# Kidney Damage in Patients with HIV Infection

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## INTRODUCTION

In addition to the drastic fall in morbidity and mortality rates in HIV positive patients following the introduction of antiretroviral therapy [1,2], current treatment strategies have also allowed complete virological control in multiexperienced patients in treatment failure with previous drug lines [3]. In addition, the newly available compact formulations recently introduced into international guidelines ensure better treatment compliance thanks to a lower pill burden and a much better tolerability profile than the old generation drugs. All these advances have overcome the longstanding conviction that organ damage in patients on antiretroviral treatment was usually due to drug toxicity. However, new acquisitions in the field have shed more light on the complex pathogenesis sustained by the virus, drugs and host risk factors, leading to the more accurate concept of HIV-related non infectious disease.

The kidney is among the organs warranting close follow-up during antiretroviral therapy as kidney function is impaired in a large percentage of HIV-infected patients. HIV-associated renal disease has become a relatively common cause of end stage renal disease requiring dialysis and it seems to be related to progression towards AIDS and death [4-6]. This paper describes the complex interaction of factors potentially responsible for kidney damage in HIV-positive patients.

### The role of HIV infection

The SMART study compared a continuous therapeutic regimen with structured treatment interruptions, disclosing the direct role of HIV infection in determining impaired kidney function [7]. The study emphasized that not only did the structured treatment interruption line have worse morbidity and mortality rates, but it also presented a higher incidence of renal events: in simple terms viral replication damages the kidney.

Without antiretroviral therapy the commonest damage encountered in HIV-infected patients with chronic kidney disease is HIV-associated nephropathy (HIVAN), probably resulting from direct infection of renal cells by the HIV virus. From an anatomopathological standpoint, HIVAN presents as a form of focal glomerulosclerosis with tubulo-interstitial damage clinically evident in a nephrotic syndrome [8-10]. Afro-American patients with a low CD4 count, high plasma levels of HIV-RNA, and a family history of kidney disease are at greatest risk, whereas sex and other risk categories for HIV infection do not seem to play a significant role.

The renal changes associated with HIV-related disease disclosed at histology include membranous nephropathy due to co-infection by HCV, HBV or *Treponema pallidum*; membranoproliferative glomuerulonephritis associated with HCV-related chronic hepatitis and mixed cryoglobulinaemia; diabetic and hypertensive nephropathy and immune complex glomerulonephritis in which IgA are directed against HIV antigens [11-18].

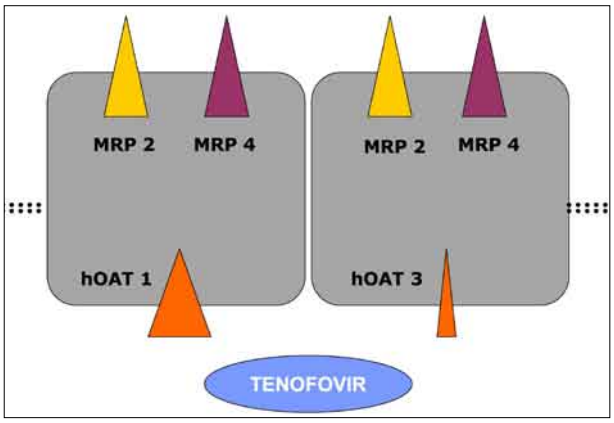
The role of HIV in kidney damage is so decisive that the leading international guidelines for antiretroviral treatment recommend instituting antiretroviral therapy in patients with HIVAN or immune complex glomerulonephritis irrespective of CD4 T cell levels so as to preserve kidney function and improve survival rates.

### The role of antiretroviral drugs.

Protease inhibitors. The first drug shown to be responsible for kidney damage was ***Indinavir***, a protease inhibitor seldom used in current therapeutic regimens. The toxicity induced by this molecule is clinically characterized by the onset of microhaematuria, moderate proteinuria, cristalluria, renal colic and possible acute renal failure, all generally reversible following drug suspension. Indinavir's toxicity appears to be due to the formation of calculi favoured by a urinary pH greater than 6, raised plasma drug concentrations and dehydration. The underlying pathophysiological mechanism responsible for toxicity is linked to Indinavir crystallization in both the kidney, namely the tubules, and in the bladder [19].

A similar mechanism is involved in the nephrotoxicity caused by ***Atazanavir***, a new generation protease inhibitor, but the incidence of clinical events is much lower than that of Indinavir. The Adverse Event Reporting System, the FDA's drug surveillance database, lists 30 cases of renal toxicity, while nephrolithiasis was found in 11 cases in a series of 1134 patients treated with Atazanavir [19].

