The Problem of Renal Function Monitoring in Patients Treated With the Novel Antiretroviral Drugs

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Chronic kidney disease (CKD) is currently considered a major comorbidity in patients affected by HIV infection. In addition, new generation antiretroviral drugs that interact with creatinine transporters were recently introduced. Rilpivirine, dolutegravir, and cobicistat, with different mechanisms, inhibit the amount of tubular secretion of creatinine causing a slight increase in serum creatinine levels and consensual eGFR creat reduction. This will require an unprecedented attention to renal issues, because the new drugs can also be associated to old antiretroviral drugs that may exert renal toxic effects. Owing to the interference of these drugs with creatinine secretion, an alternative way of estimating GFR would be desirable. At the moment, methods of direct GFR measurement have a high impact on the patient, are not readily available, or are not reliable in HIV patients. Consequently, use of classic formulas to estimate GFR is still recommended, considering the apparent reduction of eGFR creat due to these drugs. Tubular function needs to be carefully monitored with simple tests such as proteinuria, phosphatemia, urinary excretion of phosphate, normoglycemic glycosuria, and excretion of uric acid. More specific and sensitive markers of tubular damage are still not readily available in all clinical labs. HIV patients treated by the novel drugs need to be monitored on a monthly basis for the first 3 months. Subsequent monitoring should be performed on a quarterly basis or guided by comorbidities. Key words: cobicistat, dolutegravir, HIV, kidney, rilpivirine

CHRONIC KIDNEY DISEASE AND HIV INFECTION

Chronic kidney disease (CKD) is currently considered a major comorbidity in patients who are affected by HIV infection.1,2 The increase in life expectancy that followed the introduction of combination antiretroviral therapy (cART) induced the emergence of common chronic conditions, such as diabetes and hypertension, that act as major pathogenic determinants for the development of CKD.2,3 Moreover, chronic inflammation caused by the infection and probably direct renal damage mediated by viral products on kidney biology are contributory factors for the onset of CKD in these subjects. Finally, the potential toxic effect of some antiretroviral agents, such as indinavir or tenofovir (TDF), is well known with a body of evidence.4,6 Although these drugs may rarely induce clinically evident nephrotoxic renal damage, they more often represent a cofactor in the determinism of CKD.

NOVEL ANTIRETROVIRAL DRUGS

In addition to this complex scenario, new antiretroviral drugs that interact with creatinine transporters have recently become available. These drugs present a good safety and tolerability profile.
which gives them better security and manage-
ability compared to older drugs. However, some
apparent concerns may arise from their reported
effects on renal function.

The first of these compounds is rilpivirine, a non-
nucleoside reverse transcriptase inhibitor (NNRTI).
Rilpivirine has a high protein-binding capacity and
is excreted only minimally by the kidney.

In 2 large trials, rilpivirine determined a consist-
ent increase of serum creatinine (SCr) (an average
of approximately 0.1 mg/dL) in patients with nor-
mal renal function.7,8 This increase was stable over
time and was not associated with other laboratory
parameters of kidney damage; in turn, it affected
GFR estimation based on creatinine (eGFR
creat).

Rilpivirine has been reported to act as an inhibi-
tor of the renal organic cationic transporter (OCT2)
at the basolateral side of proximal renal tubular
cells (Figure 1)9 in a way that mimics the effects
of cimetidine, quinidine, or trimethoprim; all
these drugs decrease the secretion of creatinine
by the proximal renal tubule.10 GFR estimated by
formulas based on serum cystatin c (eGFR
cys) does
not show the above-mentioned reduction under
rilpivirine therapy. However, caution in using
these formulas is suggested, because of possible
variations in cystatin c generation according to the
virological status of the patient.11

Dolutegravir is a novel integrase inhibitor that is
metabolized by hepatic UGT1A1 with a minor role
of CYP3A. Renal elimination of unchanged dolute-
gravir is less than1%.12 In a comparison study of
dolutegravir versus raltegravir (SPRING), a small
increase in creatinine was observed in the dolute-
gravir arm.13 This slight, nonprogressive, initial
increase in SCr by dolutegravir is in the range of
0.1 to 0.15 mg/dL and has been demonstrated not
to affect actual glomerular filtration rate (a-GFR),
measured by the iohexol clearance.14,15

In this case, in vitro and clinical data are consis-
tent with inhibition of the OCT2.12 This transporter
is positioned at the basolateral side of the proximal
renal tubular cells and is responsible for the uptake
of creatinine by the proximal renal tubular cells from

