Published in final edited form as:
Antivir Ther. 2013 ; 18(6): 793–802. doi:10.3851/IMP2676.

Use of glomerular filtration rate estimating equations for drug dosing in HIV-positive patients

Aghogho A Okparavero[1], **Hocine Tighiouart**[2], **Zipporah Krishnasami**[3], **Christina M Wyatt**[4], **Hiba Graham**[5], **James Hellinger**[1], and **Lesley A Inker**[1,*]

[1]Department of Medicine, Tufts Medical Center, Boston, MA, USA

[2]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center; Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA, USA

[3]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[4]Department of Medicine, Mount Sinai School of Medicine, New York, NY, USA

[5]Gilead Sciences, Inc, Foster City, CA, USA

Abstract

Background—Current HIV treatment guidelines recommend using the Cockcroft-Gault equation for drug dosing adjustments. The use of newer glomerular filtration rate (GFR) estimating equations for drug dosing and the appropriateness of physician antiretroviral dosing based on estimated kidney function have not been studied in an HIV-positive population.

Methods—We evaluated concordance between measured and estimated GFR for the assignment of kidney function categories designated by the Food and Drug Administration (FDA) *Guidance for Industry* for pharmacokinetic studies, and appropriateness of physician antiretroviral drug dosing for level of kidney function in 200 HIV-positive patients on stable antiretroviral therapy. Estimated kidney function was determined using the Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD) Study and Cockcroft-Gault equations.

Results—For assignment of FDA-designated kidney function categories, concordance rates between measured and estimated GFR using the CKD-EPI, MDRD Study and Cockcroft-Gault equations were 79%, 71% and 77%, respectively. This pattern was consistent across most subgroups. When actual prescribed dosages were compared to recommended dosages based on the level of estimated kidney function, 3% to 19% of study participants were prescribed higher than recommended dosages. The largest discordance between prescribed and recommended dosages was observed for the Cockcroft-Gault equation.

Conclusions—The CKD-EPI equation has the highest concordance with measured GFR for the assignment of FDA-designated kidney function categories. Its use may lead to lower dosing related errors in HIV-infected US adults on stable antiretroviral therapy. More education is required with respect to dose adjustment for level of kidney function.

[*]**Corresponding author**LInker@tuftsmedicalcenter.org.

The remaining authors declared no competing interests.

Introduction

Kidney function assessment is an essential component in the medical management of patients with HIV. There is a high prevalence of chronic kidney disease in HIV-positive patients with estimated prevalence of GFR less than 60 ml/min per1.73 m^2 ranging from 5% to 24% compared to 6.7% in the general population [1-5]. Current guidelines recommend screening for CKD in HIV-positive individuals at the time of diagnosis [6, 7]. In addition, these guidelines recommend the use of creatinine clearance estimated by the Cockcroft-Gault equation for monitoring kidney function following initiation of highly active antiretroviral therapy (HAART) and for dosing adjustments in patients with impaired kidney function[6-8]. Yet the Modification of Diet in Renal Disease (MDRD) Study[9] and the Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI) equations[5] have been shown to be more accurate than the Cockcroft-Gault equation[10] and are currently used to report estimated GFR by clinical laboratories whenever a serum creatinine is measured[11]. In addition, the Cockcroft-Gault equation was developed using the older creatinine assay, and is therefore less accurate for use with current assays, which are traceable to higher order reference materials. As a result, the Cockcroft-Gault equation is not recommended for clinical use at this time [12-15].

In HIV uninfected populations, it has been previously demonstrated that the MDRD Study equation is more accurate than the Cockcroft-Gault equation for drug dosing purposes when compared to gold standard measured GFR [16]. In HIV-positive populations, prior studies have compared the MDRD Study and Cockcroft-Gault equations for assessing kidney function [17-22]; however, no study has evaluated these equations in comparison to measured GFR for drug dosing. We therefore sought to confirm the accuracy of these GFR estimating equations for antiretroviral dose adjustment in a cohort of 200 HIV-positive patients on stable antiretroviral therapy who had GFR measured using plasma clearance of iohexol. We also evaluated whether physicians are appropriately dosing antiretroviral medications based on the patients' level of kidney function as determined by the estimating equations.

Methods

Study population

We recruited 200 HIV-positive patients from three geographical locations (University of Alabama at Birmingham, Tufts Medical Center in Boston, and the Mount Sinai Hospital in New York) to evaluate the performance of GFR estimating equations compared to measured GFR (ClinicalTrials.gov Identifier: NCT00905151)[23]. Study participants were included if they were aged 18 years or older, had a confirmed diagnosis of HIV, and were on stable antiretroviral therapy for at least three months prior to the study. Exclusion criteria included pregnancy, use of trimethoprim, known allergy or contraindication to iohexol, recent acute kidney injury, or cognitive or physical impairments. The Institutional Review Board (IRB) at all the participating sites reviewed and approved the study protocol and all study participants provided written informed consent.

Measured GFR

Procedures for measuring GFR have been previously reported[23]. In brief, GFR was measured via plasma clearance of iohexol [24-26]. Five milliliters of iohexol (Omnipaque™ 300; GE Healthcare) was administered over a 30 second period followed by a 10 mL normal saline flush in one intravenous site. Blood samples were collected at approximately 10, 30, 120, and 240 minutes from the second intravenous line. Patients with serum creatinine > 1.5 mg/dL had an additional blood draw at 360 minutes. GFR was reported in units of milliliters per minute (mL/minute).

