HIV infection and kidney disease: literature review

M. Scarpino¹, M. Santoro², G. Pellicanò²

UOC of Infectious Diseases, G. Martino University Hospital, University of Messina, Messina, Italy

ABSTRACT: Combination antiretroviral-therapy (cART) has improved HIV-positive patients mortality and life expectancy. On the other hand, the prevalence of comorbidities, such as cardiovascular disease, hepatic and renal disease has increased. Kidney disease is one of the main causes of morbidity and mortality, especially if accompanied by older age, diabetes, hypertension, black race and hepatitis C coinfection. Renal function needs to be monitored in order to identify kidney disease during early stages. Even if certain cART regimens have been associated with kidney disease, new antiretroviral drugs with a better toxicity profile are now available. Further studies on these new regimens will bring us information on their role in the management of renal disease among HIV-infected patients.

Key words: ARF, CKD, HAART, HIV, HIVAN, Kidney.

INTRODUCTION

Combination antiretroviral therapy cART cannot eradicate HIV infection, although it has drastically diminished HIV-related mortality and morbidities¹. Non-AIDS-related diseases, such as malignancies, cardiovascular disease, bone and renal disease, have emerged as the leading cause of morbidity and mortality among HIV-positive patients²⁻⁵⁴.

Kidney disease is the most frequent comorbidity⁵⁵ and cause of end-stage renal disease (ESRD). Up to 30% of HIV-infected patients have abnormal renal function and it has been correlated with enhanced progression to AIDS and death⁶⁶⁻⁶⁹. Race is an critical risk factor, in fact, black individuals have a 11-fold increased risk for chronic kidney disease (CKD)⁶⁰. Furthermore, the two most common risk factors for CKD in the general population, such as diabetes and hypertension, are over-represented among HIV-positive individuals. A family history of renal disease, age and Hepatitis C virus coinfection are also considered risk factors. Of note, virological and immunological parameters, affect the development of kidney disease, in fact higher baseline HIV plasma viral load (>4000 copies/mL) and lower baseline CD4+ T-cell count (<200 cells/µL) have been correlated with reduced renal function in HIV-positive subjects⁷⁰.

We report an update of the literature about risk factors, screening methods, and management of HIV-related renal disease.

Renal Disease in the setting of HIV infection

HIV-associated nephropathy (HIVAN) is a collapsing form of focal glomerulosclerosis with tubulointerstitial damage. HIVAN represents the most common cause of CKD in HIV-infected individuals. In fact, it has been found in up to 60% of renal biopsies of HIV-positive patients with CKD. CKD severity depends on the renal function and estimated glomerular filtration rate (eGFR). The pathogenesis of CKD in HIV-infected patients is multifactorial, and the presence of other risk factors for CKD, such as diabetes and hypertension, is as important as in the general population⁶¹.

Of note, HIVAN is the third leading cause of ESRD in black people aged 20-64⁶²⁻⁶⁴. Since most patients present with proteinuria and reduced renal function, renal biopsy may be useful to confirm the diagnosis of HIVAN⁶⁵.

Kidney disease in patients with HIV infection is not just HIVAN. As a matter of fact, acute renal failure (ARF) is more common in HIV-infected subjects than in HIV-negative ones. ARF is characterized by a sudden reduction in GFR over days to weeks with an increase in serum creatinine level to values > 1.5 mg/dl (or > 1.3 times the laboratory upper limit of normal), which returns to baseline values within 3 months. Advanced HIV disease and HCV coinfection are risk factors for ARF⁶⁶⁻⁶⁷.
Laboratory markers and diagnostic tools to evaluate kidney dysfunction

Elevated urinary protein excretion indicates tubular damage and is evaluated qualitatively with the urine dipstick or quantitatively by spot urine protein/creatinine ratio. Urinary albumin is used to estimate glomerular damage, which is a risk factor for cardiovascular disease. Moreover, microalbuminuria has been reported to correlate with Framingham risk score and to represent an independent predictor for cardiovascular disease in subjects with a Framingham risk score <20%.

Among HIV-infected persons, the presence of proteinuria has been linked to an increased risk of CKD, ESRD, new AIDS-defining illness and mortality. Of importance, HIV infection itself is a strong independent risk factor for the presence of microalbuminuria. It has been demonstrated that there is an association between microalbuminuria and the stage of HIV infection. HIV RNA level, CD4 count, African-American race are also important determinants of overt proteinuria. Decreased CD4 count, high viral load and African-American race have all been associated with higher albumin to creatinine ratio (ACR). The Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations are creatinine-based estimates of GFR. Both are based on several parameters, such as serum creatinine level, age, sex, race and anthropometric data, but they have some limitations as they do not adjust for creatinine tubular reabsorption. A more accurate equation is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), even though the differences found between eGFR calculated using the Cockcroft-Gault formula standardized for BSA and the CKD-EPI formula were modest in the EuroSIDA study.