**Figure 1**




Renal toxicity due to Tenofovir. Although other nucleoside/nucleotide analogue reverse transcriptase inhibitors can cause kidney damage (most cases refer to ***Didanosine*** and ***Abacavir***), there is no doubt that the drug most often implicated for toxicity is ***Tenofovir***, responsible for damage in the proximal renal tubule. Tenofovir is a nucleotide analogue of adenosine 5'-monophosphate administered orally at a dose of 300 mg once daily in combination with other antiretroviral drugs in both untreated and pretreated patients. It is one of the most widely used drugs in antiretroviral therapeutic protocols, being among the preferred molecules in all international guidelines.

There is no consensus in the literature on the toxicity of Tenofovir in HIV-positive patients. Although randomized controlled trials have guaranteed Tenofovir safety of use in experienced and untreated patients, the results of leading retrospective studies and anecdotal reports of tubular toxicity must be kept in mind. In addition, co-morbidities and confounding factors such as the intake of nephrotoxic drugs often hamper the interpretation of scientific data. Table 1 lists some of the major literature reports on the tolerability of Tenofovir.

Tenofovir-induced renal toxicity has a complex pathogenetic mechanism. Renal clearance of Tenofovir, and other drugs like Adefovir and Cidofovir, involves a glomerular phase and a tubular phase of active secretion. Tenofovir penetrates the basolateral membrane of the tubular cells mainly through OAT 1 and to a lesser extent OAT3 (organic anion transporters present on the basolateral and apical membrane). Instead, extracellular clearance is an active process dependent on MRP-2 and MRP-4 (proteins associated with multidrug resistance), encoded by the ABCC4 and ABCC2 genes (Figure 1).

The tubular toxicity induced by Tenofovir seems to be due to the intracellular accumulation of the active ingredient excreted unchanged by the renal emunctory and resulting from reduced MRP-2-mediated extracellular transport combined with an increased intracellular entry proportional to the highest drug serum concentrations. This pathogenetic mechanism is thought to be prevalent in patients with prolonged exposure to Tenofovir and also receiving a protease inhibitor with a boosting agent such as Ritonavir (Lopinavir, Saquinavir, Atazanavir and Amprenavir) and in patients with predisposing risk factors for the development of impaired renal function, suggesting a dose-dependent mechanism.

The role of protease inhibitors as co-factors in the pathogenesis of Tenofovir-induced kidney damage is a much-debated topic. The results of in vitro studies suggest that protease inhibitors (Saquinavir and in particular Ritonavir) may inhibit the function of the MRP-2 and MRP-4 membrane transporters [20-23].

The most typical clinical sign of tubular damage potentially induced by Tenofovir is Fanconi syndrome characterized by the concomitant presence of normoglycaemic glycosuria, metabolic acidosis due to bicarbonaturia, proteinuria, hypokaliaemia, hyperphosphaturia with associated concurrent hypophosphataemia. Although Fanconi syndrome is often clinically silent, if not promptly recognized it can have a negative impact on bone metabolism through the chronic loss of phosphates in urine [24].

**Prevention and early identification of HAART-induced kidney damage**

Given the complexity of the pathogenetic mechanisms involved, the role played by the HIV virus and potentially nephrotoxic antiretroviral drugs, it is essential for clinicians to consider the risk factors predictive of organ injury to prevent the development of kidney damage.

The main risk factor disclosed by numerous literature reports mainly focused on Tenofovir is pre-existing chronic kidney disease. HIV-infected patients who already have a reduced glomerular filtration rate linked to a chronic kidney disease prior to initiating an antiretroviral regimen containing Tenofovir (Figure 2) are at greater risk of developing kidney damage than patients with normal renal function [25].

Other risk factors for kidney damage include advanced age, African ethnicity and some genetic polymorphisms encoding transmembrane proteins. The use of protease inhibitors or other notoriously nephrotoxic drugs, a low BMI, low CD count, high viral replication and a comorbidity like HCV, diabetes and hypertension or previous opportunistic infection are other acquired risk factors to be entertaining in the choice and management of antiretroviral therapy.

**Figure 2**

**Stadiazione di Malattia renale cronica (CKD)**

| Stadio | Descrizione | GFR (mL / min / 1,73 m²) |
|---|---|---|
| I | Danno renale con GFR normale o aumentato | ≥ 90 |
| II | Danno renale con GFR leggermente diminuito | 60–89 |
| III | GFR moderatamente diminuito | 30–59 |
| IV | GFR gravemente diminuito | 15–29 |
| V | Insufficienza renale terminale | < 15 (o dialisi) |

From the standpoint of clinical practice two measurements should be made in screening and monitoring for the early identification of patients with kidney damage: the *glomerular filtration rate* and *proteinuria*.