Estimated Kidney Function

Kidney function was estimated using the CKD-EPI, MDRD Study and Cockcroft-Gault equations (Supplemental Table 1). The CKD-EPI and MDRD Study equations are reported adjusted for body surface area, in units of mL /min per 1.73m^2, whereas the Cockcroft-Gault equation is reported unadjusted for body surface area, in units of mL/min. The recommended units for drug dosing are mL/min and the US Food and Drug Administration (FDA)-approved drug dosing labels are in mL/min. Therefore for the purposes of comparison of accuracy of drug dosage adjustment, estimated GFR using the CKD-EPI and MDRD Study equations were converted to these units, by multiplying by each participant's BSA and dividing by 1.73 m^2. For evaluation of physician practices, we also performed a sensitivity analysis using the standard reported units of mL/min per 1.73m^2.

Laboratory methods

Assays have been previously reported[23]. In brief, all assays were performed at the University of Minnesota. Iohexol concentration was determined by high performance liquid chromatography. Creatinine was measured using the Roche P-Mod using the creatininase Plus enzymatic assay (Hoffman-La Roche, Ltd, Basel, Switzerland), traceable to National Institute of Technology creatinine reference materials.

Variables

Demographic and clinical data collected during recruitment via self report and from review of the patient medical records include age, gender and race; CD4 count and HIV viral load within six months of recruitment; cardiovascular risk factors, hepatitis B and C co infection, and current medications and doses.

Statistical Analysis

Data were expressed as the mean and standard deviation, Kappa statistic, or counts and percentages, as appropriate. Differences among continuous variables were tested using linear mixed models accounting for within-patient correlation. All analyses were computed using the SAS statistical software, version 9.2; SAS Institute Inc., Cary, NC (SAS Institute Inc, www.sas.com)

Drug Simulation Study—We compared drug dosing among the different kidney function methods in two ways. First, we evaluated the concordance between measured and estimated GFR for assignment to kidney function categories recommended in the 1998 US Food and

Drug Administration Guidance for Industry: Pharmacokinetics in Patients With Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling (herein referred to as the *FDA Guidance for Industry*) kidney function categories (>80 mL/min, normal renal function; 50 to 80 mL/min, mild renal impairment; 30 to 50 mL/min, moderate renal impairment and <30mL/min, severe renal impairment)[27]. Second, to demonstrate the impact of the differences between kidney function estimates on actual medications, we compared drug dosage recommendations for five medications commonly used by participants in the study, tenofovir (Viread®), emtricitabine (Emtriva®), tenofovir/ emtricitabine (Truvada®), tenofovir/ emtricitabine/ efavirenz (Atripla™) and abacavir/ lamivudine (Epzicom™), based on measured GFR and estimated kidney function. These 5 antiretroviral medications were selected as they all require dosage adjustment for level of kidney function and provide examples of drug dosing thresholds common to other antiretroviral medications (Supplemental Table 2). Drug dosage recommendations were obtained from the Panel on Antiretroviral Guidelines for Adults and Adolescents[6]. Because of the predominant use of the Cockcroft-Gault equation in pharmacokinetic studies for drug dosing in clinical practice, we also calculated agreement between assigned categories using the Cockcroft-Gault equation and the other estimating equations.

Concordance and discordance rates as well as Kappa (κ) coefficients were calculated for agreements between the assigned kidney function categories using measured GFR and those from the 3 estimating equations. Analyses were computed overall and by subgroups of tenofovir use (yes/ no), age (≤50 or >50), sex, race (African American or other), body mass index (BMI) (<22, 22 to 30 or >30kg/m^2), and HIV RNA viral load (undetected, <1000 or ≥1000copies/mL). The significance of differences in concordance for these kidney function categories was tested in overall cohort by using binomial models accounting for within-patient correlation. We did not test significance of the difference in subgroups due to small sample size.

Assessment of Physician Drug Dosing—We next asked the question, whether clinicians are appropriately dosing drugs adjusted to the estimated level of kidney function. To answer this question, we compared actual prescribed dosages of the five medications included in the simulation analysis (Supplemental Table 2) to recommended dosages based on the level of kidney function as calculated by each of the estimating equations. For each estimating equation, we described the number of participants who were not prescribed the recommended dosage of a specific medication. Significance testing was not performed due to small sample sizes.

Results

The clinical characteristics of study participants are summarized in Table 1. Of the total participants, 33% were aged over age 50, approximately 50% were African Americans, and 73% were male. The study participants had relatively normal kidney function with a mean (standard deviation) measured GFR of 87 (26) mL/min per 1.73m^2. Overall estimated kidney function from the CKD-EPI, MDRD Study, and Cockcroft-Gault equations were 80 (24), 75 (23), and 80 (23) mL/min per 1.73m^2, respectively ($p<0.001$ for comparison to measured GFR).

Drug Simulation Study

Concordance with kidney function categories assigned by the *FDA Guidance for Industry* between the estimating kidney function equations and measured GFR are listed in Table 2. Overall, the CKD-EPI equation showed the highest concordance with measured GFR [79%, kappa statistic (κ) (95% confidence intervals) = 0.65 (0.55, 0.74)]. The MDRD Study equation showed the lowest concordance [(71%), κ=0.55 (0.45, 0.65)]. This pattern was consistent across most subgroups with the notable exception of participants of African American descent, with BMI < 22, and with HIV viral loads > 1000, where the Cockcroft-Gault had the lowest level of agreement. All equations provided kidney function estimates that were lower than measured GFR. Therefore, across all 3 estimating equations and all subgroups, use of the estimated GFR to assign drug dosage was more likely to result in a lower dose rather than a higher dose compared to what would have been prescribed if the measured GFR value was used to assign drug dosage (Supplemental Table 3).