Other biomarkers have been studied and used to estimate kidney function. Cystatin C, a cysteine protease inhibitor freely filtered by the glomerulus, reabsorbed and then catabolized by renal tubules, seems to be a good marker of moderate kidney dysfunction and a stronger predictor of death. Of importance, age, gender, race and an inflammatory state may bias the results of cystatin C. Neutrophil gelatin-associated lipocalin (NGAL), produced by neutrophils and epithelial cells, represents an early, sensitive marker of acute kidney injury. Serum NGAL levels are lower in HIV-infected patients and increase to normal levels after virological response to HAART.

All HIV-positive patients should be assessed for existing kidney disease at the time of HIV diagnosis with a screening urinalysis; if there is no evidence of proteinuria at initial evaluation, patients should undergo annual screening for renal disease, including risk assessment, eGFR and urine dipstick analysis. More frequent monitoring is recommended in the presence of CKD risk factors or treatment with nephrotoxic drugs. If there is significant proteinuria, haematuria, decreasing eGFR or eGFR <60 ml/min, current guidelines suggest to perform renal ultrasound, discontinue or adjust drug dosages where appropriate and refer to a nephrologist, for further evaluation and potentially biopsy.

As for the role of renal ultrasound, the diagnostic value of renal echogenicity is useful in ruling out HIV-associated nephropathy when a grade 0 or I echogenicity is found or establishing the diagnosis of HIV-associated nephropathy in the presence of grade III echogenicity. The limitation of using echogenicity alone is that renal echogenicity is not a useful measure among 50% of HIV patients with renal disease who have grade II renal echogenicity.

When renal biopsy cannot be performed, combining CD4 T-cell count >200 with the absence of nephrotic range proteinuria can be useful in excluding HIV-associated nephropathy with a pretest probability <50%. In any case, the combination of nephrotic range proteinuria and CD4 count <200 has not a strong diagnostic value in detecting HIV-associated nephropathy. Other factors such the rate of increase in serum creatinine and renal echogenicity should be taken into account to establish pretest probability. Recently, Jotwani et al. found that among HIV-infected African American women the presence of 2 APOL1 risk alleles correlates with albuminuria but not with other markers of kidney damage, including IL-18, KIM-1, NGAL and A1M. This population had a faster decline of kidney function and a higher incidence of CKD (10% annual eGFR decline compared with women having 0/1 risk allele).

Treatment of Renal Disease in HIV-Infected Patients

Since HIV infection, either directly or indirectly, is implicated in the development of HIVAN, antiretroviral therapy is an important tool for the treatment of HIV-related renal disease. cART has a critical effect on both preservation and improvement of kidney function in HIV-infected subjects. The beneficial effects have been validated by renal biopsy, demonstrating an overt improvement of histo-pathological features. On the contrary, the long-term use of HAART has been related with increased risk of progression to ESRD. However, the development of CKD may also be affected by the prolonged survival and increased prevalence of hypertension and diabetes among cART-treated patients.

It is paramount to manage diabetes and hypertension promptly and properly. Blood pressure should be monitored regularly and antihypertensive treatment started accordingly. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers are the first-choice drugs, because they improve renal hemodynamics, reduce urinary protein excretion and slow the progression to ESRD. Glycemic control is also mandatory. Diabetic patients have to maintain glycated hemoglobin level <7%, preprandial plasma glucose level of 90-130 mg/dl and peak postprandial plasma glucose level <180 mg/dl (data from The American Diabetes Association).

In the PREVEND TI study it was observed that fosinopril, but not pravastatin, had an effect on microalbuminuria. On the other hand, pravastatin had a significant beneficial effect on Framingham score after a four-year follow up.
Antiretroviral Therapy and kidney function

Renal disease has been mostly correlated with the use of indinavir and TDF, even though isolated reports of nephrotoxicity have been reported with all antiretroviral drugs.

Patients treated with zidovudine, didanosine or integrase inhibitors can develop ARF and the possibility of rhabdomyolysis with pigment-related kidney injury has also to be considered.

