

## Performance of creatinine and cystatin C-based glomerular filtration rate estimating equations in a European HIV-positive cohort

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### Abstract

**Objective:** To validate glomerular filtration rate (GFR) estimating equations in Caucasian HIV-infected patients based on serum creatinine and/or serum cystatin C.

**Design:** Single-center, cross-sectional evaluation of the predictive performance of GFR estimators

**Methods:** GFR was measured by iohexol plasma clearance. Serum creatinine (Scr) and serum cystatin C (Scyst) were measured by traceable and standardized methods. We evaluated the performance of the Modification of Diet in Renal Disease (MDRD) and the CKD-Epidemiology Collaboration (CKD-EPI) equations. We also studied the performance of the cystatin C-based equation (CKD-EPI Scyst) and the combined cystatin and creatinine-based equation (CKD-EPI combined), as recently proposed by the CKD-EPI group.

**Results:** Two hundred and three subjects (18% of women) were included. Mean age was  $49 \pm 10$  years. Mean measured GFR (mGFR) was  $95 \pm 24$  mL/min/1.73m<sup>2</sup>. CKD-EPI and CKD-EPI combined significantly outperformed the MDRD equation. The percentage of estimating results within 30% of mGFR was 75%, 82% and 81% for the MDRD, CKD-EPI and CKD-EPI combined equation, respectively. Results favoring the CKD-EPI and CKD-EPI combined equation were especially observed for patients with mGFR over 90 mL/min/1.73 m<sup>2</sup>.

**Conclusion:** In our European HIV cohort, we confirmed that the creatinine-based CKD-EPI equation should replace MDRD study equation. However, global performance of this equation remains worse than the performance observed in the general population. This lesser performance is particularly relevant in patients with measured GFR under and around 60 mL/min/1.73 m<sup>2</sup>. Moreover, the specific interest of Scyst-based equations is not confirmed in this population.

**Keywords :** chronic kidney disease ; creatinine ; cystatin C ; glomerular filtration rate ; HIV

### Introduction

An accurate tool for estimating glomerular filtration rate (GFR) in HIV-infected patients is both necessary and challenging. It is necessary because some of the most active anti-retroviral drugs are either nephrotoxic and/or undergo a renal metabolism that requires dosage adjustment in case of decreasing GFR [1]. Likewise, a reliable evaluation of GFR is critical for the detection of Chronic Kidney Disease (CKD) and its related complications which are becoming particularly prevalent in those patients [2,3]. In the meantime, estimating renal function remains challenging mainly due to the fact that serum creatinine (Scr), as a GFR marker, is likely to be suboptimal in those patients prone to alteration and variation of their muscle mass [4].

Current guidelines of the Infectious Disease Society of America recommend the use of the Modification of Diet in Renal Disease (MDRD) study equation for estimating GFR in HIV-infected patients [5]. This equation is however known to underestimate the true level of renal function in patients with normal, or close to normal GFR values [6,7]. The use of this equation is thus problematic for the detection of CKD and often leads to overdiagnosis [8,9]. The CKD-Epidemiology Collaboration (CKD-EPI) equation has been specifically

developed to correct the GFR underestimation induced by the MDRD study equation [10]. Several, but not all, studies have demonstrated that this equation offers better performance than the MDRD study equation [11-13].

Another step toward the amelioration of GFR evaluation is to turn to a more reliable marker of GFR than Scr. Serum cystatin C (Scyst) has the potential to circumvent many of the shortcomings of Scr and has long been proposed as a promising GFR biomarker [14]. Additionally, new drugs interfering with tubular secretion of Scr (e.g. dolutegravir and cobicistat) are becoming available [15,16]. In this context, GFR estimation based on Scyst might be clinically useful. Thus far, a thorough evaluation of Scyst has however been hampered by the absence of standardization for Scyst measurement. Very recently, a certified reference material has been characterized and developed for Scyst [17], making traceability and standardization of Scyst measurement possible. Two equations specifically developed in order to be used with standardized Scyst, have been validated in a large population: the Scyst-based CKD-EPI equation (CKD-EPI Scyst) - incorporating Scyst alone - and the Scyst/Scr-based CKD-EPI equation (CKD-EPI combined) [18].