Assessment of glomerular function must be confined to creatinaemia determination alone as its interpretation is often hampered by multiple extrarenal factors. Prediction algorithms should be used to calculate the filtrate considering the serum creatinine level, age,

**Table 1**

| Author | Study design | Patient number | Results |
|---|---|---|---|
| Schooley RT.<br>AIDS 2002 [28] | 48 wk RCT | | Safe |
| Gallant JE<br>AIDS 2009 [29] | Observational cohort | 201 pts on TDF versus 231 on NRTI | No evidence of renal toxicity<br>Greater decline in eGFR between patients who took TDF +PI versus TDF+NNRTi |
| Gallant JE<br>JAMA 2004 [30] | RCT naive | | Non significant nephrotoxicity |
| Izzedine H<br>Nephrol Dial Transplant 2005 [31] | RCT naive | | Non significant nephrotoxicity |
| Malik A<br>J Infect 2005 [32] | Case report | | Fanconi syndrome and renal failure |
| Verhelst D<br>Am J Kidney Dis 2002 [33] | | | Fanconi Syndrome |
| Gallant JE<br>Clin Infect Dis 2005 [34] | Observvational cohort | 344 patients on TDF versus 314 on alternative NRTI | Significant decline in eGFR in TDF patients versus NRTI, most pronounced in the first 6 months |
| Fux CA<br>CROI 2009 [35] | Cross-sectional (Swiss HIV Cohort) | 1202 pts | Increased risk of proximal tubulopathy with TDF (OR = 3.3) or |
| Novoa SR<br>AIDS 2010 [36] | Cross sectional | 92 pts (TDF versus TDF sparing versus naive) | dose-dependent toxicity |
| Arribas J<br>J Acquir Immune Defic Syndr 2008 [37] | RCT, 144 wks | 517 patients | No significant nephrotoxity of TDF |
| Ole Kirk<br>CROI 2010 Abstract 107LB [38] | Cohort (EuroSIDA study)<br>3-4 years of follow-up | 21482 patients/years | Cumulative exposure to TDF, ATV, or IDV each associated with increased risk of CKD, while results for LPV were less clear<br>Risk of CKD after stopping TDF remained elevated for 1 yr |
| Daar E<br>CROI 2010 Abstract 59LB [39] | RCT 96 weeks | 1857 patients | Decline in creatinine clearence with TDF/FTC+ ATV/rtv compared to other arms |
| Izzedine H<br>AIDS 2004 [40] | RCT (GS 902-GS 903) | GS 902 : 189 patients<br>GS 903 : 552 patients | No significant nephrotoxicity of TDF |

sex, ethnicity and anthropometric measurements. The most widely used algorithms are the *Cockcroft-Gault* formula and the equation in the *Modification of Diet in Renal Disease (MDRD) Study* although they present some limitations. The Cockcroft-Gault formula overestimates glomerular filtration, while the MDRD equation underestimates the glomerular filtrate for high values. A third equation was recently introduced by the *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) to overcome both these limits and some authors prefer this tool to measure glomerular filtrate in HIV-infected patients.

For proteinuria determination, is should be emphasized that even when glomerular filtrate is normal, the presence of proteins in urine is almost always an early marker of kidney disease. In particular, albumin in urine is a sign of glomerular damage and hence the albumin/creatinine ratio will disclose glomerular disease. Loss of small amounts of albumin (30-300 mg/24h), in the range defining so-called microalbuminuria, is clinically important as it has been associated with an increased cardiovascular risk. Lastly, proteinuria may occur with tubular damage: in these cases albumin is not the main urinary protein. A 24 hour urine test is the best means of measuring proteinuria and can also be done by urine spot testing (dipstick).

A global approach to HUV-infected patients should include measurement of the glomerular filtrate and proteinuria determination at the first visit and in any case prior to starting antiretroviral treatment. If glomerular filtration is reduced, namely values below 60 ml/min with proteinuria > 300 mg/24h (or dipstick proteinuria ≥ 1) the patient should be referred to the nephrologist for further diagnostic investigation. If baseline tests are normal, they can be repeated annually except in patients treated with Tenofovir who should undergo quarterly testing. Serum phosphate levels should also be measured in patients receiving Tenofovir as low blood phosphate levels may be a surrogate marker of tubular damage [26].

In conclusion, these tests are compulsory in all HIV-infected patients but are especially important in those with diabetes, hypertension, patients with a glomerular filtration rate < 90 mL/min and those with HCV co-infection [27].

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