13]

Studies designed to derive new GFR estimating equations or to validate existing ones should contain hundreds, if not thousands, of patients for adequate statistical power and generalizability in clinical practice. The MDRD equation was derived in approximately 1,600 patients[13] and the CKD Epidemiology Collaboration (CKD-EPI) has pooled thousands of individuals from several research and clinical populations.[11] No such large-scale studies have been performed in the setting of HIV infection. Two reports comparing Cockcroft-Gault estimates with 24-hour creatinine clearance measurements in HIV-infected patients yielded discrepant results, with Cockcroft-Gault overestimating creatinine clearance in one report and underestimating it in the other report.[14,15] Sample sizes were small (42 and 47 patients), and the patient population was not representative of patients encountered today. Combination antiretroviral therapy was not yet available and many patients were hospitalized for acquired immune deficiency syndrome–related complications. As new studies are designed, non–creatinine-based estimates, particularly cystatin C levels, should be assessed.

Longitudinal studies in elderly cohorts and in people with heart disease show that cystatin C level is a better prognosticator of mortality than creatinine-based estimates of kidney function.[16] To assess whether cystatin C level is a better measure of GFR or if it is linked to mortality through another pathway, stored serum samples were analyzed in 3,418 individuals with kidney disease pooled from 4 research cohorts in which direct measures of GFR (urinary clearance of ^{125}I-iothalamate or chromium-51-ethylenediaminetetraacetic acid) were available.[17] Cystatin C accounted for 82% of the variability in GFR, was superior to serum creatinine alone (74% of the variability), and was roughly equivalent to MDRD eGFR. A formula inclusive of cystatin C, age, sex, and race was more accurate than creatinine-based estimates. Future studies will focus on patients with normal GFR because it is unclear how much more precision in estimating GFR is necessary for better management of patients with established CKD and GFR less than 60 mL/min/1.73 m^2.

The utility of cystatin C in HIV infection was tested in a cross-sectional study of 1,008 HIV-infected participants from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) cohort, which originally was designed to evaluate the prevalence and correlates of changes in fat distribution, insulin resistance, and dyslipidemia in HIV.[18] Mean cystatin C levels were higher in HIV-infected patients compared with controls, although eGFR was similar. By using a cut-off value of 1 mg/dL, increased cystatin C levels were seen in 31% of HIV patients. Among patients with an increased cystatin C level, 17% had albuminuria and 2% had an MDRD eGFR of less than 60 mL/min/1.73 m^2. Cystatin C level was correlated with risk factors for kidney disease, including hypertension and low levels of high-density lipoprotein, but also with HIV-related risk factors, such as low CD4 cell count and hepatitis C virus co-infection. These data confirm and extend a European report of higher cystatin C levels in HIV without discernable differences in eGFR.[19] In the absence of direct measures of GFR, it cannot be determined whether patients with HIV had impaired kidney function or to what extent demographic or nonrenal factors con-