In HIV infected patients, a few studies - with contradictory results - have sought to evaluate whether alternative Scyst and/or Scr-based equations might improve GFR estimation in comparison to the MDRD study Equation [19-24]. All these studies had however limitations [4]. Very recently, Inker and colleagues reported that the CKD-EPI equation along with the two new equations based on Scyst were all significantly more accurate than the MDRD study equation in a cohort of 200 HIV positive patients [25]. Importantly, while it is so far the only study that has used calibrated Scr and Scyst, the Inker study has exclusively enrolled North American patients. Given the well-known differences in ethnicity, body composition, conditions of HIV acquisition and prevalence of viral co-infection, their findings do not necessarily extend to non-US populations.

Using standardized measures and similar methodology we thus studied the performance of these new CKD-EPI equations with the aim to recommend the most appropriate equation for practioners taking care of HIV-infected patients in Europe.

## **Subjects and Methods**

### *Study Population*

Patients were recruited from the department of infectious diseases of the university hospital of Saint-Etienne (France). Eligible patients were 18 years old, with confirmed HIV status. Exclusion criteria were pregnancy, history of allergy, thyroid dysfunction, recent acute kidney injury, and treatment by metformin, steroids, trimethoprim, or cimetidine. The protocol was submitted and approved by Saint-Etienne's hospital institutional review board. The study was conducted in full compliance with the amended declaration of Helsinki following approval from the local ethical committee.

### *GFR measurement*

GFR measurements were based on plasma clearance of iohexol (Omnipaque 300 GE Healthcare). After administration of 10 mL of iohexol intravenously, two blood samples were collected at approximately 120 and 240 minutes with exact time recorded. Iohexol plasma concentration was determined by High Performance Liquid Chromatography and Mass Spectrometry [26]. GFR was calculated using previously described protocol [27]. Measured GFR was reported to body surface area (BSA) as estimated by the Dubois & Dubois formula [28].

### *Laboratory Methods*

Blood and urine samples were stored at -80°C. Scr was measured by IDMS-traceable enzymatic method (Orthoclinical diagnostics, United Kingdom, CV 5.6% at 0.71 mg/dL, and 2.1% at 5.82 mg/dL). Scyst was measured by IFCC-traceable (International Federation of Clinical Chemistry) nephelometric method (Siemens, Germany) on a Siemens BN Prospec analyzer (CV of 2.9% at 1.03 mg/L and 2.1% at 1.93 mg/L) [17]. HIV-viral load was determined by Abbott m2000 real-time HIV-1 assay (Abbott diagnostics, France). CD4+ lymphocytes count -was measured by flow cytometry at the time of GFR measurement. Urine microalbumin was determined by immunonephelometry on a Siemens BN ProSpec. Sensitivity of the assay is 0.16 mg/dL with inter-assay CV's of 3.0%.

### Data collection

Clinical variables collected at the time of GFR measurement were: sex, age, height, weight, time since HIV-infection diagnosis, history of injecting drug use, smoking status, history of hypertension, dyslipidemia and/or diabetes mellitus (DM), HAART regimen, hepatitis B virus and hepatitis C virus status, liver cirrhosis. In the study, DM was defined as a diagnosis of DM prior to the study or use of oral anti-diabetic agents or insulin at the time of enrollment. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg or the use of antihypertensive agents. Dyslipidemia was defined as triglycerides greater than 2 g/L or use of fibrates at the time of enrollment, or LDL-cholesterol greater than 1.60 g/L or use of statins at the time of enrollment.

Biological variables collected at the time of GFR measurement were: HIV viral load, CD4 positive lymphocyte count, C-reactive protein (CRP), urinary albumin/creatinine ratio (ACR), serum Scyst and Scr.

Analysis of the performance of GFR estimating equations and statistics GFR was estimated with the MDRD study equation [29], the CKD-EPI equation [10], the CKD-EPI Cys equation and the CKD-EPI combined equation [18] (Table 1). We considered the African-American (AA) coefficient factor as not applicable to black subjects from Africa, Europe or Antilles [30].

Simple linear regression was used to calculate the Pearson's correlation coefficients between measured GFR (inGFR) and estimated GFR (eGFR) by the four equations.

The predictive performance of the four GFR estimates was assessed with the following parameters:

- (1) Absolute bias, defined as the mean difference between eGFR and mGFR, a negative value meaning that eGFR under-estimates true GFR.
- (2) Relative bias, calculated as absolute bias/mGFR x 100
- (3) Precision, evaluated by the standard deviation of the mean difference between eGFR and mGFR (absolute and relative)
- (4) Accuracy, defined as the proportion of eGFR values within +/- 30% of the mGFR.
- (5) Agreement, evaluated by the Bland and Altman method [31].

