Racial Disparities in Creatinine-based Kidney Function Estimates Among HIV-infected Adults

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Objective: The aim of our study was to investigate whether current eGFR equations in clinical use might systematically overestimate the kidney function, and thus misclassify CKD status, of Black Americans with HIV. Specifically, we evaluated the impact of removing the race coefficient from the MDRD and CKD-EPI equations on comparisons between Black and White HIV-infected veterans related to: 1) the prevalence of reduced eGFR; 2) the distribution of eGFR values; and 3) the relationship between eGFR and all-cause mortality.

Design: Retrospective cohort study.

Setting: The Department of Veterans Affairs (VA) HIV Clinical Case Registry (CCR), which actively monitors all HIV-infected persons receiving care in the VA nationally.

Patients/Participants: 21,905 treatment-naïve HIV-infected veterans.

Main Outcome Measures: Estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula with and without (MDRD-RCR) the race coefficient and all-cause mortality.

Results: Persons with eGFR <45 mL/min/1.73m^2 had a higher risk of death compared with those with eGFR >80 mL/min/1.73m^2 among both Blacks (HR=2.8, 95%CI: 2.4-3.3) and Whites (HR=1.9, 95%CI: 1.4-2.6), but the association appeared to be stronger in Blacks (P=.038, test for interaction). Blacks with eGFR 45-60 mL/min/1.73m^2 also had a higher risk of death (HR=1.7, 95%CI: 1.4-2.1) but Whites did not (HR=0.86, 95%CI: .67-1.10; test for interaction: P<.0001). Racial differences were substantially attenuated when eGFR was re-calculated without the race coefficient.

Conclusions: Our findings suggest that clinicians may want to consider estimating glomerular filtration rate without the race coefficient in Blacks with HIV. *Ethn Dis*. 2016;26(2):213-220; doi:10.18865/ed.26.2.213

Keywords: Estimated Glomerular Filtration Rate; Human Immunodeficiency Virus; Chronic Kidney Disease; Racial Disparities; Mortality

Introduction

With the widespread use of highly active antiretroviral therapy (HAART), deaths in human immunodeficiency virus (HIV) patients attributed to acquired immunodeficiency syndrome (AIDS)-defining illnesses are declining.[1] However, chronic diseases including chronic kidney disease (CKD) have been increasingly associated with morbidity and mortality in HIV patients.[1,2] Recent studies have shown a large disparity in prevalence and incidence of end stage renal disease (ESRD) by race among persons with HIV.[3-5]

Despite Blacks with HIV-infection having a higher incidence of ESRD and higher prevalence of known CKD risk factors compared with Whites,[4,6-10] the prevalence of reduced estimated glomerular filtration rate (eGFR <60 mL/min/1.73m^2) is similar between Whites and Blacks with HIV.[11] One possible explanation for this observation is that Blacks with HIV may have rapidly progressive CKD leading to a lower prevalence of mildly reduced GFR among Blacks.[4,12] An alternative hypothesis is that the detection of reduced eGFR is delayed in Blacks with HIV because the most frequently used GFR estimating equations overestimate their GFR, and thus Blacks with mildly reduced GFR are misclassified as having a normal GFR.

The Modification of Diet in Renal Disease equation (MDRD) was derived in a mostly White population with low GFR and without HIV infection.[13] The equation includes a race coefficient that raises the calculated eGFR in all Blacks by approximately 21% compared with non-Black persons with

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the same serum creatinine, age, and sex, but this may overestimate eGFR among Blacks.[14] The updated equation for creatinine-based eGFR estimation, the CKD-EPI, uses a somewhat smaller race coefficient that raises the calculated eGFR in Blacks by 16%.[15] While most laboratories use the MDRD equation to calculate eGFR, neither the MDRD nor the CKD-EPI have been well validated in Black patients with a broad spectrum of HIV severity.[16-19] Furthermore, several studies among Black Africans showed that removing the race coefficient improved GFR estimation compared with a gold standard.[20,21]

The aim of our study was to investigate whether current eGFR equations in clinical use might systematically over-estimate the kidney function, and thus misclassify CKD status, of Black Americans with HIV.

