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FULL PAPER

Glomerular filtration rate estimated by cystatin C formulas in HIV-1 patients treated with dolutegravir, rilpivirine or cobicistat

Nadia Galizzi[1,2], Laura Galli[1], Andrea Poli[1], Vincenzo Spagnuolo[1,2], Antonella Castagna[1,2], Nicola Gianotti[1]

[1]*Infectious Diseases, IRCCS Istituto Scientifico San Raffaele, Milano, Italy;*
[2]*Università Vita-Salute San Raffaele, Milano, Italy*

SUMMARY

As dolutegravir (DTG), rilpivirine (RPV) and cobicistat affect creatinine, but not cystatin C, tubular transport or serum concentration, the aim of the study was to compare estimated glomerular filtration rates (eGFRs) calculated by means of a standard creatinine formula with those calculated by means of the cystatin C formula in patients receiving these drugs.

This was a cross-sectional study of HIV-1 infected patients with eGFR <90 ml/min/1.73 m^2 (CKD-EPI-creatinine formula) on-treatment with regimens including DTG, RVP or cobicistat; cystatin C was measured after the switch to these regimens. eGFR was calculated by means of the CKD-EPI formulas (CKD-EPI-creatinine: $eGFR^{crea}$; CKD-EPI-cystatin C: $eGFR^{cyst}$). $eGFR^{cyst}$ was compared with the last eGFR assessed before ($eGFR^{crea}_{pre}$) and after the switch ($eGFR^{crea}_{post}$). The primary end-point of the study was the difference between $eGFR^{cyst}$ and $eGFR^{crea}_{post}$. One hundred and twenty patients were included. $eGFR^{crea}_{pre}$ was 80 (70-92) ml/min/1.73 m^2. $eGFR^{crea}_{post}$ was significantly lower than $eGFR^{cyst}$ (65 [59-75] vs. 80 [69-95] mL/min/1.73m^2; p<0.001); $eGFR^{cyst}$ did not differ from $eGFR^{crea}_{pre}$ (p=0.544). The difference between $eGFR^{cyst}$ and $eGFR^{crea}_{post}$ was not significantly different among regimen groups (p=0.056).

In HIV-patients with reduced eGFR treated with DTG, RPV or cobicistat, measuring eGFR by means of the CKD-EPI cystatin C formula is probably more relevant.

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INTRODUCTION

Dolutegravir, rilpivirine and cobicistat are antiretroviral drugs recommended by Italian, European and international guidelines for treating HIV-infected patients in all disease stages (Antinori *et al.,* 2017; European AIDS Clinical Society, 2017; Günthard *et al.,* 2016). Serum creatinine usually increases during treatment with these drugs because its transport at the tubular level is reduced (Cohen *et al.,* 2011; German *et al.,* 2012; Koteff *et al.,* 2013; Lepist *et al.,* 2014; Molina *et al.,* 2011). In particular, rilpivirine and dolutegravir inhibit the organic cation transporter 2 (OCT2) at the basolateral membrane of the proximal tubular cell, which implicates a reduced reabsorption of creatinine from blood to the proximal tubule (Cohen *et al.,* 2011; Koteff *et al.,* 2013; Molina *et al.,* 2011). Cobicistat predominantly inhibits the multidrug and toxin extrusion (MATE1) renal transporter, which is present at the luminal membrane of the proximal tubular membrane and is responsible for the efflux of creatinine through the tubular cells (German *et al.,* 2012; Lepist *et al.,* 2014). Whichever the mechanism, the final effect is an apparent worsening of the glomerular filtration rate (GFR) when estimated by means of creatinine formulas. The worsening is considered only apparent because when GFR is measured by iohexol it does not vary significantly during treatment with these drugs (German *et al.,* 2012; Koteff *et al.,* 2013).