**Table 1.** GFR estimates (Scr serum creatinine, Scyst serum cystatine C).

Basis of equation and sex	Scr and Scyst values	Equation for estimating GFR
MDRD		$175 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ if female}]$
CKD-EPI		
Female	Scr ≤ 0.7 mg/dL	$144 \times (\text{Scr}/0.7)^{0.329} \times 0.993^{\text{age}}$
	Scr > 0.7 mg/dL	$144 \times (\text{Scr}/0.7)^{-1.209} \times 0.993^{\text{age}}$
Male	Scr ≤ 0.9 mg/dL	$141 \times (\text{Scr}/0.9)^{-0.411} \times 0.993^{\text{age}}$
	Scr > 0.9 mg/dL	$141 \times (\text{Scr}/0.9)^{-1.209} \times 0.993^{\text{age}}$
CKD-EPI Scyst	Scyst ≤ 0.8 mg/L	$133 \times (\text{Scyst}/0.8)^{-0.499} \times 0.996^{\text{age}} [x0.932 \text{ if female}]$
	Scyst > 0.8 mg/L	$133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{age}} [x0.932 \text{ if female}]$
CKD-EPI combined		
Female	Scr ≤ 0.7 mg/dL and Scyst ≤ 0.8 mg/dL	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}}$
	Scr ≤ 0.7 mg/dL and Scyst > 0.8 mg/dL	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}}$
	Scr > 0.7 mg/dL and Scyst ≤ 0.8 mg/dL	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}}$
	Scr > 0.7 mg/dL and Scyst > 0.8 mg/dL	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}}$
Male	Scr ≤ 0.9 mg/dL and Scyst ≤ 0.8 mg/dL	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}}$
	Scr ≤ 0.9 mg/dL and Scyst > 0.8 mg/dL	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}}$
	Scr > 0.9 mg/dL and Scyst ≤ 0.8 mg/dL	$135 \times (\text{Scr}/0.9)^{-0.601} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}}$
	Scr > 0.9 mg/dL and Scyst > 0.8 mg/dL	$135 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}}$

The relative performance of the GFR estimating equations was evaluated by comparing: (i) the precision using F-test and (ii) the accuracy using McNemar paired test or McNemar's exact test in case of sparse data (some cells < 5). The relative performance of the GFR estimating equations was evaluated on the whole population and in subgroups defined by mGFR, by age, BMI, smoking status, HIV-viral load, CD4 positive cells count, and

HAART regimen containing or not tenofovir. Additionally, we evaluated the performance of the equations for classification of patients having an iohexol clearance above or below 60 mL/min/1.73m<sup>2</sup> using the net reclassification index statistic.

Statistical analysis were performed with SPSS version 17.0 (SPSS, Chicago, IL) and R 2.15.1 (R development Core Team, Vienna, Austria), and GraphPad Prism 6 (GraphPad Software, Lajolla, CA).

**Table 2.** Patients characteristics Mean (SD) for continuous variables, n (%) for categorical variables.

Main characteristics of the population	
Age (year)	49 ±10 [22-84]
Female	37 (18%)
Time since HIV infection diagnosis (years)	11 ±7
Weight (kg)	71 ±13 [42-108]
Height (cm)	172 ± 8 [155-195]
African origin	15 (7)
Body mass index (kg/m <sup>2</sup> )	24 ± 4 [17-37]
<18	11 (5)
<25	132 (65)
25<BMI<30	50 (25)
30>BMI	21(10)
Diabetes	13 (6)
Hypertension	36 (18)
Smoker	77 (38)
Drug abuser	11 (5)
HAART	189 (93)
Tenofovir usage	111 (55)
HIV Viral Load	
Undetected	169 (83)
<1000 copies/mL	15 (7)
>1000 copies/mL	18 (9)
CD4 (cells/μL)	593 ± 262
Hepatitis B	10 (5)
Hepatitis C	19 (9)
ACR(mg/g) (n = 202)	
<30	163 (81)
30-300	34 (17)
300-1000	3 (1)
>1000	2 (1)
Creatinine (mg/dL)	0.87 ± 0.19
Cystatin C (mg/L)	0.9 ± 0.26
Iohexol GFR (mL/min/1.73m <sup>2</sup> )	95 ± 24 [18-189]
Chronic Kidney Disease (CKD) stage	
1. GFR≥90 mL/min/1.73m <sup>2</sup>	118 (58)
2. GFR 60-89 mL/min/1.73m <sup>2</sup>	67 (33)
3. GFR 30-59 mL /min/1.73m <sup>2</sup>	16 (8)
4. GFR 15-29 mL/min/1.73m <sup>2</sup>	2 (1)
Hyperfiltrating status (GFR>120 mL/min/1.73 m <sup>2</sup> )	25 (12)