Comparisons of the CKD-EPI and MDRD Study equations to the Cockcroft-Gault equation are shown in Table 3. In the overall population, the CKD-EPI creatinine equation had a greater concordance with Cockcroft-Gault than the MDRD Study equation [(85%), κ=0.77 (0.69, 0.85) vs. (79%), κ=0.69 (0.60, 0.77)]. This was seen in all subgroups with exception of the BMI subgroup of <22 kg/m^2, where the MDRD Study equation had a higher concordance with Cockcroft-Gault. Overall, the CKD-EPI equation provided higher kidney function estimates compared to the Cockcroft-Gault equation, while the MDRD Study equation provided lower kidney function estimates.

The CKD-EPI equation showed the highest levels of agreement with measured GFR (Table 4, top part) and with Cockcroft-Gault (Table 4, bottom part) for drug dosing recommendations for the five specific examples of antiretroviral medications (Table 4, top part). The Cockcroft-Gault equation had similar concordance but lower kappa values relative to the MDRD Study equations for all 5 medications.

Assessment of Physician Drug Dosing

To assess whether clinicians are appropriately prescribing adjusted drug dosages given the estimated level of kidney function, we compared actual prescribed dosages of the same five medications to recommended dosages based on the level of kidney function as calculated by each of the 3 estimating equations. The number of participants who were not prescribed the recommended dosage of a specific medication is summarized in Table 5 for each FDA-assigned kidney function category and each estimating equation. Depending upon the medication prescribed and equation used to estimate kidney function, the number of discrepancies ranged from 3% to 19% across all 5 medications. The actual prescribed dosages were always higher than those recommended based on the level of kidney function as calculated by any of the 3 estimating equations. For example, of the 125 participants on tenofovir, 7 (6%) of study participants were prescribed higher doses compared to what they would have received if the CKD-EPI equation was used to determine their kidney function. Of these, 118 study participants would have received a 300 mg once daily dose of tenofovir if kidney function was determined by the CKD-EPI equation compared to 124 that actually received that dose. This proportion was even higher if the MDRD study [9 (7%)] and

Cockcroft-Gault equation [10 (8%)] were used. For all medications, the largest discordance between prescribed dosage and recommended dosage was for the Cockcroft-Gault formula. Supplemental Table 7 describes the characteristics of the people who were prescribed higher doses than recommended. As expected, their GFR was low and accordingly, they were older and were more likely to have diabetes than the overall stdy population, When these analyses were repeated for the CKD-EPI and MDRD Study equations using the standard units of mL/min per 1.73m^2 as reported by clinical laboratories, even greater discordance between actual prescribed and recommended doses were seen than for these same equations when calculated in units of mL/min, and were approximately equal to that observed with use of the Cockcroft-Gault equation (Supplemental Table 6).

Discussion

A single method for estimation of kidney function for all populations and purposes would facilitate their use in clinical practice. The Cockcroft-Gault equation is assumed by many to be the most appropriate method to assess kidney function for drug dosing purposes, but the CKD-EPI and MDRD Study equations are reported by clinical laboratories. Our results showed the CKD-EPI equation had the highest concordance with measured GFR for both the FDA *Guidance for Industry* assigned kidney function categories and for dosing recommendations for specific antiretroviral medications. Additionally, in evaluation of physician practices, actual prescribed dosages for antiretroviral medications tended to be higher than those recommended by current antiretroviral drug treatment guidelines using any of the three estimating equations, with the greatest discordance seen with the Cockcroft-Gault equation. These results have implications for clinical practice and guidelines for management of HIV-positive patients.

The Cockcroft-Gault, MDRD Study and CKD-EPI estimating equations are the most commonly used equations for assessing kidney function in clinical practice. The Cockcroft-Gault equation was developed in 1976 in a study including 249 male Caucasian patients with a mean creatinine clearance of 73 mL/min[10]. This equation was the primary method for kidney function assessment during the 1980's and 1990's and was therefore recommended as one method to estimate kidney function for use in pharmacokinetic studies by the FDA *Guidance for Industry*. The equation was not developed using creatinine assays that are traceable to higher order reference materials and because the assay is no longer in existence, it cannot be re-expressed for such[28]. The MDRD Study equation and more recently the CKD-EPI creatinine equation were developed in larger and more diverse populations, are expressed for serum creatinine assays that are traceable to higher order methods, and have been shown to be more accurate then the Cockcroft-Gault equation in most populations, including HIV-positive individuals[5, 9, 23, 29, 30]. More importantly, with the widespread use of standardized creatinine assays, the results of pharmacokinetic studies performed prior to this era are substantially different with the use of modern creatinine assays, regardless of the equation used. Therefore, it is irrelevant that the Cockcroft-Gault was used to estimate kidney function for pharmacokinetic studies[13]. The most recent Kidney Disease: Improving Global Outcomes (KDIGO) CKD Guidelines recommend that only eGFR equations that have been expressed using standardized methods be used[14, 15]. A KDIGO controversies conference on Drug Dosing in CKD recommended

that the most accurate method to estimate GFR should also be used for drug dosage assessment[14].

Several studies have compared concordance of kidney function estimating equations for drug dosing adjustments in non HIV populations [16, 31-40]. Among these studies, concordance rates ranged from 64 to 99% [16, 31, 32, 34, 37-40]. However, most of these studies did not include gold standard reference methods or standardized creatinine values, and/or used differing units, making the results difficult to compare and interpret [28]. In the two studies that included measured GFR as the gold standard, the MDRD study equation had greater concordance with measured GFR than the Cockcroft-Gault equation [16, 35]. The reason for the difference in results between this study and these prior studies is likely related to the level of GFR. The MDRD Study equation performs best at lower levels of GFR. To our knowledge, no prior study has evaluated this question in HIV populations, nor has a prior study evaluated the CKD-EPI equation for drug dosing purposes in any population.