Indinavir has been reported to cause nephroliathiasis and chronic interstitial nephritis. Renal adverse effects may occur even after discontinuation of indinavir therapy and may be prevented by adequate hydration. Several investigations have reported crystalluria and nephroliathiasis with atazanavir/ritonavir (ATV/RTV), with an incidence of 7.3-23.7 per 1000 person-year. In some cases, pure ATP stones have been identified, while other reports were associated chronic interstitial nephritis. One study suggested that CKD may be a risk factor for ATV-associated nephroliathiasis. ATV/RTV has also been associated with CDK progression and eGFR reduction.

The typical presentation of TDF-associated kidney toxicity is proximal tubulopathy, likely related to the effect on mitochondrial DNA polymerase γ and decreased mitochondrial DNA replication leading to renal function impairment. TDF use is associated with proteinuria, mostly of tubular origin. Labarga et al. also reported that TDF exposure was linked to an increased risk of kidney tubular abnormalities over time, in the absence of impaired glomerular function. Furthermore, another study reported that each year of TDF was associated with a 33% increased risk of CKD. Since serum creatinine is a late marker of kidney dysfunction, urinary phosphate wasting reflective of proximal tubular dysfunction may be a more sensitive marker for TDF-induced kidney injury. After TDF interruption, it may take several months to normalize serum phosphate and observe eGFR improvement. Of note, after discontinuation of TDF, eGFR did not return to baseline levels in none of the patients after a mean follow-up of 23 months.

Gallant et al. compared the changes in kidney function in patients taking nucleoside reverse-transcriptase inhibitors with those on TDF. TDF was correlated with a greater eGFR decrease; other risk factors were lower renal function at baseline, low BMI, older age, diabetes, a lower CD4+ T-cell count, underlying CKD and the presence of genetic polymorphisms in the genes encoding MRP2, MRP4 and MRP7. Furthermore, a retrospective analysis in HIV-infected patients with baseline CKD stage 0 or 1, started on either TDF or abacavir from 1998 to 2008, showed that progression to CKD 2 occurred in 48.8% vs. 23.7% of patients on TDF or abacavir, respectively; progression to CKD 3 was reported in 5.8% of the TDF group vs. 0% of the abacavir group.

Gervasoni et al. reported that women with low body weight, but not men, had the highest risk of being overexposed to TDF plasma concentration, increasing their risk to develop renal and/or bone disorders. Especially, women with a body weight <50 kg had significantly higher plasma tenofovir concentrations than those weighting >50 kg.

In a large pre-exposure prophylaxis (PrEP) randomized, -o-controlled trial, with median follow-up of 18 months and maximum follow-up of 36 months, daily oral TDF-based PrEP resulted in a small but non-progressive decline in eGFR that was not accompanied by a substantial increase in the risk of clinically relevant eGFR decline. PrEP effects were reversible after drug treatment discontinuation.

TDF use has also been associated with Fanconi syndrome (FS), a proximal tubule disease characterized by proteinuria, hypophosphatemia, euglycemic glycosuria, hypouricemia, hypokalemia and metabolic acidosis. In a prospective, controlled study, Gupta et al. have shown that previous or current use of LPV/r, but not other PIs, and lower eGFR at TDF initiation were significantly and independently associated with the development of FS. Elevated TDF levels may lead to worsening of renal function and may be related with PI use or decreased initial renal function. Moreover, the majority of the proximal tubulopathy markers returned to normal levels within 8 weeks after TDF interruption, although proteinuria persisted in several patients. Lower level dipstick proteinuria at time of TDF discontinuation was also a favorable indicator for renal function recovery. Renal tubular disease/FS has also been reported in patients who received ATV/RTV with TDF/FTC. In a meta-analysis, TDF-containing regimens were correlated with higher risk of acute renal damage and a significant decline of kidney function. Urinary β₂-microglobulin and α₁-microglobulin have been shown to be potential screening tools for TDF-induced kidney tubulopathy, especially in early detection of TDF nephrotoxicity.

Ritonavir-boosted protease inhibitors (PIs/r) have been associated with an increased risk of TDF toxicity, probably due to the fact that PIs/r compete with TDF for the same renal transporters, reducing its secretion and potentiating its nephrotoxicity. In fact, patients receiving TDF and PI/r had a greater median decline in GFR than those taking TDF and a NNRTI at 6 months (p=0.01), with trends at 12 (p=0.08) and 24 months (p=0.08). There was no difference in median GFR decline between patients receiving NRTI and PI/r compared with those taking NNRTI and NNRTI. Another observational longitudinal cohort study found that renal dysfunction was more frequent if TDF was associated with PI/r than NNRTI (9.44% vs. 5.01%, p=0.003). In the D:A:D cohort of 22,603 patients on HAART with normal baseline renal function, the decline in eGFR was associated with the use of TDF, ritonavir-boosted atazanavir and ritonavir-boosted lopinavir.