The aim of our study was to investigate whether current eGFR equations in clinical use might systematically over-estimate the kidney function, and thus misclassify CKD status, of Black Americans with HIV. We are unaware of any large registry or cohort of Blacks living in the United States with HIV that contains gold standard GFR measures. Thus, we explored this research question using the outcome of all-cause mortality as a surrogate for chronic kidney disease as CKD has been shown to be strongly associated with death[22-25] in a national registry of HIV-infected veterans. Specifically, we evaluated the impact of removing the race coefficient from the MDRD and CKD-EPI equations on comparisons between Black and White HIV-infected veterans related to: 1) the prevalence of reduced eGFR; 2) the distribution of eGFR values; and 3) the relationship between eGFR and all-cause mortality.

Methods

Data sources used to assemble the analytic cohort have been described in detail elsewhere.[11] The Department of Veterans Affairs (VA) HIV Clinical Case Registry (CCR) actively monitored all HIV-infected persons receiving care in the VA nationally, and automatically extracted demographic, clinical, laboratory, pharmacy, utilization, and death information from the VA electronic medical record to a centralized database.[26]

Patients

We included treatment-naïve HIV-infected veterans (defined by no prior exposure to any anti-retroviral therapy [ARV]) at the time they entered clinical care in the Veterans Health Administration (VHA) system and who subsequently received mono or combined ARV with regular care and laboratory monitoring. Among 65,675 HIV-infected persons treated in the VHA between 1985 and 2011, 30,632 patients initiated ARV in the modern era of combination antiretroviral therapy (after 1997). Baseline was defined as the date of starting antiretroviral therapy as in our prior studies.[27,28] We excluded patients with prevalent kidney failure (receipt of chronic dialysis treatment or kidney transplant), and those who did not have at least one HIV-1 viral load, CD4 count, outpatient visit, and assessment of kidney function. We also excluded those who did not have a race listed and those who were neither African American nor Caucasian, which left 21,905 patients in the analytic cohort.

Outcomes

Primary study outcomes were: 1) estimated glomerular filtration rate (eGFR); and 2) all-cause mortality. Estimated GFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula based on age, sex, race, and serum creatinine, as this equation is used in VA clinical practice.[29] Estimated GFR was also calculated using the MDRD equation with the race coefficient removed (MDRD-RCR). As secondary analyses, we calculated the CKD-EPI equation with and without the race coefficient.[15] Reduced eGFR was defined by two consecutive outpatient measures of eGFR <60mL/min/1.73m^2. All-cause mortality was determined using data on vital status and date of death obtained from the VA HIV Clinical Case Registry. Deaths were ascertained to January 2011.

Chronic Kidney Disease Risk Factors

Demographic information (age, sex, and race) from the VA HIV CCR was supplemented with Medicare database information.[30,31] We defined comorbid conditions as described previously.[32] Baseline covariates were defined at entry

into the registry. Proteinuria was defined as two consecutive urine dipstick measurements ≥30mg/dL. Body mass index (BMI) was calculated based on clinical records. Blood pressure, CD4 T-cell counts, HIV RNA level, LDL, HDL, triglycerides, total cholesterol, albumin, and serum glucose were obtained from clinical and laboratory records.

Statistical Analysis

We first compared demographic and clinical characteristics of Black and White HIV-infected veterans. We then categorized eGFR (<30, 30-45, 45-60, 60-80, >80 mL/min/1.73m^2) using the MDRD equation stratified by race, and then repeated the categories using the MDRD-RCR. Next, we compared baseline clinical characteristics of Blacks, stratified by eGFR category: <60, 60-72, and >72 mL/min/1.73m^2. We specifically distinguished the 60-72mL/min/1.73m^2 category, as these Blacks are the ones re-classified to eGFR<60 mL/min/1.73m^2 when the race coefficient is removed from the MDRD equation. Finally, we used Cox proportional hazards regression models to compare the associa-