The use of a cystatin C-based formula (Chronic Kidney Disease - Epidemiology collaboration = CKD-EPI-cystatin C) for estimating GFR in HIV-infected patients is debated because cystatin C concentrations in blood increase during inflammatory diseases (e.g. HIV infection) or other conditions, such as tabagism (Gagneux-Brunon *et al.,* 2013; Knight *et al.,* 2004; Ohkuma *et al.,* 2016; Yamada *et al.,* 2014). Indeed, in HIV-infected subjects with viral replication, estimating GFR through a cystatin C formula may overestimate renal impairment (Inker *et al.,* 2012; Jaroszewicz *et al.,* 2006; Mauss *et al.,* 2008). Furthermore, other studies were unable to show a better accuracy in estimating GFR using a cystatin C, compared to a creatinine-based formula, in HIV-infected persons (Jones *et al.,* 2008; Odden *et al.,* 2007).

However, all of these studies were performed in patients not receiving drugs that modify the tubular transport of creatinine. Cystatin C blood concentrations are not influenced by drugs modifying the tubular transport of creatinine (Cohen *et al.,* 2011; Grubb *et al.,* 1985; Molina *et al.,* 2011; Yoshino *et al.,* 2017): estimating GFR by means of a cystatin C formula might provide more realistic values in patients treated with dolutegravir, rilpivirine or cobici-

Key words:
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Corresponding author:
Nadia Galizzi
E-mail: galizzi.nadia@hsr.it

stat (Cohen *et al.,* 2011; Palich *et al.,* 2018; Yoshino *et al.,* 2017).

Aim of the present study was to compare estimated GFRs (eGFRs) calculated by means of a standard formula based on creatinine with those calculated by means of a cystatin C formula in patients treated with dolutegravir, rilpivirine or cobicistat.

METHODS

We performed a cross-sectional study on HIV-1 infected patients older than 18 years old on-treatment with regimens including dolutegravir, rilpivirine or cobicistat (with either elvitegravir, emtricitabine and tenofovir disoproxil fumarate [E/C/F/TDF] or with a protease inhibitor [PI/c]) and with eGFR calculated with the CKD-EPI standard formula for creatinine <90 mL/min/1.73 m^2 at the last visit before enrollment. Cystatin C was measured after the switch to these regimens. eGFR was calculated by means of the CKD-EPI formulas (CKD-EPI-creatinine: $eGFR^{crea}$; CKD-EPI-cystatin C: $eGFR^{cyst}$; CKD-EPI-creatinine-cystatin C [combined]: $eGFR^{crea\text{-}cyst}$) (Gagneux-Brunon *et al.,* 2013; Inker *et al.,* 2012). $eGFR^{cyst}$ and $eGFR^{crea\text{-}cyst}$ were compared with the last eGFR assessed before switching to dolutegravir, rilpivirine or cobicistat ($eGFR^{crea}_{pre}$) and with the creatinine-based eGFR measured after the switch ($eGFR^{crea}_{post}$), the same day on which cystatin C was also measured. The study protocol was approved by the Ethics Committee of San Raffaele Hospital and all the patients provided written informed consent.

The primary end-point of the study was the difference between $eGFR^{cyst}$ and $eGFR^{crea}_{post}$; secondary end-points were the differences in $eGFR^{cyst}$ - $eGFR^{crea}_{pre}$, $eGFR^{crea\text{-}cyst}$ - $eGFR^{crea}_{post}$, $eGFR^{crea\text{-}cyst}$ - $eGFR^{crea}_{pre}$.

Results were described as median and quartiles (Q1, Q3) or frequency (%). Comparisons between paired eGFR values determined by different CKD-EPI formulas (i.e. $eGFR^{crea}_{pre}$, $eGFR^{crea}_{post}$, $eGFR^{cyst}$, $eGFR^{crea\text{-}cyst}$) were made using the Wilcoxon signed rank test. The Kruskal-Wallis test was applied to compare eGFR values among antiretroviral treatment groups. Paired eGFR values were also described according to $eGFR^{crea}_{post}$ < or ≥60 mL/min/1.73 m^2 as this threshold is considered for the diagnosis of CKD (Inker et al. 2014).

The Bland-Altman plot was used to inspect the degree of agreement between the 2 measures of eGFR ($eGFR^{crea}_{post}$ and $eGFR^{cyst}$). In the Bland-Altman analysis, the mean values of the two eGFRs (x-axis) were plotted against the difference between the two methods (y-axis) (Bland JM and Altman DG. 1986). The 95% confidence interval of the mean difference is also shown in the plot and illustrates the magnitude of the systematic difference.