A number of clinical trials have shown initial reduction in eGFR of 10-15% in patients in whom TDF was initiated with RTV or COBI-boosted protease inhibitors or integrase inhibitors. COBI inhibits the tubular secretion of creatinine, leading to a slight increase (<10%) in serum creatinine levels and an eGFR reduction. These changes are reversible upon drug withdrawal.

Tenofovir alafenamide fumarate (TAF) is a novel prodrug and is used at a lower dosage compared with TDF, with lower serum levels of the parent drug. The renal toxicity, which is observed in some patients under TDF therapy,
is less evident in patients treated by TAF. In fact, in contrast to TDF, TAF does not interact with OAT1 or OAT3 organic anion transporters, producing only minimal OAT-mediated cytotoxicity, in vitro. These data confirm a better renal safety profile of TAF compared with TDF119. In two randomized clinical trials, treatment with a co-formulated tablet of EVG/COBI/FTC/TAF provided non-inferior virological suppression to an already approved and guidelines-recommended tablet of EVG/COBI/FTC/TDF. Of importance, compared to TDF, TAF showed significantly more favorable effects on renal and bone parameters120.

Rilpivirine, a NNRTI with a virologic efficacy comparable to EFV, has a high protein binding capacity and is excreted only minimally by the kidney. In two large trials, rilpivirine use was also associated with an increase in serum creatinine (approximately 0.1 mg/dl) in patients with normal renal function. Of importance, this increase was stable over time and other laboratory parameters of kidney dysfunction remained in the normal range. eGFR formula based on serum cystatin C did not show any reduction during rilpivirine therapy, even if cystatin C levels may be altered by the virological and immunological status of the patient119.

Dolutegravir, a novel integrase inhibitor with a renal elimination <1%, induces a serum creatinine increase and moderate reduction (10-15%) of eGFR. These laboratory changes appeared within a week from treatment onset, plateau and then revert towards the baseline values, during dolutegravir treatment119. However, it has been demonstrated that dolutegravir does not affect actual eGFR measured by iohexol clearance. In fact, other markers of tubular damage (serum cystatin C, along with urinary B2-microglobulin, N-acetyl-beta-D-glucosaminidase and retinol-binding protein) were not significantly correlated with dolutegravir pharmacokinetic parameters119.

It is possible to distinguish HIVAN from cART nephrotoxicity evaluating historical information and physical examination, laboratory tests or renal ultrasonography. Signs of uncontrolled HIV infection in association to uncontrolled blood pressure and poor diabetic control are responsible for HIVAN, while proximal tubulopathy with hypophosphatemia or either a partial or full-blown FS suggest cART-associated nephrotoxicity, especially if TDF is part of the regimen. Adequate CD4 T-cell count and undetectable HIV viral load suggest that HIVAN is unlikely the cause of kidney disease. High-grade proteinuria, evaluated by either spot protein/creatinine measurement or 24h urine collection, can be indicative of HIVAN rather than cART nephrotoxicity. Low-grade or tubular proteinuria suggest cART-related kidney injury and dipstick positive glucosuria in the setting of normal serum glucose concentration supports FS and TDF-related injury. The presence of hyaline/proteinaceous casts and scattered RTE cells on urine microscopy are typically present in patients with HIVAN. As for renal ultrasonography, very large and intensely echogenic kidneys with high-grade proteinuria and bland urine sediment are usually indicative of HIVAN121.

As for the management of HIV-positive patients treated with potentially nephotoxic drugs, especially in association with the novel drugs that impact on creatinine excretion, there is a need for frequent monitoring, on a monthly basis for the first three months and quarterly thereafter. In the presence of a rise in creatinine concentrations of less than 0.3–0.4 mg/dl during the first 2-8 weeks of therapy, treatment may be maintained. A greater or progressive increase in creatinine should alert for the presence of nephrotoxicity. Patients that experience a decrease of eGFR >25% or show de novo occurrence of signs of tubular dysfunction need a nephrology consultation119.

CONCLUSIONS

Renal disease is an increasing cause of morbidity and mortality in HIV-positive patients.

Careful evaluation of renal function is paramount to identify early stages of kidney disease. Clinically management includes monitoring of serum creatinine and urinary albumin or protein and treatment of comorbidities, including hypertension and diabetes.

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

REFERENCES