Table 1. Baseline clinical characteristics, stratified by race

	Black, n=12,029	White, n=9,876
Age, years	47 (41, 53)	48 (40, 55)
Female, %	397 (3.3%)	165 (1.7%)
Comorbid conditions, %		
Hypertension	3398 (28%)	2583 (26%)
Diabetes	815 (6.8%)	531 (5.4%)
Smoking	2232 (19%)	1923 (19%)
Hepatitis C virus	3382 (28%)	1866 (19%)
Illicit drug use	3459 (29%)	2231 (23%)
Measurements		
CD4+ Count, cells/mm^3	283 (130, 459)	344 (185, 548)
HIV Viral Load (1000 copies/mL)	17 (1, 94)	5 (0, 75)
Systolic blood pressure, mm Hg	127 (115, 140)	127 (116, 138)
Diastolic blood pressure, mm Hg	78 (70, 86)	77 (70, 84)
Body mass index, kg/m^2	25 (22, 28)	25 (22, 28)
Total cholesterol, mg/dL	168 (141, 197)	177 (149, 209)
Triglycerides, mg/dL	126 (87, 189)	163 (108, 254)
Low density lipoprotein, mg/dL	98 (75, 124)	103 (81, 130)
High density lipoprotein, mg/dL	40 (32, 51)	36 (29, 45)
Glucose, mg/dL	94 (86, 107)	96 (87, 106)
Albumin, g/dL	3.8 (3.4, 4.2)	4.0 (3.7, 4.4)
Proteinuria	3231 (27%)	1584 (16%)
MDRD eGFR	101 (86, 117)	90 (78, 104)
MDRD eGFR <60[a]	706 (5.9%)	523 (5.3%)
MDRD without race coef. eGFR	84 (71, 97)	90 (78, 104)
MDRD without race coef. eGFR <60[a]	1356 (11.3%)	523 (5.3%)
CKD-EPI eGFR	101 (85, 116)	93 (80, 104)
CKD-EPI eGFR <60[a]	807 (6.7%)	525 (5.3%)

Continuous variables reported as median (IQR).
Proteinuria defined by urinalysis protein >30 mg/dL
a. Units for eGFR are in mL/min/1.73m^2.
HIV, human immunodeficiency virus; MDRD, 4 Variable Modification of Diet in Renal Disease Study equation; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation.

Table 2. Baseline clinical characteristics, stratified by baseline eGFR category

	Black, eGFR <60[a], n = 706	Black, eGFR 60-72[a], n = 589	Black, eGFR >72[a], n = 10,734	White, eGFR <60[a], n=523
Age, years	53 (47, 59)	52 (47, 59)	46 (40, 52)	58 (51, 64)
Comorbid conditions				
Diabetes, n (%)	95 (13.5%)	65 (11.0%)	655 (6.1%)	64 (12.2%)
Measurements				
CD4+, cells/mm^3	217 (83, 369)	253 (123, 405)	290 (136, 467)	296 (155, 504)
HIV VL (1000 copies/mL)	21 (0, 100)	11 (0, 84)	17 (1, 93)	1 (0, 48)
SBP, mm Hg	136 (120, 151)	130 (118, 143)	127 (115, 139)	130 (118, 144)
DBP, mm Hg	81 (71, 91)	79 (70, 89)	78 (70, 86)	77 (69, 85)
Proteinuria, n (%)	467 (66%)	239 (41%)	2525 (24%)	197 (38%)
Albumin, g/dL	3.3 (2.7, 3.8)	3.7 (3.2, 4.1)	3.9 (3.5, 4.2)	3.9 (3.5, 4.3)

Continuous variables reported as median (IQR).
Proteinuria defined by urinalysis protein 30 mg/dL or greater.
a. Units for eGFR are in mL/min/1.73m^2.
HIV, human immunodeficiency virus; VL, viral load; SBP, systolic blood pressure; DBP, diastolic blood pressure.

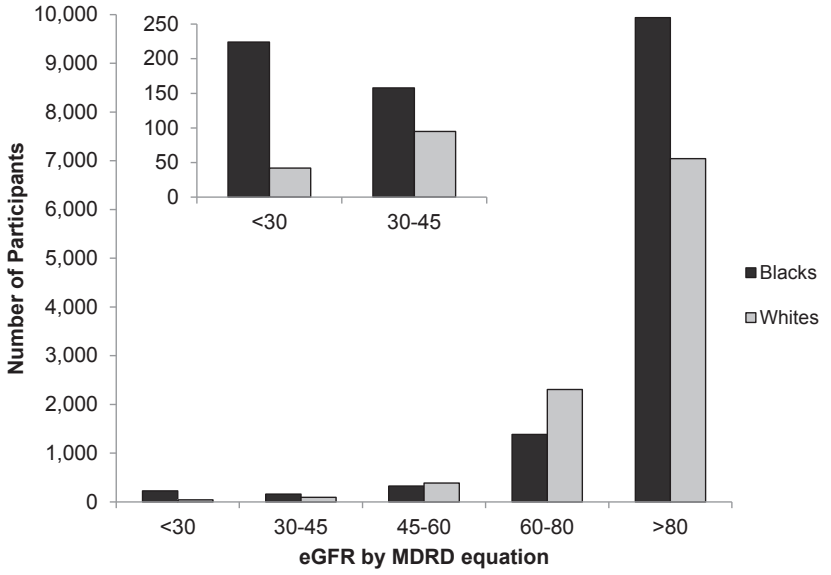

Figure 1. Distribution of baseline eGFR in Blacks and Whites, using the Four Variable Modification of Diet in Renal Disease Study equation (MDRD)