RESULTS

One hundred and twenty consecutive patients were included in this analysis: 86% were male, with a median age of 51.9 (46.3, 57.6) years, on antiretroviral therapy (ART) for 9.9 (5.0, 18.5) years. Twenty-nine percent of them were receiving dolutegravir, 23% rilpivirine, 18% E/C/F/TDF, 20% to PI/c, or a combination of two of these (10%). In 52 patients, the backbone regimen included TDF; 96% of patients had HIV RNA <50 copies/ml and a median CD4+ of 745 (526, 872) cells/μL. More details are provided in *Table 1*.

Table 1 - *Baseline characteristics of the 120 study patients at the time of cystatin C determination.*

	Median (IQR) or N (%)
Age	51.9 (46.3 - 57.6)
Gender, M	103 (85.8%)
Race, White	117 (97.5%)
Body Mass Index (BMI)	24.6 (22.2 - 27.2)
≥25	51 (44%)
≥30	19 (15%)
Smoking	
Yes/Former Smoker	52 (43%)
No	62 (52%)
Missing	6 (5%)
HIV Risk Factor	
MSM	64 (53%)
Heterosexual	25 (21%)
IDU	7 (6%)
Unknown/Other	24 (20%)
Years Of ART	9.91 (4.95 - 18.5)
CDC Stage C	25 (20.8%)
Nadir CD4+	232.5 (136 - 342.5)
ART naive	11 (9.2%)
Pre-switch Type of Regimen	
NRTI-Based	5 (4.2%)
NNRTI- Based	23 (19.2%)
PI- Based	55 (45.8%)
INSTI- Based	14 (11.7%)
Other Regimens	12 (10.0%)
Anti-HCV Antibodies	
Positive	17 (14.2%)
Missing	4 (3.3%)
HBsAg	
Positive	8 (6.7%)
Missing	16 (13.3%)
Diabetes	10 (8.3%)
Hypertension	23 (19.2%)
Ongoing Diuretic Therapy	8 (6.7%)
Type of Regimen	
E/C/F/TDF	22 (18.3%)
DTG- Based	35 (29.2%)
PI/c- Based	24 (20%)
RPV- Based	27 (22.5%)
Combination	12 (10%)
TDF	52 (43%)
HIV-RNA	
Undetectable	91 (76.5%)
Detectable below 50 copies/mL	23 (19.3%)
≥50 copies/mL	5 (4.2%)
Years with HIV-RNA <50 copies/mL	4.5 (1.27 - 7.97)
CD4+ (cells/μL)	745 (526 - 872)
CD8+ (cells/μL)	881.5 (651.5 - 1265.5)
CD4+/CD8+	0.82 (0.5 - 1.2)

MSM = man who have sex with men; IDU = Intravenous drug user; ART = antiretroviral therapy; NRTI = Nucleoside reverse transcriptase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor: PI = Protease inhibitor; INSTI = Integrase strand transfer inhibitor; HBsAg = Hepatitis B surface antigen; TDF = Tenofovir disoproxil fumarate; E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; DTG = Dolutegravir; PI/c = Protease inhibitor boosted with cobicistat; RPV = Rilpivirine; combination = Regimen which included the association of dolutegravir or rilpivirine or cobicistat.

Table 2 - *eGFRs according to different formulas, before and after the switch to antiretroviral drugs modifying the tubular transport of creatinine.*