Values expressed as mean ±SD [range] or number (percent). ACR, urinary Albumine/Creatinine Ratio; GFR, Glomerular Filtration Rate; HAART, Highly active anti-retroviral therapies.

## Results

Two hundred and five HIV-infected patients were enrolled between February 2011 and June 2012. Two of them were excluded from the analysis because one was a kidney transplant recipient and because the iohexol protocol was corrupted in the second one. Characteristics are summarized in Table 2. Mean age was 49 ± 10 years, 18 % of patients were female. Mean body mass index was 24 ± 4 kg/m and 93 % of the patients were Caucasian. Most patients were receiving HAART and had undetected HIV viral load at the time of GFR measurement (93 % and

83 %, respectively). HAART regimen contained tenofovir in 55 % of the patients. History of diabetes mellitus and hypertension was present in 6 and 18 % of the patients, respectively. Evidence for proteinuria (defined as ACR>30 mg/g) was found in 39 patients (19%). Mean measured GFR was  $95 \pm 24$  mL/min/1.73m<sup>2</sup>. Fifty eight percent (n = 118) of the patients had mGFR greater than 90 mL/min/1.73m<sup>2</sup> and only 9% (n = 18) had niGFR less than 60 mL/min/1.73m<sup>2</sup>.

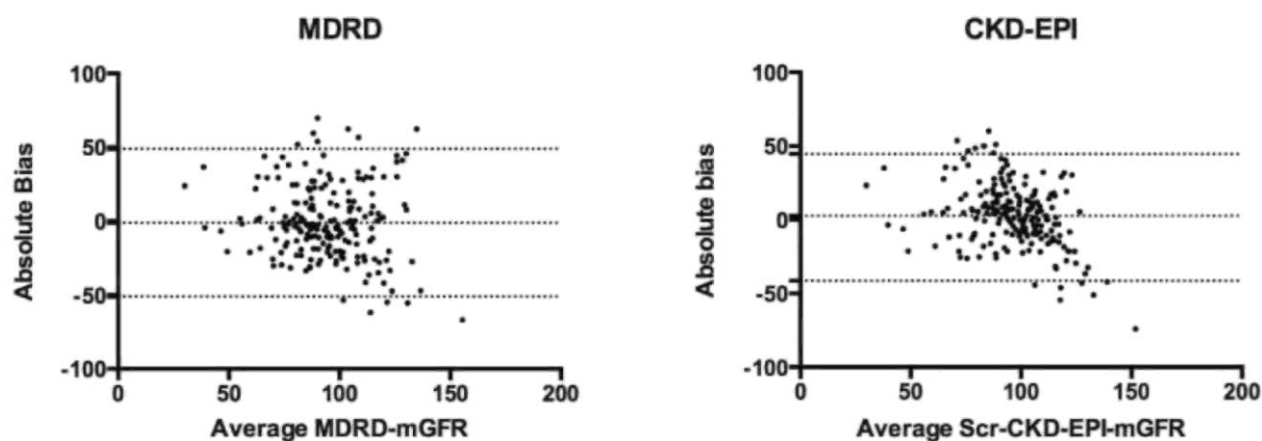
Considering the whole study population (Table 3 and Fig. 1), the CKD-EPI equation provided the best accuracy of prediction (82%), the MDRD study equation the worst (75%). The combined equation exhibited comparable performance (Accuracy of 81%) as compared to the CKD-EPI equation. Importantly, both the CKD-EPI and CKD-EPI combined equations demonstrated a significantly better accuracy than the MDRD study equation (p = 0.002, p = 0.016 respectively Mac Nemar Test). By comparison, the equation based solely on Scyst did not significantly improve the accuracy of prediction (80% vs 75% for the CKD-EPI Scyst equation and the MDRD study equation, respectively, p = 0.12, Mac Nemar Test).