tion of baseline eGFR categories for each eGFR equation with all-cause mortality in Blacks and Whites, adjusted for age, sex, race and a race-by-CKD interaction term. Separate models were constructed for each eGFR estimating equation: MDRD, MDRD-RCR, CKD-EPI, and CKD-EPI without race coefficient (CKD-EPI-RCR). Analyses were conducted using Stata, version 11 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute, Inc. Cary, NC). Our study was approved by the Committee on Human Research of the San Francisco VA Medical Center and the VA Public Health Strategic Healthcare Group.

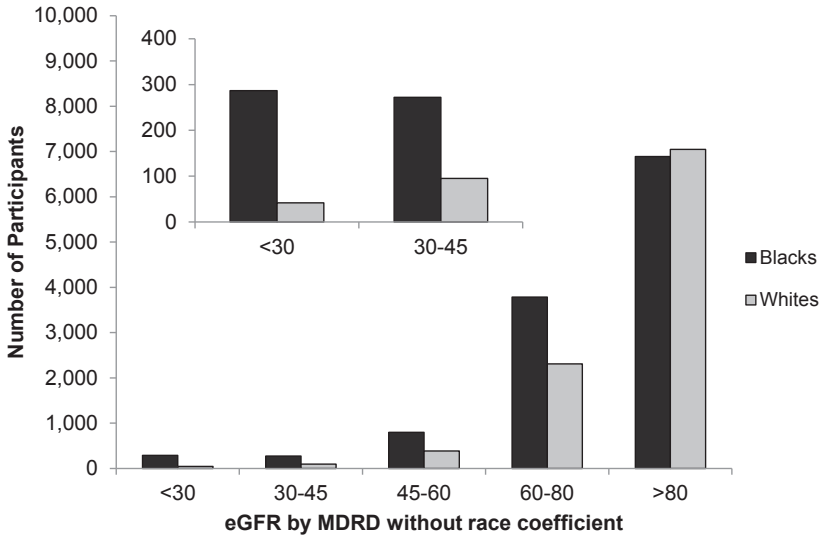

Figure 2. Distribution of baseline eGFR in Blacks and Whites, using the MDRD equation with the race coefficient removed (MDRD-RCR)

Results

Among the 21,905 HIV-infected persons included in this study, the mean age was 47 years and nearly all were male (97%), although women comprised a higher proportion of Blacks (3.3% vs. 1.7%). (Table 1) Compared with White veterans, Black veterans had a higher prevalence of diabetes, hepatitis C exposure, and illicit drug use. Among measured characteristics, CD4+ cell count and serum albumin levels were somewhat lower in Blacks. Proteinuria was almost twice as common in Blacks as compared with White veterans. Overall, there were 3950 deaths during 161,934 person-years of follow-up. The median follow-up time was 7.4 years (interquartile range 3.4–11.3 years).

The median eGFR was 101 mL/min/1.73m^2 in Blacks vs 90 in Whites using the MDRD equation, and 101 vs 93 using the CKD-EPI equation. In contrast, when we calculated eGFR using the MDRD without the race coefficient (MDRD-RCR), the median eGFR was 6 mL/min/1.73m^2 *lower* among Black veterans, compared with Whites (median 84 vs 90, Table 1). The prevalence of reduced eGFR (<60mL/min/1.73m^2) was similarly low (5%-7%) in Blacks and Whites when calculated using either the MDRD or CKD-EPI equations (Table 1). When we used the MDRD-RCR, the prevalence of reduced GFR in Blacks was more than twice as high as in Whites (11% vs 5%).

We next evaluated the distribution of eGFR categories by race (Figure 1). Using the MDRD, Blacks were more likely than Whites to have eGFR <45 mL/min/1.73m^2 (3.2% vs 1.4%), but were also more likely to have eGFR >80 mL/min/1.73m^2

(83% vs 71%). With the MDRD-RCR equation, (Figure 2), Blacks were more likely than Whites to have eGFR ≤80 mL/min/1.73m^2 (43% vs 29%).