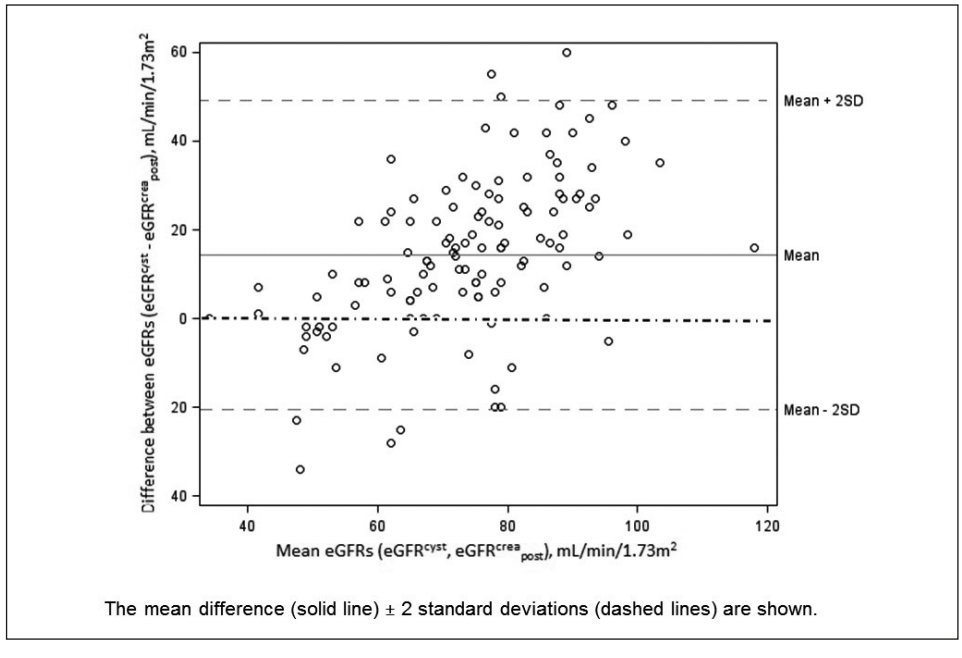
	Median (IQR) or N (%)	*P-value§*
$eGFR^{crea}_{pre}$	80 (70 - 92)	
$eGFR^{crea}_{post}$ ≤60 (n=36)	68 (57-79)	
$eGFR^{crea}_{post}$ >60 (n=84)	86 (74-95)	
$eGFR^{crea}_{post}$	65 (59-75)	
$eGFR^{cyst}$	80 (69-95)	
$eGFR^{crea}_{post}$ ≤60	66 (50-82)	
$eGFR^{crea}_{post}$ >60	87 (76-99)	
$eGFR^{crea\text{-}cyst}$	79 (72-86)	
$eGFR^{crea}_{post}$ ≤60	65 (61-73)	
$eGFR^{crea}_{post}$ >60	83 (77-89)	
Difference $eGFR^{cyst}$ - $eGFR^{crea}_{post}$	15 (4.5-26)	<0.0001
$eGFR^{crea}_{post}$ ≤60	10 (-1/+28)	<0.0001
$eGFR^{crea}_{post}$ >60	16 (6-25)	<0.0001
Difference $eGFR^{crea\text{-}cyst}$ - $eGFR^{crea}_{post}$	12.0 (9.0-16.0)	<0.0001
$eGFR^{crea}_{post}$ ≤60	12 (9-17)	<0.0001
$eGFR^{crea}_{post}$ >60	12 (9-15)	<0.0001
Difference $eGFR^{crea\text{-}cyst}$ - $eGFR^{cyst}$	-2.82 (-11.03/+6.1)	0.034
Difference $eGFR^{cyst}$ - $eGFR^{crea}_{pre}$	0 (-13/+14)	0.544
Difference $eGFR^{crea\text{-}cyst}$ - $eGFR^{crea}_{pre}$	-0.4 (-12.18/+7.75)	0.275

$eGFR^{crea}_{pre}$ = GFR estimated with the CKD-EPI-creatinine formula calculated using the last serum creatinine value available before the switch to a dolutegravir-, rilpivirine- or cobicistat-based regimen; $eGFR^{crea}_{post}$ = GFR estimated with the CKD-EPI-creatinine formula after the switch to a dolutegravir-, rilpivirine- or cobicistat-based regimen; $eGFR^{cyst}$ = GFR estimated with CKD-EPI-cystatin C formula after the switch to a dolutegravir-, rilpivirine- or cobicistat-based regimen; $eGFR^{crea\text{-}cyst}$ = GFR estimated with the combined (creatinine and cystatin C) CKD-EPI formula after the switch to a dolutegravir-, rilpivirine- or cobicistat-based regimen.
Results are expressed as mL/min/1.73 m².
§Comparisons within groups by Wilcoxon signed rank test.