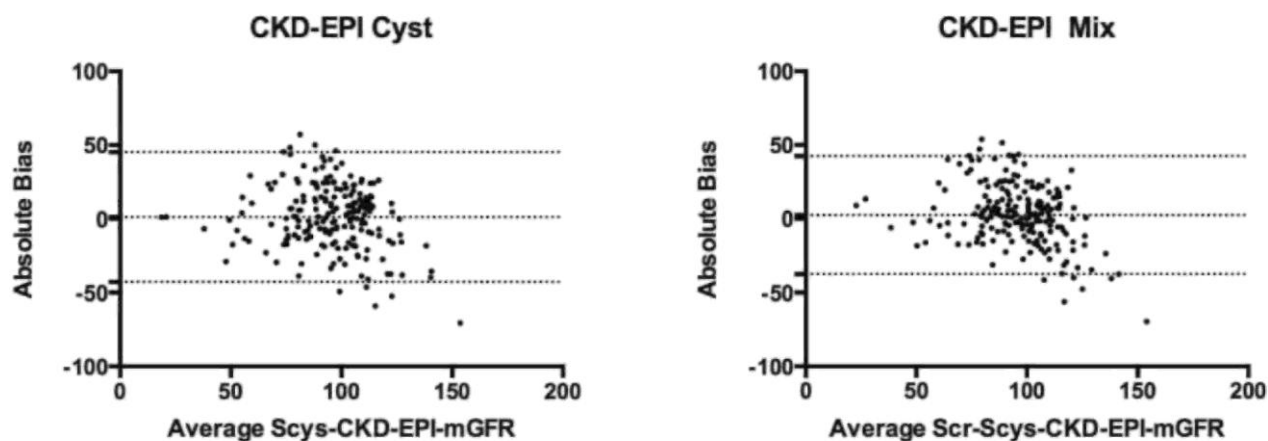
**Table 3.** Predictive performances of the MDRD study, CKD-EPI, CKD-EPI-Scyst, and CKD-EPI-combined equations in HIV patients (n = 203).

GFR estimates	R	Bias		Absolute Precision mL/min/1.73m <sup>2</sup> (relative in %)	Accuracy 30%
		Absolute (mL/min/1.73m <sup>2</sup> )	Relative (%)		
MDRD	0.41	-1.1	+4.2	25 (33%)	75
CKD-EPI	0.51	+2.6	+8.3	22 (31%)	82*
CKD-EPI Scyst	0.54	+1.2	+5	22 (26%)	80
CKD-EPI combined	0.58	+2.5	+6.9	20 (26%)	81*

\*p<0.05 versus MDRD study equation, R: correlation coefficient.

**Fig. 1.** Bland and Altman plots of the MDRD study, CKD-EPI, CKD-EPI Scyst, CKD-EPI combined (n = 203).





**Table 4.** Predictive performances of the MDRD study, CKD-EPI, CKD-EPI Scyst, and CKD-EPI combined equations in HIV patients according to different GFR levels.

GFR estimates	Bias		Absolute Precision mL/min/1.73m <sup>2</sup> (relative in %)	Accuracy 30%
	Absolute (mL/min/1.73m <sup>2</sup> )	Relative (%)		
<i>mGFR &lt; 60 mL/min/1.73 m<sup>2</sup> (n = 18)</i>				
MDRD	+27	+61	25 (58%)	22
CKD-EPI	+29	+66	24 (55%)	22
CKD-EPI Scyst	+18	+34	22 (41%)	44
CKD-EPI combined	+23	+47	21 (40%)	22
<i>mGFR &gt; 60 mL/min/1.73 m<sup>2</sup> (n = 185)</i>				
MDRD	-4	-1	23 (24%)	80
CKD-EPI	0	+3	20 (20%)	88*
CKD-EPI Scyst	0	+2	21 (22%)	83
CKD-EPI combined	+1	+3	20 (20%)	87*
<i>mGFR: 60-90 mL/min/1.73 m<sup>2</sup> (n = 67)</i>				
MDRD	+7	+10	20 (26%)	75
CKD-EPI	+12	+16	16 (22%)	76
CKD-EPI Scyst	+11	+14	19 (26%)	67
CKD-EPI combined	+11	+15	17 (23%)	73
<i>mGFR: 90-120 mL/min/1.73 m<sup>2</sup> (n = 93)</i>				
MDRD	-4	-3	19 (19%)	87
CKD-EPI	-1	0	13 (13%)	99*
CKD-EPI Scyst	-1	0	15 (15%)	98*
CKD-EPI combined	0	+1	13 (12%)	98*
<i>mGFR &gt; 90 mL/min/1.73 m<sup>2</sup> (n=118)</i>				
MDRD	-10	-8	23 (19%)	83
CKD-EPI	-7	-5	18 (15%)	95*
CKD-EPI Scyst	-7	-5	20 (16%)	92*
CKD-EPI combined	-6	-4	18 (14%)	95*
<i>mGFR &gt; 120 mL/min/1.73 m<sup>2</sup> (n = 25)</i>				
MDRD	-33	-24	20 (13%)	68
CKD-EPI	-29	-20	18 (11 %)	80
CKD-EPI Scyst	-29	-21	19 (12%)	72
CKD-EPI combined	-28	-20	17 (10%)	84