Table 1. A Summary of Current Formulae Available to Estimate GFR

eGFR Measure	Validation	Performance and Clinical Utility
Serum creatinine	113D–amino acid derivative, freely filterable with varying degrees of tubule secretion and extrarenal elimination	Relatively large variability in plasma concentrations owing to extrarenal factors such as variations in muscle mass and dietary intake, drugs inhibiting secretion (trimethoprim and cimetidine), and increased intestinal elimination at low GFR
Creatinine-based eGFR Cockcroft-Gault Ccr = ([140-age] × weight)/72 × Scr × 0.85 (for female subjects)	Developed in 1973 using 24-hour urinary creatinine clearance from 249 hospitalized men	Reasonably reliable at GFR levels < 60 mL/min Tends to overestimate GFR in patients with normal kidney function Widely used to measure kidney function in pharmacokinetic studies and to guide drug dosing according to kidney function
The MDRD equation eGFR mL/min/1.73 m^2 = 186 × (Scr) $^{-1.154}$ × (age$^{-.203}$ × .742 if female) × 1.212 (if black race)	Developed in 1999 using iothalamate clearance measurements from 1,628 people with GFR levels of 20-60 mL/min/1.73 m^2 Re-expressed in 2005 for use with a standardized creatinine assay: 175 × (standardized Scr) $^{-1.154}$ × (age$^{-.203}$ × .742 if subject is female) × 1.212 (if the subject is black)	Shows little bias (mGFR – eGFR) when eGFR is < 60 Bias increases when eGFR exceeds 60 mL/min/1.73 m^2 Bias differs according to race, particularly at eGFR > 60 Underestimates mGFR by 9.5 and 11.1 mL/min at eGFR 60-89 and 90-119, respectively Patients with GFR > 60 mL/min may be misclassified as having CKD Approximately 82% of eGFR measurements are within 30% of mGFR
Cystatin C	13-kd protein filtered at the glomerulus and reabsorbed and catabolized by tubule cells	Serum levels more closely correlated with eGFR than serum creatinine More closely linked to cardiovascular events than serum creatinine or MDRD equation Relation between serum levels and mGFR are affected by age, sex, and race, but less so than Screat Assay requires standardization Extrarenal factors affecting serum levels require further clarification

Table 1. Continued

eGFR Measure	Validation	Performance and Clinical Utility
Cystatin C–based eGFR eGFR = $76.7 \times CysC^{-1.19}$ eGFR = $127.7 \times CysC^{-1.17} \times age^{-0.13} \times 0.91$ (if female) $\times 1.06$ (if black race) eGFR = $177.6 \times Scr^{-0.65} \times CysC^{-0.57} age^{-0.20} \times 0.82$ (if female) $\times 1.11$ (if black race)	Validated in 3,418 subjects, mostly with CKD (mGFR $<$ 60 mL/min 1.73 m^2) using samples from 4 large clinical trials	Less affected by age, sex, and race than creatinine-based estimates Best fitting equation for mGFR $<$ 60 mL/min includes cystatin, creatinine, age, sex, and race Prediction equations slightly overestimate mGFR $>$ 90 mL/min Unknown performance as a CKD screening tool because formulae have not been validated against mGFR $>$ 60 mL/min in large patient populations
Cystatin C and HIV	Measured in 1,008 HIV-infected patients and 290 controls from the FRAM study	Serum cystatin C levels approximately 20% higher in HIV compared with controls 31% of HIV patients had levels $>$ 1.0 mg/dL compared with 4% of controls, whereas only 2% of HIV-infected patients had eGFR $<$ 60 mL/min Higher serum levels associated with lower HDL, higher uric acid, higher CRP, lower serum glucose, albumin-creatinine ratio $>$ 30, low CD4, HCV co-infection, and heroin use

Abbreviations: HCV, hepatitis C virus; HDL, high-density lipoprotein; CRP, C-reactive protein.
Data from Stevens et al,[11,17] Levey et al,[13] Shlipak,[16] and Odden et al.[18]

tributed to the observed differences. In a recent analysis of National Health and Nutrition Examination Survey (NHANES) III participants, cystatin C levels increased with age, and were influenced by gender, race, and ethnicity.[20 21] These data on creatinine and cystatin C based GFR estimates are summarized in Table 1.

Future studies that directly measure GFR will help define the best method for detecting reduced kidney function and the optimal role of cystatin C in HIV infection. It remains to be determined whether standardized laboratory assays of cystatin C will provide the clinician with more reliability in tracking kidney function over time, and whether this will translate into different practice patterns for prescribing medications or for referral to a nephrologist. It also remains to be determined whether cystatin C predicts clinical outcomes in HIV or whether it is more useful than existing tests, such as urinary albumin excretion, which also predicts future cardiovascular and renal events.[21] New studies will help determine how accurate measures of GFR complement new screening tests and how these measures may change standards of care for treating HIV infection.

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