Due to the relationship between serum creatinine and muscle mass, creatinine based estimating equations are less accurate at extremes of body weight. Many assume that the Cockcroft-Gault would therefore be more accurate because it includes weight. Here, we showed that the Cockcroft-Gault had lower concordance to measured GFR than the CKD-EPI and MDRD Study equations for people with BMI < 22 kg/m^2. For people with BMI > 30 kg/m^2, the Cockcroft-Gault and CKD-EPI had similar concordance. We had previously reported in non HIV-positive population that the MDRD Study equation had greater concordance with measured GFR than the Cockcroft-Gault equation across the full range of weight, regardless of whether actual or ideal body weight was used in the calculation of the Cockcroft-Gault equation[16].

Among participants with decreased kidney function, actual dosages of the antiretroviral medications were higher than recommended based on measured GFR or any of the three estimating equations. This finding was similar regardless of whether we used estimated GFR adjusted or unadjusted for body surface area. This may suggest that clinicians are not considering the level of kidney function when dosing antiretroviral medications. Alternatively, a decision to give a higher dose may be based on other clinical factors such as patient compliance. Given the risk of antiretroviral drug resistance emerging in the face of inadequate drug dosing, clinicians may be reluctant to prematurely reduce doses for antiretroviral agents. Our study cannot distinguish between these possibilities and cannot determine the consequences of incorrect dosing.

There are several implications to our findings. First, guidelines for antiretroviral drug dosing may require revisions. The Infectious Diseases Society of America (IDSA) and the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents both recommend using either the Cockcroft-Gault or MDRD Study equations for baseline kidney function assessment for the management of chronic kidney disease and baseline evaluation and follow up after commencement of antiretroviral therapy (ART), respectively[6-8]. Similarly, the 1998 FDA *Guidance for Industry* recommends creatinine clearance estimated by the Cockcroft-Gault equation for determination of kidney

function and drug dosing guidelines in pharmacokinetic studies[27], and the draft revised guidelines now include the MDRD Study equation as an alternative[41]. Our results suggest that these recommendations should be further revised to include the CKD-EPI equation. We also recommend that guidelines be written to instruct clinicians to use the most appropriate method to assess kidney function for an individual, as was recommended by a recent Kidney Disease: Improving Global Outcomes (KDIGO) consensus conference[14]. For example, in a patient with low muscle mass secondary to neuromuscular disease or an amputation, any creatinine estimating equations will not be accurate. In those circumstances, a 24-hour urine collection to measure creatinine clearance or measured GFR using an exogenous filtration marker is necessary. Second, the better performance of the CKD-EPI equation throughout the GFR range, as we have shown previously, means that GFR can know and ability to be reported for all values, even those greater than 60 ml/min per $1.73m^2$[5, 23]. This, provides another piece of support for the reporting of CKD-EPI creatinine equations vs. the MDRD Study equation by clinical laboratories, as has been implemented by the two largest laboratories in the United States so far[5, 42-45]. Third, further study is required to better understand the discrepancy between physician prescriptions and recommended drug doses based on estimated kidney function. Use of GFR estimates to guide drug dosing decisions may be facilitated by the reporting of GFR in units of mL/min by clinical laboratories instead of in ml/min per $1.73m^2$ as is currently performed.

Strengths of this study are the availability of a reference method for GFR determined by plasma clearance of iohexol. We included a diverse population reflecting the current US HIV epidemic, including a large number of African Americans and women, increasing generalizability of our results. Additionally, the serum creatinine assays are traceable to higher order methods that improve test reproducibility and reduce error, and analyses were performed using the same units across all equations, which allows for a valid comparison across all equations. There are several limitations to this study. First, we used drug dosage recommendations as an outcome rather than observed drug efficacy and safety. Second, we had limited power to draw definitive conclusions within important subgroups, including the small number of patients with very low GFR. The difference in accuracy between the MDRD Study and CKD-EPI equation is smaller at lower levels of GFR. Thus, the reported discordance rates for the MDRD Study equation may not accurately reflect discordance at lower levels of GFR where drug dosing adjustment is more common. However, our study population may be more reflective of the HIV-positive patient population seen in clinical practice. Third, contributions of tubular reabsorption or secretion to the renal clearance of these medications were not considered, as well as other factors such as protein binding, volume of distribution, drug absorption and metabolism. However, most pharmacokinetic studies do not measure these directly, and tubular handling of many drugs actively secreted by transporters along the renal proximal tubule is not likely reflected by tubular handling of creatinine[16]. Fourth, study participants' creatinine levels at the time of the study visit were assumed to be at the same levels as the time their drug dosages were determined. Fifth, we did not have data on dosages for the prescribed medications for all participants. In addition, we could only evaluate medications used in the United States. However, conclusions from this study can be applied to antiretroviral medications frequently used in developing countries such as didanosine (Videx®) and zidovudine (Retrovir®), which have similar dose

adjustment thresholds to the medications used in our study. Sixth, conversion of GFR estimates from the CKD-EPI and MDRD Study equations to units of ml/min per 1.73m^2 may be imprecise as the method to calculate BSA is itself a formula, and may have errors.