The median $eGFR^{crea}_{pre}$ was 80 (70, 92) mL/min/1.73 m²; cystatin C determinations were performed 8.4 months (IQR: 4.2-19.2) after the switch. The $eGFR^{crea}_{post}$ was 65 (59, 75) mL/min/1.73 m², while the $eGFR^{cyst}$ was 80 (69, 95) mL/min/1.73m² (median difference: 15 [4.5, 26] mL/min/1.73 m²; p<0.0001); $eGFR^{cyst}$ was not significantly different form $eGFR^{crea}_{pre}$ (median difference: 0 [-13, 14] mL/min/1.73 m²; p=0.544) (*Table 2* and *Figure1*).

$eGFR^{cyst}$ - $eGFR^{crea}_{post}$ differences were 17 (8, 27) mL/min/1.73 m² (p<0.0001) for rilpivirine-based, 17 (9, 28) mL/min/1.73 m² (p<0.0001) for dolutegravir-based, 16.5 (0.3, 22) mL/min/1.73 m² (p=0.009) for E/C/F/TDF-based, and 7 (1, 13) mL/min/1.73 m² (p=0.006) for PI/c-based regimens. The difference between $eGFR^{cyst}$ and $eGFR^{crea}_{post}$ was not significantly different among regimen groups (p=0.056); more details are provided in *Table 3*.

Figure 1 - *Values of eGFR calculated by CKD-EPI formulas.*



The Bland-Altman plot (*Figure 2*) showed that the distribution of the differences between the two eGFR measures ($eGFR^{cyst}$ - $eGFR^{crea}_{post}$) was found to be largely mono-directional with positive values for the differences. The mean difference was not zero and on average the eGFR formula method ($eGFR^{cyst}$) measured 14.2 mL/min/1.73 m² more than the $eGFR^{crea}_{post}$. The bias (mean difference $eGFR^{cyst}$ - $eGFR^{crea}_{post}$) of 14.2 mL/min/1.73 m² was not constant for all the eGFR values, tended to increase in parallel with the mean values of eGFR and the differences were more evident in patients with mean eGFR >60 mL/min/1.73 m². The median difference $eGFR^{crea\text{-}cyst}$ - $eGFR^{crea}_{post}$ was 12 (9, 16) mL/min/1.73 m² (p<0.0001) and the median difference $eGFR^{crea\text{-}cyst}$ - $eGFR^{crea}_{pre}$ was -0.4 (-12.2, 7.8) mL/min/1.73 m² (p=0.275).

Smokers had lower values of $eGFR^{cyst}$ than non-smokers [79 (60, 88) mL/min/1.73 m² vs 86 (72, 102) mL/min/1.73 m², p=0.009]; smokers and non-smokers showed similar values of $eGFR^{crea\text{-}cyst}$ [smokers: 79 (65, 83) mL/min/1.73m²; non-smokers: 80 (72, 90) mL/min/1.73 m², p=0.086].

DISCUSSION

Our data are consistent with those from other studies (Cohen *et al.,* 2011; Odden *et al.,* 2007) and with the hypothesis that the worsening of renal function during regimens based on dolutegravir, rilpivirine or cobicistat is only apparent. In fact, the finding that $eGFR^{cyst}$ was not significantly different from $eGFR^{crea}_{pre}$ seems to support the hypothesis that there was no significant change in actual GFR after the switch to these drugs modifying the tubular transport of creatinine. Thus, the CKD-EPI-cystatin C for-

Table 3 - *Differences in eGFR calculated by means of different formulas according to the type of the ongoing regimen.*