\*p < 0.05 versus MDRD study equation (Mc Nemar Test).

Performances of the equation (bias, precision and accuracy) strongly varied according to the GFR levels (Table 4). While these performances were clearly insufficient in patients with mGFR under 60 mL/min/1.73 m<sup>2</sup>, they were globally better above this cut-off. This was especially true for patients with mGFR between 90 and 120 mL/min/1.73 m<sup>2</sup> (accuracy between 87 and 99%). In this GFR range, the accuracy of the MDRD equation remained significantly inferior as compared to the 3 other equations (Table 4). None Scyst-based equations permitted to significantly improve the reclassification of patients around the threshold of 60 mL/min/1.73m<sup>2</sup> (Table 5).

Figure 2 shows the accuracy of the CKD-EPI equation and the 2 equations based on Scyst in different clinical subgroups. No advantage for the Scyst-based prediction was apparent.

## Discussion

Estimating GFR in HIV patients is now recommended [5] as these patients seem at higher risk for CKD [1,2,4].

In our cohort of European patients, we studied the performance of the most recent Scr- and Scyst-based equations [10,18,29]. Considering the whole population, we demonstrate that the CKD-EPI equation has a better accuracy than the MDRD study equation.

Regarding the new Scyst-based equations, we show that none of them provide a more accurate estimation than the CKD-EPI equation. We thus confirm, for the first time in European patients, that the CKD-EPI equation should be the equation of first choice in the HIV-infected population. [10,25]. This result is not unexpected as the vast majority of our patients had normal or high mGFR [10,13,18]. As compared to data recently published in the general population, the performance of both the CKD-EPI Scyst and the CKD-EPI combined equation is somewhat disappointing. However our findings are consistent with other data obtained from another HIV cohort [25]. Several hypotheses can be drawn to explain the lack of advantage for Scyst in those patients. Many factors have indeed been proposed to influence Scyst levels independently of any GFR change, as inflammation and tobacco for instance [14,32-34]. More specifically, it has been suggested that HIV viral load could also influence Scyst levels [35,36]. In our cohort, accuracies are similar for the three equations in the group of smokers in comparison with the non-smokers. However, we observe a trend for a better accuracy of the CKD-EPI as compared to the CKD-EPI Scyst in patients with detectable HIV-viral load.

Performances of the four equations were particularly poor in patients with GFR under 60 mL/min/1.73m<sup>2</sup>. This observation is at odds with what is usually reported in the general population where the predictive performance of equations usually improves with decreasing GFR [29]. Here again, the same observation was previously made in HIV-infected patients [25]. Our observation was consistent with this previous study and further suggests the difficulty in accurately evaluating renal function in HIV-infected patients, a population with specific characteristics that make it different from the general population in many regards. These patients with lower mGFR are probably the patients who are frailer, notably in term of muscular mass (they were, in our cohort, older than patients with niGFR > 60 mL/min/1.73m<sup>2</sup>, data not shown).

In the context of CKD screening, it is particularly important to assess the performance of the equation "around" 60 mL/min/1.73 m<sup>2</sup> which is considered as the "threshold" value for CKD diagnosis by several, but not all, authors [37,38]. In this view, the rather good results observed when considering the whole population must here again be tempered. In the subgroup of mGFR between 60 and 90 mL/min/1.73 m<sup>2</sup>, a subgroup which is both clinically and quantitatively important, all the equations - even the CKD-EPI equation - exhibit suboptimal performance with accuracy below 80%.