In conclusion, the CKD-EPI creatinine equation expressed in units of mL/min had greater concordance with measured GFR for dosing recommendations than the MDRD Study and Cockcroft-Gault equations and can be used for drug dosing. More education may be required with respect to antiretroviral dose adjustment for level of kidney function in HIV-positive individuals. Reporting of GFR estimates in units of mL/min, for consistency with the FDA Guidance, would facilitate this practice. Clinical judgment should be used for the interpretation of any GFR estimate and confirmatory tests such as a 24 hour urinary creatinine clearance should be considered in patients at extremes of muscle mass[25].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was funded by Gilead Sciences, Inc. under an investigator-initiated protocol (NCRR L1RR025752) and supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1 RR025752 (Tufts Medical Center) and UL1 RR029887 (Mount Sinai School of Medicine) and also the Center for Clinical and Translational Sciences (CCTS) through Grant Number UL1 RR025777 (University of Alabama at Birmingham). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosure Statement: All the authors received funding from Gilead Sciences, Inc. under an investigator-initiated protocol (NCRR L1RR025752) for this work. HG is an employee of Gilead Sciences Inc. CW has received funding for investigator-initiated research from the Gilead Foundation.

References

1. Flandre P, Pugliese P, Cuzin L, et al. Risk factors of chronic kidney disease in HIV-infected patients. Clin J Am Soc Nephrol. 2011; 6:1700–1707. [PubMed: 21566114]
2. Naftalin C, Nathan B, Hamzah L, Post FA. HIV-associated kidney disease in the context of an aging population. Sex Health. 2011; 8:485–492. [PubMed: 22127033]
3. Estrella MM, Parekh RS, Astor BC, et al. Chronic kidney disease and estimates of kidney function in HIV infection: a cross-sectional study in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr. 2011; 57:380–386. [PubMed: 21646913]
4. Fernando SK, Finkelstein FO, Moore BA, Weissman S. Prevalence of chronic kidney disease in an urban HIV infected population. Am J Med Sci. 2008; 335:89–94. [PubMed: 18277114]
5. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]
6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services; Oct 14. 2011 Available from http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf [Accessed March 25, 2012]
7. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2005; 40:1559–1585. [PubMed: 15889353]
8. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2009; 49:651–681. [PubMed: 19640227]

9. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006; 145:247–254. [PubMed: 16908915]
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16:31–41. [PubMed: 1244564]
11. Miller WG. Estimating glomerular filtration rate. Clin Chem Lab Med. 2009; 47:1017–1019. [PubMed: 19728841]
12. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating Equations for Glomerular Filtration Rate in the Era of Creatinine Standardization: A Systematic Review. Ann Intern Med. 2012
13. Stevens LA, Levey AS. Use of the MDRD study equation to estimate kidney function for drug dosing. Clin Pharmacol Ther. 2009; 86:465–467. [PubMed: 19844220]
14. Matzke GR, Aronoff GR, Atkinson AJ Jr. et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011
15. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter. 2013; 3(Suppl):1–150.
16. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis. 2009; 54:33–42. [PubMed: 19446939]
17. Stohr W, Walker AS, Munderi P, et al. Estimating glomerular filtration rate in HIV-infected adults in Africa: comparison of Cockcroft-Gault and Modification of Diet in Renal Disease formulae. Antivir Ther. 2008; 13:761–770. [PubMed: 18839777]
18. Barraclough K, Er L, Ng F, et al. A comparison of the predictive performance of different methods of kidney function estimation in a well-characterized HIV-infected population. Nephron Clin Pract. 2009; 111:c39–48. [PubMed: 19052469]
19. Beringer PM, Owens H, Nguyen A, et al. Estimation of glomerular filtration rate by using serum cystatin C and serum creatinine concentrations in patients with human immunodeficiency virus. Pharmacotherapy. 2010; 30:1004–1010. [PubMed: 20874037]
20. Bonjoch A, Bayes B, Riba J, et al. Validation of estimated renal function measurements compared with the isotopic glomerular filtration rate in an HIV-infected cohort. Antiviral Res. 2010; 88:347–354. [PubMed: 20887753]
21. Vrouenraets SM, Fux CA, Wit FW, et al. A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. Clin Nephrol. 2012; 77:311–320. [PubMed: 22445475]
22. Praditpornsilpa K, Avihingsanon A, Chaiwatanarat T, et al. Comparisons between validated estimated glomerular filtration rate equations and isotopic glomerular filtration rate in HIV patients. AIDS. 2012; 26:1781–1788. [PubMed: 22713478]
23. Inker LA, Wyatt C, Creamer R, et al. Performance of Creatinine and Cystatin C GFR Estimating Equations in an HIV-positive population on Antiretrovirals. J Acquir Immune Defic Syndr. 2012; 61:302–309. [PubMed: 22842844]
24. Schwartz GJ, Furth S, Cole SR, Warady B, Munoz A. Glomerular filtration rate via plasma iohexol disappearance: pilot study for chronic kidney disease in children. Kidney Int. 2006; 69:2070–2077. [PubMed: 16612328]
25. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol. 2009; 20:2305–2313. [PubMed: 19833901]
26. Brochner-Mortensen J. A simple method for the determination of glomerular filtration rate. Scand J Clin Lab Invest. 1972; 30:271–274. [PubMed: 4629674]
27. Food and Drug Administration Guidance for Industry. Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. U.S. Department of Health and Human Services; Rockville, MD: 1998.
28. Stevens LA, Padala S, Levey AS. Advances in glomerular filtration rate-estimating equations. Curr Opin Nephrol Hypertens. 2010; 19:298–307. [PubMed: 20393287]