![Figure 1](image_url)

**Figure 1.** Renal tubular transporters. Urinary creatinine is secreted by tubule at approximately 10% of
total amount. Creatinine is an endogenous substrate of OCT2 (uptake in tubule cells).10,32 Creatinine efflux
in urine seems mediated by MATE1 and MATE2-K.
After initiating the cART, with reduction and possibly disappearance of HIV RNA from circulation and an increase in CD4 cells, the cystatin C production rate declines. As a result, patients starting their first cART treatment show an increase of eGFR of 20 to 25 mL/min when they change from the initial viremic and systemic inflamed state to a chronic nonviremic condition; this increment is mostly apparent and is at least in part due to the reduced serum levels of cystatin C.21

**MANAGEMENT OF HIV PATIENTS TREATED WITH THE NOVEL DRUGS**

GFR can be estimated by applying validated formulas such as the CKD-EPI based on creatinine to monitor renal function in patients treated with one of the above-mentioned drugs.23 Antiretroviral regimens that include rilpivirine, dolutegravir, or cobicistat will produce an apparent reduction of eGFRcreat that, in normal conditions, should not exceed 25% compared with the basal level. A greater reduction of eGFRcreat needs to be evaluated carefully, because it may represent a sign of true renal function impairment. Patients who have a basal GFR lower than 60 mL/min/1.73 m² may experience an even higher reduction of eGFR, owing to the proportionally greater tubular secretion that accounts for creatinine excretion in conditions of moderate renal impairment. In these conditions, tubular secretion may be higher than 35% of total excretion.24

In addition to the evaluation of glomerular filtration, the tubular function needs to be carefully monitored. Simple tests may help manage this issue. Proteinuria should always be looked for in patients who are exposed to potential nephrotoxic drugs. Dipstick proteinuria has a high negative predictive value, but a low positive predictive value.25 It can only be a screening test. Any patient with an altered dipstick proteinuria needs a more accurate evaluation. We recommend performing quantitative proteinuria estimation as total protein and albumin over creatinine ratio (PCR and ACR, respectively). These measurements can be done on morning spot urine samples, which avoids the burden of timely collected urine. ACR greater than 30 mg/g indicates moderately increased albuminuria; if it is greater than 300 mg/g, it is a sign of severe albuminuria or frank proteinuria.26 PCR higher than 150 mg/g is also an altered value. The ratio between ACR and PCR may help discriminate between glomerular and tubular proteinuria. A ratio greater than 0.4
indicates glomerular proteinuria, while a ratio lower than 0.4 is a marker of tubular proteinuria.²⁷

Tubular proteinuria can also be detected by specific markers such as urinary excretion of retinol binding protein, α-1-microglobulin, β-2-microglobulin, and NGAL (neutrophil gelatinase-associated lipocalin).²⁸ These are sensitive markers of tubular damage, yet are not readily available in all clinical labs.

Tubular dysfunction can also be assessed as an increased urinary excretion of phosphate, better estimated as the TmPO₄/GFR ratio and as hypo-phosphatemia (<2.5 mg/dL).²⁹ An increased fractional excretion of uric acid can also be easily assessed and is a marker of early tubular damage. Finally, normoglycemic glycosuria appears as an advanced sign of tubular dysfunction.³⁰

We suggest that HIV patients who are treated by potential nephrotoxins, especially in association with the novel drugs that affect creatinine excretion, need to be monitored on a monthly basis for the first 3 months. Patients who experience a decrease of eGFR (creatinine clearance) greater than 25% or show the de novo occurrence of signs of tubular dysfunction need a nephrological consult. Generally, new abnormalities attenuate after week 16 of cART.³¹ Consequently, for abnormalities that are not present by week 16, subsequent monitoring should be performed on a quarterly basis or guided by comorbidities.

In conclusion, the introduction of new antiretroviral agents that potentially affect renal function and their foreseeable wide therapeutic application in the near future is raising some concerns. Clinicians should carefully monitor renal function to identify possible alterations suggestive of a true renal functional impairment. Patients should also be monitored for the presence of other risk factors for kidney disease, such as growing age of HIV patients and putative nephrotoxicity of other drugs in the ARV regimens. Results from clinical trials conducted with these novel agents are in some way reassuring, but physicians in routine clinical practice will need evaluation strategies for the long-term surveillance of eventual toxicities.

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