We also compared kidney and HIV-related risk factors for low GFR among Blacks stratified by eGFR (Table 2). GFR strata were chosen to represent those classified as low eGFR by MDRD (MDRD eGFR <60 mL/min/1.73m^2), those who would be newly classified to low GFR with the MDRD-RCR (MDRD eGFR 60-72 mL/min/1.73m^2), and those classified as no CKD by both methods (MDRD eGFR >72 mL/min/1.73m^2). There were 706 Black veterans classified as low GFR regardless of the race coefficient and an additional 589 Black participants were reclassified as having a low GFR by the MDRD-RCR. Blacks with eGFR of 60-72 mL/min/1.73m^2 had similar rates of hypertension, diabetes and other CKD risk factors compared with Whites with an eGFR <60 mL/min/1.73m^2. Clinical characteristics of this group were intermediate between Black veterans with an eGFR <60 and >72 mL/min/1.73m^2 (Table 2).

Finally, we compared associations of baseline eGFR by MDRD with longitudinal mortality risk, stratified by race (Figure 3). Persons with eGFR <45 mL/min/1.73m^2 had a higher risk of death compared with those with eGFR >80 mL/min/1.73m^2 among both Blacks (HR=2.8, 95%CI: 2.4-3.3) and Whites (HR=1.9, 95%CI: 1.40-2.57) , although the association appeared to be stronger in Blacks (P=.038, test for interaction). By contrast, persons with eGFR 45-60 mL/min/1.73m^2 had a higher risk of death among Blacks (HR=1.7, 95%CI: 1.4-2.1) but not among Whites (HR=.86, 95%CI: .67-1.10; test for interaction: P<.0001). The eGFR 60-80 mL/min/1.73m^2 showed little association with mortality in either race (test for interaction: P=.39). Similar results were seen when we repeated the analysis using the MDRD-RCR equation, although racial differences were smaller (Figure 4). Analyses with the CKD-EPI equation with and without the race coefficient yielded similar results (Figures 5 and 6).

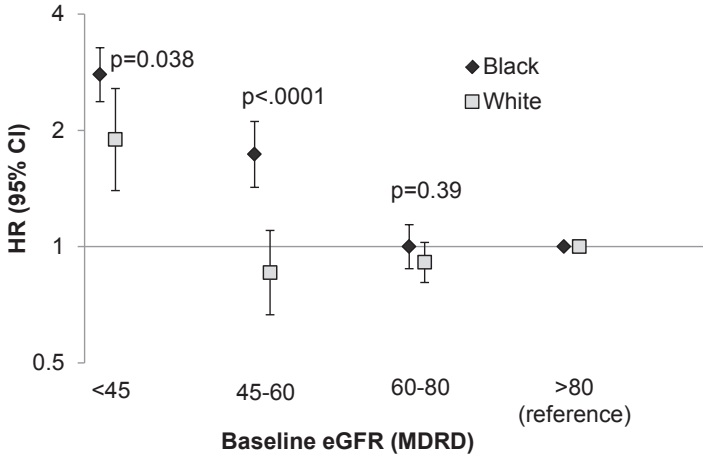

Figure 3. Association of baseline eGFR with all-cause mortality by race, using the Four Variable Modification of Diet in Renal Disease Study equation (MDRD)

Discussion

In this population of HIV-infected veterans, we found that the burden of kidney disease is underestimated when using current formulae to estimate kidney function in clinical practice. Specifically, we showed that Blacks had a higher prevalence of risk factors for reduced eGFR than Whites. However, similar proportions of Blacks and Whites had reduced eGFR using the MDRD equation. With the MDRD-

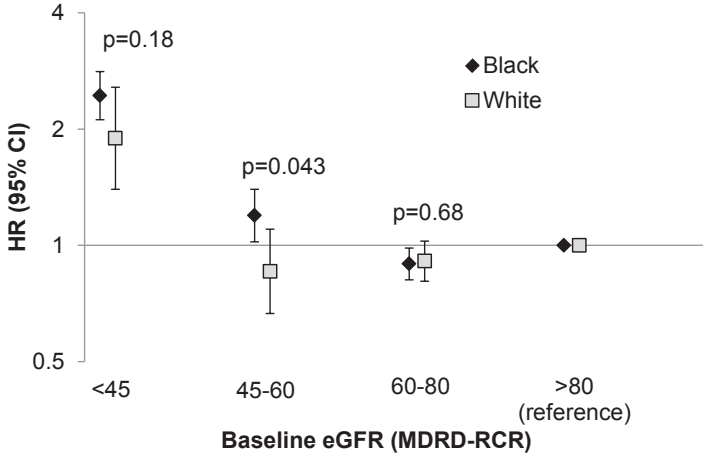

Figure 4. Association of baseline eGFR with all-cause mortality by race, using the MDRD equation with the race coefficient removed (MDRD-RCR)