29. Stevens LA, Coresh J, Feldman HI, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population. J Am Soc Nephrol. 2007; 18:2749–2757. [PubMed: 17855641]
30. Coresh J, Stevens LA. Kidney function estimating equations: where do we stand? Curr Opin Nephrol Hypertens. 2006; 15:276–284. [PubMed: 16609295]
31. Golik MV, Lawrence KR. Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: cockcroft-gault and modification of diet in renal disease. Pharmacotherapy. 2008; 28:1125–1132. [PubMed: 18752383]
32. Healy MF, Speroni KG, Eugenio KR, Murphy PM. Adjusting eptifibatide doses for renal impairment: a model of dosing agreement among various methods of estimating creatinine clearance. Ann Pharmacother. 2012; 46:477–483. [PubMed: 22474135]
33. McFarland MS, Markley BM, Zhang P, Hudson JQ. Evaluation of Modification of Diet in Renal Disease study and Cockcroft-Gault equations for sitagliptin dosing. J Nephrol. 2012; 25:515–522. [PubMed: 21928236]
34. Hermsen ED, Maiefski M, Florescu MC, Qiu F, Rupp ME. Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for dosing antimicrobials. Pharmacotherapy. 2009; 29:649–655. [PubMed: 19476418]
35. de Lemos ML, Hsieh T, Hamata L, et al. Evaluation of predictive formulae for glomerular filtration rate for carboplatin dosing in gynecological malignancies. Gynecol Oncol. 2006; 103:1063–1069. [PubMed: 16875719]
36. Bookstaver PB, Johnson JW, McCoy TP, Stewart D, Williamson JC. Modification of Diet in Renal Disease and modified Cockcroft-Gault formulas in predicting aminoglycoside elimination. Ann Pharmacother. 2008; 42:1758–1765. [PubMed: 19047358]
37. Wargo KA, Eiland EH 3rd, Hamm W, English TM, Phillippe HM. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. Ann Pharmacother. 2006; 40:1248–1253. [PubMed: 16835312]
38. Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group--a cautionary tale. Nephrol Dial Transplant. 2007; 22:2894–2899. [PubMed: 17575316]
39. Melloni C, Peterson ED, Chen AY, et al. Cockcroft-Gault versus modification of diet in renal disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol. 2008; 51:991–996. [PubMed: 18325437]
40. Moranville MP, Jennings HR. Implications of using modification of diet in renal disease versus Cockcroft-Gault equations for renal dosing adjustments. Am J Health Syst Pharm. 2009; 66:154–161. [PubMed: 19139480]
41. Food and Drug Administration 2010 Draft Renal Impairment Guidance. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. U.S. Department of Health and Human Services; Rockville, MD: 2010.
42. Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis. 2010; 56:486–495. [PubMed: 20557989]
43. Inker L, Schmid CH, Tighiouart H, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. N Engl J Med. 2012; 367:10–19.
44. Quest Diagnostics. [Accessed October 25 2011] Estimated Glomerular Filtration Rate (eGFR) Web Calculator. 2011. Available from http://www.questdiagnostics.com/hcp/egfr.html
45. LabCorp. [Accessed October 25 2011] Lab Horizons. 2011. Available from https://www.labcorp.com/wps/wcm/connect/97cc5680489499ed88f4ef1d8cc08f20/LabHorizons+Vol+11+No+10+(Sept+2011)--FINAL.pdf?MOD=AJPERES&CACHEID=97cc5680489499ed88f4ef1d8cc08f20&CACHEID=6400b30048921344ab8ffb30c787aa90

Table 1

Clinical Characteristics

	Total N (%)	Measured GFR (mL/min) Mean (SD)	Estimated GFR (mL/min) Mean (SD)		
			CKD-EPI	MDRD Study	Cockcroft-Gault
All patients[a]	200 (100)	97 ± 31	89 ± 28	83 ± 27	89 ± 30
(mL/min per 1.73^2)	200 (100)	87 ± 26	80 ± 24	75 ± 23	80 ± 23
Age group, years					
≤50	132 (66)	103 ± 31	95 ± 27	88 ± 26	96 ± 29
>50	68 (34)	84 ± 28	77 ± 27	74 ± 26	76 ± 29
Sex					
Women	55 (28)	85 ± 30	79 ± 26	73 ± 23	85 ± 34
Men	145 (73)	101 ± 31	93 ± 28	87 ± 27	91 ± 29
Race					
African Americans	104 (52)	97 ± 34	91 ± 31	86 ± 29	87 ± 32
White or other	96 (48)	96 ± 28	87 ± 25	80 ± 24	92 ± 29
BMI group, kg/m^2					
<22	35 (18)	83 ± 29	82 ± 28	77 ± 28	70 ± 23
22-30	129 (65)	97 ± 31	90 ± 28	84 ± 26	89 ± 27
>30	36 (18)	106 ± 33	92 ± 30	86 ± 28	109 ± 36
Hypertension [b]	60 (31)	96 ± 34	85 ± 27	80 ± 26	86 ± 28
Diabetes Mellitus	16 (8)	85 ± 26	81 ± 29	76 ± 26	80 ± 29
Hepatitis B	22 (11)	85 ± 25	80 ± 23	75 ± 21	81 ± 25
Hepatitis C	51 (26)	87 ± 27	86 ± 29	80 ± 27	84 ± 32
CD4 count group, cells/ul[b]					
<350	47 (25)	95 ± 30	88 ± 29	82 ± 27	87 ± 32
≥350	144 (75)	97 ± 32	90 ± 28	84 ± 27	91 ± 30
Viral load group, copies/m[b]					
Undetected	111 (61)	93 ± 32	86 ± 29	80 ± 27	86 ± 30
<1000	57 (31)	106 ± 30	97 ± 26	90 ± 25	100 ± 30
≥1000	14 (8)	94 ± 32	90 ± 32	86 ± 29	80 ± 28
Tenofovir use/exposure					
Yes	125 (63)	97 ± 31	89 ± 28	83 ± 26	91 ± 31
No	75 (38)	96 ± 33	89 ± 30	83 ± 29	87 ± 29
Source of HIV Transmission					
Injection	24 (12)	93 ± 27	92 ± 25	86 ± 23	88 ± 26
Male-to-male	75 (38)	97 ± 30	92 ± 30	86 ± 29	89 ± 29
Heterosexual	51 (26)	102 ± 32	89 ± 29	83 ± 27	96 ± 35
Other	50 (25)	92 ± 34	84 ± 27	78 ± 25	83 ± 28

Note: Values are mean ± standard deviation or number (percentage).