Variable	*RPV-based (n=27)*	*E/C/F/TDF (n=22)*	*DTG-based (N=35)*	*PI/c-based (n=24)*	*Combination (n=12)*	*P-value§*
$eGFR^{crea}_{pre}$	90 (78-102)	87 (81-96)	78 (68-92)	72 (62-78)	66 (55-78)	<0.0001
$eGFR^{crea}_{post}$	71 (62-76)	71 (65-78)	65 (59-75)	65 (55-73)	57 (45-61)	0.001
$eGFR^{cyst}$	87 (79-101)	82 (70-95)	84 (72-105)	75 (60-87)	73 (50-82)	0.021
$eGFR^{crea\text{-}cyst}$	82 (74-90)	85 (77-88)	80 (71-88)	76 (67-81)	67 (61-76)	0.005
Difference $eGFR^{cyst}$ - $eGFR^{crea}_{post}$	17 (8-27) P<0.0001§§	16.5 (0.3-22.0) P=0.009§§	17 (9-28) P<0.0001§§	7 (1/+13) P=0.006§§	14 (0.5-31) P=0.010§§	0.056
Difference $eGFR^{cyst}$ - $eGFR^{crea}_{pre}$	0 (-18/+10) P=0.495§§	0 (-16/+9) P=0.529§§	7 (-8/+21) P=0.151§§	0.5 (-9/+12) P=0.735§§	1.5 (-10/+23) P=0.719§§	0.477

RPV = Rilpivirine; E/C/F/TDF = Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; DTG = Dolutegravir; PI/c = Protease inhibitor boosted with cobicistat; Combination = regimen which included the association between dolutegravir or rilpivirine or cobicistat; $eGFR^{crea}_{pre}$ = GFR estimated with the CKD-EPI-creatinine formula calculated using the last serum creatinine value available before the switch to a DTG-, RVP- or COBI-based regimen; $eGFR^{crea}_{post}$ = GFR estimated with the CKD-EPI-creatinine formula after the switch to a DTG-, RVP- or COBI-based regimen; $eGFR^{cyst}$ = GFR estimated with CKD-EPI-cystatin C formula after the switch to a DTG-, RVP- or COBI-based regimen; $eGFR^{crea\text{-}cyst}$ = GFR estimated with the combined (creatinine and cystatin C) CKD-EPI formula after the switch to a DTG-, RVP- or COBI-based regimen.
Results are expressed as median (IQR) and mL/min/1.73 m²; §by Kruskal Wallis test; §§by Wilcoxon signed rank test.