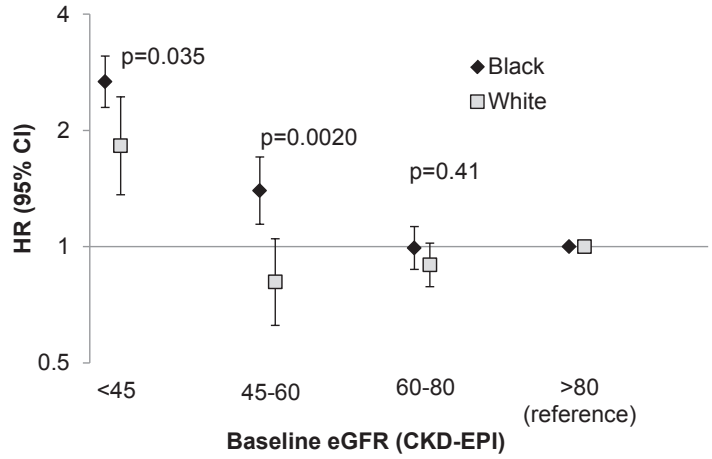

Figure 5. Association of baseline eGFR with all-cause mortality by race, using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)

RCR equation, there was higher prevalence of reduced eGFR in Blacks, as compared with Whites, mirroring the higher prevalence of CKD risk factors and proteinuria in Blacks. This population of Blacks with "newly classified" reduced eGFR had higher prevalence of most risk factors (diabetes, hypertension, proteinuria, lower serum albumin, lower CD4, higher HIV VL) compared with Whites who had eGFR <60 mL/min/1.73m^2. This supports the concept that these intermediate eGFR levels in Blacks are likely indicative of established CKD. Thus, we believe that the stronger mortality association of CKD by MDRD with mortality in Blacks, as compared with Whites, is an artifact of misclassification (Figure 2). In other words, we believe Blacks likely have a lower "true" GFR by the time their eGFR by MDRD drops below 60.

To our knowledge, no prior studies have evaluated the effect of removing the race coefficient from the MDRD equation on the diagnosis of reduced eGFR in HIV-infected patients in the United States. However, several recent studies have questioned the MDRD race coefficient for estimating eGFR in Blacks without HIV infection. A newer eGFR estimating equation, the CKD-EPI, utilizes a race coefficient of 15.9%, rather than 21.2%; Black race was common in the CKD-EPI cohort (32%)[15] as compared with the MDRD cohort. Using ^{125}I-iothalamate as a gold standard, Poggio et al[19] reviewed a large cohort of patients who had been evaluated for either renal transplant or renal transplant donation. In those with CKD, Blacks had only a 6.6% higher mean measured GFR as compared with Caucasians and compared with the 16%-21% higher estimates suggested by the CKD-EPI and MDRD equations, respectively. Similarly, in those evaluated for donation, there was no difference in mean measured GFR by race; this suggested that using the MDRD equation to estimate eGFR might significantly overestimate GFR in the Blacks in this cohort. Among sickle cell disease patients in Sub-Saharan Africa and the French West Indies, the CKD-EPI and MDRD equations without race coefficients better predicted the GFR by iohexol clearance as compared with the traditional CKD-EPI and MDRD equations.[33] As in our study, Peralta et al showed that the diagnosis of low eGFR in Blacks was very sensitive to the race coefficient used in the GFR estimating equation in the bi-racial CARDIA cohort of young adults living in the United States.[14]

Studies that have attempted to validate the MDRD equations in Black HIV-infected persons have had mixed results. A recent study of ART-naïve Kenyans with HIV showed that both