[a] $p<0.001$ for comparison of each kidney function estimate to measured GFR

[b] 5 patients had missing data for hypertension; 1 patient for diabetes mellitus, 9 patients for CD4 count and 18 patients for viral load

Tenofovir (Viread®)

Table 2

Concordance between assigned Kidney Function Categories using measured GFR versus Estimated GFR equations in Selected Subgroups

	Concordant (%) Kappa (95% CI)		
	CKD-EPI	**MDRD Study**	**Cockcroft-Gault**
Overall[a]	79 0.65 (0.55, 0.74)	71 0.55 (0.45, 0.65)	77 0.61 (0.52, 0.71)
Tenofovir Use/Exposure			
Yes	80 0.63 (0.51, 0.75)	70 0.50 (0.38, 0.62)	78 0.59 (0.47, 0.71)
No	77 0.67 (0.52, 0.82)	72 0.62 (0.46, 0.77)	75 0.64 (0.49, 0.79)
Age group (years)			
≤50	84 0.67 (0.54, 0.80)	75 0.55 (0.42, 0.68)	81 0.62 (0.48, 0.75)
>50	69 0.57 (0.41, 0.74)	63 0.51 (0.34, 0.67)	68 0.56 (0.40, 0.72)
Sex			
Women	80 0.71 (0.56, 0.87)	69 0.57 (0.40, 0.74)	78 0.69 (0.54, 0.85)
Men	79 0.60 (0.47, 0.73)	72 0.52 (0.40, 0.65)	76 0.57 (0.44, 0.69)
Race			
African Americans	84 0.74 (0.63, 0.85)	79 0.67 (0.55, 0.79)	74 0.60 (0.48, 0.73)
White or other	74 0.54 (0.37, 0.70)	63 0.42 (0.27, 0.57)	79 0.63 (0.48, 0.78)
BMI group (kg/m^2)			
<22	66 0.54 (0.32, 0.76)	66 0.54 (0.32, 0.76)	54 0.43 (0.22, 0.64)
22-30	82 0.69 (0.57, 0.81)	74 0.58 (0.46, 0.70)	79 0.64 (0.51, 0.76)
>30	81 0.63 (0.39, 0.86)	67 0.44 (0.20, 0.68)	89 0.71 (0.48, 0.95)
HIV RNA viral load (copies/mL)			
Undetected	76 0.63 (0.50, 0.76)	66 0.53 (0.40, 0.66)	79 0.68 (0.57, 0.80)
<1000	84 0.63 (0.44, 0.81)	79 0.53 (0.34, 0.73)	79 0.53 (0.34, 0.73)
≥1000	79 0.66 (0.30, 1.00)	79 0.66 (0.30, 1.00)	64 0.49 (0.11, 0.86)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; MDRD Study, Modification of Diet in Renal Disease Study; BMI, body mass index

[a] $p<0.003$ for comparison for the difference in concordance of each equation to measured GFR.

Concordance for MDRD Study equation and CKD-EPI equations were statistically different (p=0.0006), while Cockcroft-Gault concordance was not statistically different to MDRD study equation or CKD-EPI ($p > 0.09$ for both)

Tenofovir (Viread®)

Kidney Function categories from Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. Rockville: U.S. Department of Health and Human Services; May 1998 [22]

Table 3

Concordance between assigned Kidney Function Categories using the Cockcroft-Gault Equation versus CKD-EPI and MDRD Study equations in Selected Subgroups

	Concordant (%) Kappa (95% CI)	
	CKD-EPI	**MDRD Study**
Overall[a]	85 0.77 (0.69, 0.85)	79 0.69 (0.60, 0.77)
Tenofovir Use/Exposure		
Yes	87 0.79 (0.70, 0.89)	79 0.68 (0.57, 0.79)
No	81 0.73 (0.59, 0.87)	79 0.70 (0.56, 0.84)
Age group, years		
≤50	91 0.83 (0.73, 0.92)	85 0.74 (0.63, 0.84)
>50	74 0.64 (0.48, 0.79)	68 0.57 (0.40, 0.73)
Sex		
Women	84 0.77 (0.63, 0.91)	76 0.67 (0.52, 0.83)
Men	86 0.76 (0.66, 0.86)	80 0.69 (0.58, 0.79)
Race		
African Americans	82 0.73 (0.63, 0.84)	79 0.69 (0.58, 0.81)
White or other	89 0.81 (0.69, 0.92)	79 0.69 (0.56, 0.81)
BMI group, kg/m^2		
<22	66 0.60 (0.41, 0.79)	77 0.72 (0.54, 0.89)
22-30	92 0.86 (0.78, 0.94)	83 0.74 (0.64, 0.84)
>30	81 0.61 (0.40, 0.82)	67 0.41 (0.21, 0.62)
HIV RNA viral load, copies/mL		
Undetected	81 0.74 (0.63, 0.85)	73 0.64 (0.53, 0.76)
<1000	95 0.88 (0.75, 1.00)	90 0.77 (0.60, 0.95)
≥1000	86 0.77 (0.48, 1.00)	86 0.77 (0.48, 1.00)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; MDRD Study, Modification of Diet in Renal Disease Study; BMI, body mass index