To the best of our knowledge, only the study recently published by Inker and colleagues has used calibrated Scyst and Scr. In this study, the authors studied the performances of the MDRD, CKD-EPI, CKD-EPI Scyst and CKD-EPI combined equations in 200 HIV patients from USA [25]. Interestingly, they measured, like us, GFR with iohexol plasma clearance. While cohorts' characteristics are quite different between Inker's study and ours (52% of African-American in the Inker's study; mean BMI 27 kg/m in Inker's vs 24 kg/m ; more Intravenous drug user in the American Cohort, higher proportion of patients with undetected viral load in ours), our findings are mostly in agreement and provide a confirmation in a European cohort of the superiority of the CKD-EPI equation in HIV-infected patients.

**Table 5.** Net reclassification improvements (NRI) of CKD-EPI Scyst and combined equations compared to CKD-EPI equation at 60 mL/min/1.73m<sup>2</sup>.

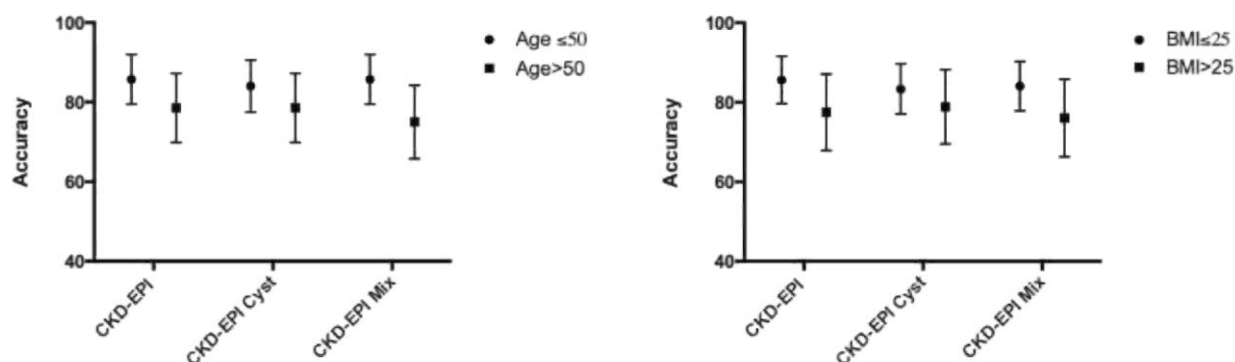
	Total reclassified*	N	mGFR<60 ml/min/1.73m <sup>2</sup>			mGFR <sup>3</sup> 60 ml/min/1.73m <sup>2</sup>			Overall NRI [CI95%]	
			Correctly reclassified CKD-EPI cys<60 vs CKD-EPI <sup>3</sup> 60 <sup>§</sup>	Incorrectly reclassified CKP-EPI cys>60 vs CKD-EPI<60 <sup>§</sup>	Net difference	N	Coirectly reclassified CKD-EPI cys <sup>3</sup> 60 vs CKD-EPI<60 <sup>§</sup>	Incorrectly reclassified CKD-EPI cys<60 vs CKDEPI <sup>3</sup> 60 <sup>§</sup>		Net difference
CKD-EPI cys vs CKD-EPI	10 (4.9%)	11	2 (11.1%)	1 (5.6%)	5.5%	185	2(1.1%)	5 (2.7%)	-1.6%	3.9% [-15%;23%]
CKD-EPI combined vs CKD-EPI	5 (2.5%)	18	1 (5.6%)	1 (5.6%)	0%	185	1 (0.5%)	2 (1-1%)	-0.6%	-0.6% [-16%;15%]

\*number of cases (percentage over all population). §: number of cases (percentage over subgroup population). mGFR: measured GFR.