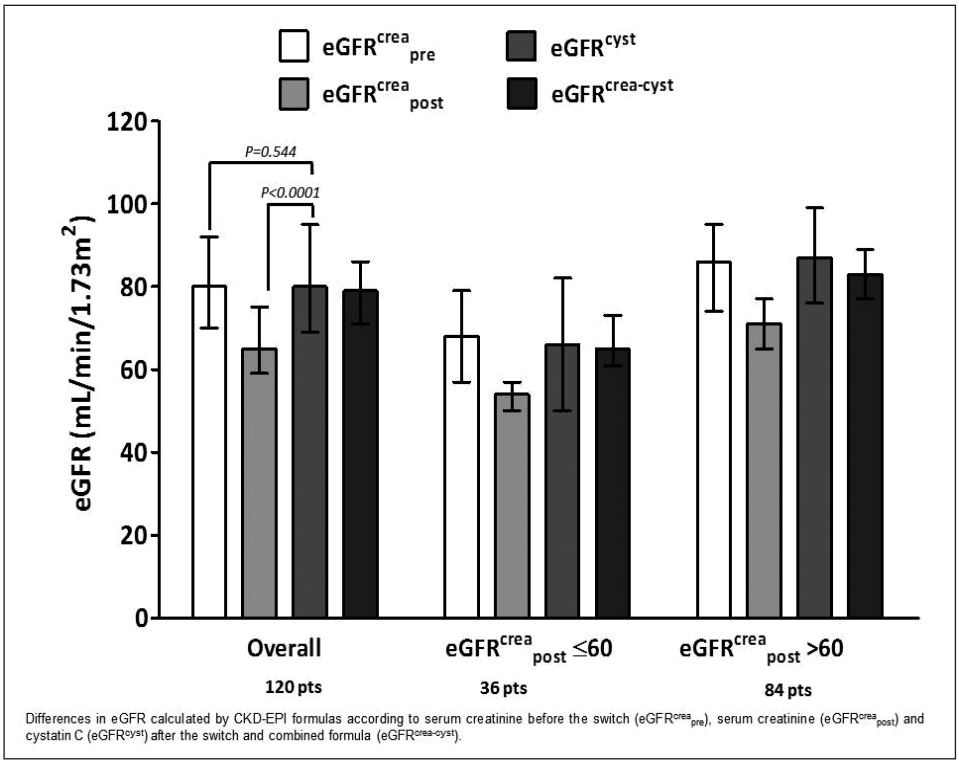


Figure 2 - *Bland-Altman plot of the difference between $eGFR^{cyst}$ and $eGFR^{crea}_{post}$ values (mL/min/1.73 m²) against their means. $eGFR^{cyst}$ = GFR estimated with CKD-EPI-cystatin C formula after the switch to a dolutegravir-, rilpivirine- or cobicistat-based regimen; $eGFR^{crea}_{pre}$ = GFR estimated with the CKD-EPI-creatinine formula calculated using the last serum creatinine value available before the switch to a dolutegravir-, rilpivirine- or cobicistat-based regimen.*

mula seems more suitable than the CKD-EPI-creatinine formula to monitor GFR in patients treated with antiretroviral drugs known to affect the tubular transport of creatinine.

Ninety-six percent of our patients had baseline HIV-RNA <50 copies/mL and hence, presumably, a low level of inflammation, thus limiting the potential bias introduced by this condition in the correct evaluation of $eGFR^{cyst}$. Furthermore, we performed a sensitivity analysis excluding patients with HIV-RNA >50 copies/mL and results did not differ (data not shown).

By contrast, the lower $eGFR^{cyst}$ among smokers (due to the higher plasma concentrations of cystatin C caused by cigarette smoking), while in agreement with previous studies (Knight *et al.,* 2004; Ohkuma *et al.,* 2016; Yamada *et al.,* 2014), may have led to an underestimation of the difference between $eGFR^{cyst}$ and $eGFR^{crea}$.

The use of the regimens investigated in this study is expected to increase and will involve most HIV-infected patients in the near future: our results may thus be particularly interesting as we were able to compare cystatin C-based formulas with creatinine-based formulas to estimate GFR in patients treated with all the available antiretrovirals known to modify the tubular transport of creatinine. Importantly, the analyses stratified according to the antiretroviral regimen showed results consistent with the overall findings. Moreover, our study provides the difference between $eGFR^{cyst}$ and $eGFR^{crea}_{post}$ for each regimen in a critical clinical setting ($eGFR^{crea}$ <90 mL/min/1.73 m^2).

Plotting the difference against the mean allowed us to investigate any possible relationship between measurement differences and the true value. Since we do not know the true value, the mean of the two measurements is the best estimate we have (Bland and Altman, 1986) that also avoids the bias to find a relation between difference and magnitude when there is none (Bland and Altman, 1995). As the Bland-Altman plot defined a bias of +14.2 mL/min/1.73 m^2, the plot allowed us to evaluate a moderate positive trend of differences, proportional to the magnitude of the measurement, becoming higher when the eGFR is higher.

It must be underlined that the "bias" associated with the creatinine formula in estimating eGFR likely applies to all patients, including those with a normal renal function. However, we decided to concentrate our attention on patients with a decreased GFR at baseline because these patients are at higher risk of developing CKD.

The limitations of our study include the relatively small number of patients evaluated and the lack of cystatin C measurements before the switch. Moreover, our findings may not be directly generalized to patients with normal renal function as they were obtained almost exclusively in patients with eGFR <90 mL/min/1.73 m^2. We could not confirm our results by measuring iohexol clearance, the gold standard method to assess the GFR. Finally, the evaluation of eGFR by the cystatin C formula may be limited in clinical practice by the cost associated with the determination of cystatin C or with the availability of this test in many clinical centers.

Our results should be hopefully confirmed by a prospective larger scale study comparing the different eGFR formulas with the determination of iohexol clearance.

In conclusion, we suggest that in patients treated with drugs modifying the tubular transport of creatinine and reduced eGFR, creatinine is not easily interpretable and so measuring eGFR by means of the CKD-EPI cystatin C formula is probably more relevant from a clinical perspective.

Conflicts of Interest and Source of Funding

Nadia Galizzi, Laura Galli, Andrea Poli and Vincenzo Spagnuolo have no potential conflicts to declare.

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