[a]Concordance rates were statistically different, p< 0.001

Tenofovir (Viread®)

Kidney Function categories from Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. Rockville: U.S. Department of Health and Human Services; May 1998 [22]

Table 4

Concordance between Drug Dosing Recommendations using Measured Glomerular Filtration Rate (top) and the Cockcroft-Gault Equation (bottom) Versus Estimated Kidney Function for specific drug examples

Drug (Dosing levels)	CKD-EPI	MDRD Study	Cockcroft-Gault
	Concordant (%) Kappa (95% CI)	Concordant (%) Kappa (95% CI)	Concordant (%) Kappa (95% CI)
Comparison with Measured Glomerular Filtration Rate			
Tenofovir (5); Emtricitabine (4)	95 0.60 (0.36, 0.84)	93 0.52 (0.28, 0.75)	93 0.49 (0.23, 0.75)
Tenofovir/ emtricitabine (3)	95 0.60 (0.36, 0.84)	93 0.52 (0.28, 0.75)	93 0.49 (0.23, 0.75)
Tenofovir/ emtricitabine/ efavirenz; Abacavir/ lamivudine (2)	95 0.53 (0.29, 0.77)	93 0.46 (0.23, 0.70)	93 0.41 (0.16, 0.65)
Comparison with the Cockcroft-Gault Equation			
Tenofovir (5); Emtricitabine (4)[a]	96 0.75 (0.57, 0.93)	94 0.66 (0.47, 0.85)	-
Tenofovir/ emtricitabine (3)[a]	96 0.75 (0.57, 0.93)	94 0.66 (0.47, 0.85)	-
Tenofovir/ emtricitabine/ efavirenz; Abacavir/ lamivudine (2)	96 0.71 (0.52, 0.90)	95 0.64 (0.44, 0.84)	-

Abbreviations: mGFR, measured GFR; CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; MDRD Study, Modification of Diet in Renal Disease Study

Tenofovir (Viread®), tenofovir/ emtricitabine (Truvada®), tenofovir/ emtricitabine/ efavirenz (Atripla™), abacavir/ lamivudine (Epzicom™)

[a] $p<0.05$ for difference in concordance rates among kidney function estimates

Dosing recommendations from Panel on Antiretroviral Guidelines for Adults and Adolescents.

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Department of Health and Human Services. October 14, 2011; 1-166 [3].

Table 5

Assessment of Physician Drug Dosing using unadjusted Estimating Equations

Drug (N Dosing level)	Recommended Dosages (PO)	GFR range (mL/min)	N received this dose	CKD-EPI		MDRD Study		Cockcroft-Gault	
				N in this GFR category	N not dosed correctly	N in this GFR category	N not dosed correctly	N in this GFR category	N not dosed correctly
Nucleoside Reverse Transcriptase Inhibitor (NRTI)									
Tenofovir (5)	300 mg once daily	>49	124	118	6	116	8	115	9
	300mg every 48h	30 to 49	0	7	0	9	0	10	0
	300mg twice weekly	10 to 29	1	0	1	0	1	0	1
	No recommendation	<10/ No HD	0	0	0	0	0	0	0
	300mg every 7d	HD	0	0	0	0	0	0	0
	Total (%)		**125 (100)**		**7 (6)**		**9 (7)**		**10 (8)**
Emtricitabine (4)	200mg daily	>49	103	98	5	96	7	95	8
	200mg every 48h	30 to 49	0	5	0	7	0	8	0
	200mg every 72h	15 to 29	0	0	0	0	0	0	0
	200mg every 96h	<15 or HD	0	0	0	0	0	0	0
	Total (%)		**103 (100)**		**5 (5)**		**7 (7)**		**8 (8)**
Combination Pills									
Tenofovir/ emtricitabine (3)	1 tablet once daily	>49	43	39	4	37	6	35	8
	1 tablet every 48h	30 to 49	0	4	0	6	0	8	0
	Not recommended	<30 or HD	0	0	0	0	0	0	0
	Total (%)		**43 (100)**		**4 (9)**		**6 (14)**		**8 (19)**
Tenofovir/ emtricitabine/ efavirenz (2)	1 tablet once daily	>50	37	36	1	35	2	36	1
	Not recommended	<50	0	1	0	2	0	1	0
	Total (%)		**37 (100)**		**1 (3)**		**2 (5)**		**1 (3)**
Abacavir/ lamivudine (2)	1 tablet once daily	>50	24	21	3	21	3	22	2
	Not recommended	<50	0	3	0	3	0	2	0

Antivir Ther. Author manuscript; available in PMC 2014 August 20.

Drug (N Dosing level)	Recommended Dosages (PO)	GFR range (mL/min)	N received this dose	CKD-EPI		MDRD Study		Cockcroft-Gault	
				N in this GFR category	N not dosed correctly	N in this GFR category	N not dosed correctly	N in this GFR category	N not dosed correctly
	Total (%)		**24 (100)**		**3 (13)**		**3 (13)**		**2 (8)**

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD Study, Modification of Diet in Renal Disease Study; GFR, glomerular filtration rate

Tenofovir (Viread®), Emtricitabine (Emtriva®), tenofovir/ emtricitabine (Truvada®), tenofovir/ emtricitabine/ efavirenz (Atripla™), abacavir/lamivudine (Epzicom™)