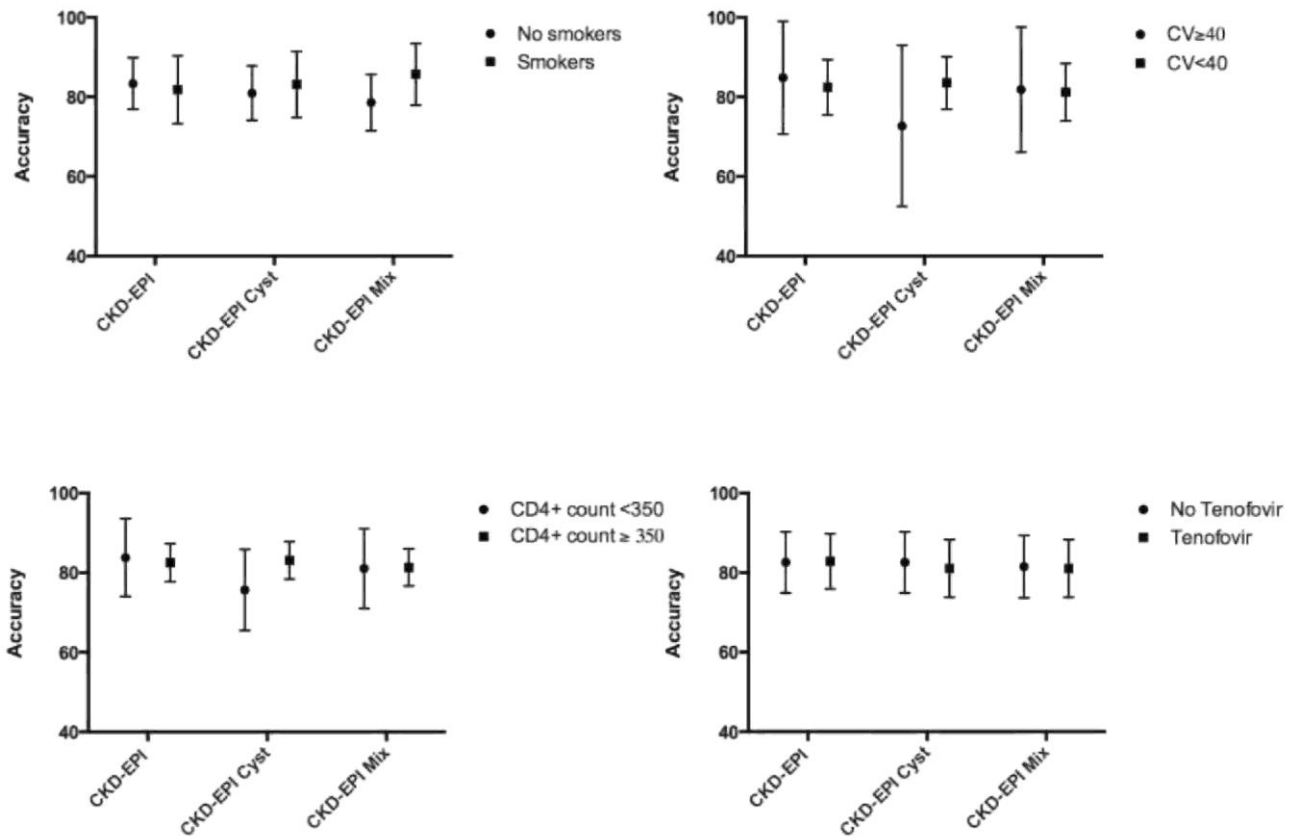
Some limitations of our study must be considered. The study population includes only few patients with mGFR under 60 mL/min/1.73m<sup>2</sup>. Results observed in the subgroup of low GFR must thus be considered with caution. Our patients are almost exclusively Caucasians. Only 15 patients were identified as blacks (of note, no ethnic coefficient was specifically used for those patients). For patients with marked renal impairment (less than 10% of our study population), an additional and later measurement of iohexol is usually recommended but was not performed in our study. Finally, since very few patients were not receiving HAART and had a detectable HIV viral load, our results cannot be extrapolated to all HIV-infected patients.

In conclusion, we demonstrate that the CKD-EPI equation outperforms the MDRD study equation in European HIV-infected patients. Recent equations including standardized Scyst values do not provide any advantage in this population. The current guidelines regarding the preferential utilization of the CKD-EPI equation in the general population are thus also valid for estimating renal function of HIV-infected patients in the US as well as in Europe. Clinicians must however keep in mind that the estimation of renal function provided by the CKD-EPI equation remains probably suboptimal for HIV-positive patients with decreased GFR.

**Fig. 2.** Accuracies in different sub-groups of patients The number of patients for each subgroups was 119 and 84 for age ≤ 50 years and >50 respectively, 132 and 71 for BMI ≤ 25 and >25 kg/m<sup>2</sup> respectively, 77 in the groups of smokers vs 126 no smokers, 33 patients with a HIV viral load detectable, 37 with a CD4 positive count under 350/mm<sup>3</sup>, 111 were receiving tenofovir.







## Acknowledgements

## Conflicts of interest

The authors declare they have no conflict of interest.

Financial support: University Hospital of Saint-Etienne, France

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