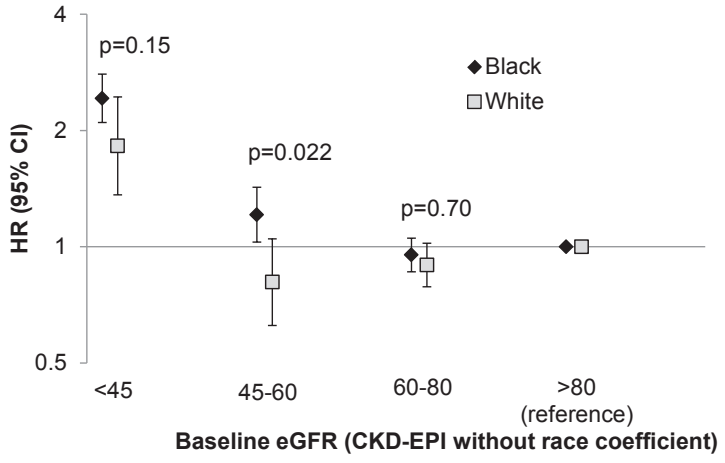

Figure 6. Association of baseline eGFR with all-cause mortality by race, using the CKD-EPI equation with the race coefficient removed

the CKD-EPI and MDRD better predicted iohexol derived GFRs when the race coefficient was removed[20] and similar results were recently described in a South African population as well.[21] Furthermore, among HIV-infected women in the WIHS cohort, eGFR was substantially lower when estimated with cystatin C compared with creatinine among Black participants, whereas cystatin C and creatinine produced similar estimates among White participants.[18] By contrast, Inker et al[34] compared the MDRD as well as several creatinine and/or cystatin-based CKD-EPI equations to the gold standard of GFR measured by iohexol clearance. Overall there was not a significant difference between the median measured and calculated GFR by race. However, only 27 of 200 participants had a measured GFR <60 mL/min/1.73m^2 and a subgroup analysis by race in this group was not reported.

In this population of HIV-infected veterans, we found that the burden of kidney disease is underestimated when using current formulae to estimate kidney function in clinical practice.

Accurate assessment of eGFR in Blacks with HIV-infection is critically important as they have at least a 3-fold higher incidence of ESRD compared with Whites with HIV.[5] Further, Blacks with HIV and two *APOL*1 alleles have a particularly high risk for ESRD even among Blacks.[35] Delay in the diagnosis of CKD by systematic overestimation of GFR may lead to inappropriately dosed medications or continuation of medications which may be harmful to the kidneys (for example tenofovir or NSAIDs). Furthermore, it may cause a delay in initiation of renal protective strategies.[36] At later stages of kidney disease, overestimation of GFR may delay transplant evaluation and preemptive fistula placement. Misclassification of GFR category could also hinder research aimed at improving renal outcomes for HIV-infected patients.

A major strength of our study is that the VA health system is the largest HIV care provider in the US, which allowed us a large national cohort, and we had capture of a broad range of clinical information in the electronic medical record. In addition, we had a balance of White and Black participants to facilitate comparisons. A major limitation is that our results may not be generalizable to non-veterans, women, those living outside the United States and those without access to medical care. Furthermore, there may be residual confounding, particularly from comorbid conditions or socioeconomic risk factors, in our analysis of eGFR as a predictor of mortality. As in many clinical registry studies, we were also limited by lack of a gold standard measure of GFR.

In summary, using the MDRD equation without the race coefficient reclassifies a large number of Black veterans as having CKD. This reclassified group has a substantially worse risk factor profile for CKD than the Blacks who remain in the normal eGFR range. Our work suggests that providers should question the eGFR estimates generated by either the MDRD or CKD-EPI equations in Blacks with HIV, particularly when assessing mortality risk. Meanwhile, we believe that because Blacks with HIV are known to have substantially higher risk for ESRD than Whites, clinical diagnostic tools should be adjusted toward a greater sensitivity for early detection of CKD and not a prioritization on specificity that might delay diagnosis. Providers may choose to consider the eGFR calculated for non-Blacks as a potentially safer alternative that prioritizes the early detection of kidney disease.

Conflict of Interest

Scherzer, R: honorarium from Merck for participating in a Renal Expert Input Forum; honorarium was donated to NCIRE to support kidney research

Author Contributions

Research concept and design: Anker, Scherzer, Peralta, Shlipak; Acquisition of data: Scherzer; Data analysis and interpretation: Anker, Scherzer, Peralta, Powe, Banerjee, Shlipak; Manuscript draft: Anker; Statistical expertise: Scherzer; Acquisition of funding: Shlipak, Powe, Peralta; Administrative: Shlipak; Supervision: Shlipak.

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