HIV and the kidney: what the anaesthesiologist should know

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Introduction

It is estimated that 20–25% of HIV-positive patients will require surgery at some stage during their illness. In a study conducted among patients presenting for theatre at Chris Hani Baragwanath Hospital in 2006, a prevalence of HIV infection of 30% was found. In one subgroup, the prevalence was as high as 43%. Thirty percent of these patients (10% of the study population) had a CD4 count of < 200 cells/µL.

With the introduction of highly active anti-retroviral treatment (HAART), the focus of attention in HIV-positive patients has shifted from opportunistic infections to the chronic comorbidities associated with HIV. HIV is a multisystem disease, and it has been recognised that the prevalence of renal disease is increasing in the ageing HIV population. This is reflected by the following statistics:

- Up to 30% of HIV-infected patients have abnormal kidney function.
- Six percent of hospitalised HIV patients develop acute renal failure.
- In the HIV population, the prevalence of chronic kidney disease is estimated to be 17%.
- One study found that 11% of HIV-positive patients have microalbuminuria, compared to 2% in the control group.
- In African Americans, HIV and diabetes mellitus confer similar risks of developing end stage renal disease (ESRD) (hazard ratio 4.56 and 4.15, respectively) compared to white patients, where HIV infection is not associated with an increased risk of ESRD (hazard ratio 0.76).

Aetiology

Renal disease in the HIV-infected patient may present as acute renal failure or chronic kidney disease. It may be caused directly or indirectly by HIV, may be unrelated to HIV, or may be drug-related due to direct nephrotoxicity or secondary to the metabolic vasculopathy induced by the protease inhibitors.

Acute renal failure

Acute renal failure (ARF) in the HIV-positive patient is most often caused by prerenal renal failure (due to hypovolaemia and renal hypoperfusion secondary to vomiting, diarrhoea or sepsis) and acute tubular necrosis (due to renal ischaemia or medication exposure). ARF in the HIV setting is associated with advanced HIV infection (CD4 count < 200 cells/µL and viral load > 10,000 copies/ml), use of antiretroviral medication, and hepatitis C co-infection. The differential diagnosis of ARF is vast (see Table I).

Chronic kidney disease

The National Kidney Foundation defines chronic kidney disease as an estimated glomerular filtration rate (GFR) of < 60 ml/minute/1.73 m² or kidney damage (presence of proteinuria or an anatomical abnormality, with or without a reduction in GFR) which is present for more than three months. Up to 32% of HIV-positive patients have proteinuria or an increased serum creatinine.

Factors contributing to the rise in prevalence of renal disease in the HIV population include:

- The increased life expectancy that came with the advent of HAART. HIV-positive patients may now experience the same age-associated comorbidities as their age-related HIV-negative counterparts, such as hypertensive nephrosclerosis, diabetic nephropathy and atherosclerotic renal artery stenosis. Similarly, they are likely to experience the same non-HIV-related disease as the general population. Frequent glomerular diseases include classic focal segmental glomerulosclerosis.
Table I: Differential diagnosis of acute renal failure in HIV disease

<table>
<thead>
<tr>
<th>HIV-related causes</th>
<th>Non-HIV-related causes</th>
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<td><strong>Glomerular</strong></td>
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<td>HIV-associated nephropathy</td>
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<td>Immune complex glomerulonephritides</td>
<td>Hypovolaemia, congestive heart failure</td>
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<td>(lupus-like, IgA nephritis)</td>
<td>Acute tubular necrosis</td>
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<td>Thrombotic microangiopathy</td>
<td>Ischaemia, sepsis, drugs, intravenous contrast agents</td>
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<td><strong>Drug-related causes</strong></td>
<td>Postrenal</td>
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<tr>
<td>Tubular disorders/acute tubular necrosis</td>
<td>Nephrolithiasis, prostate disease, cancer</td>
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<tr>
<td>Anti-microbials: gentamicin, amphotericin B</td>
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<td>Antiretrovirals: tenofovir</td>
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<tr>
<td>Acute interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td>Indinavir, antimicrobials, etc</td>
<td></td>
</tr>
<tr>
<td>Obstruction/crystalluria</td>
<td></td>
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<tr>
<td>Indinavir, atazanavir, sulfadiazine, cotrimoxazole, aminoglycosides</td>
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<td><strong>Non-HIV-related causes</strong></td>
<td><strong>Other causes</strong></td>
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<tr>
<td>Common causes in the general population</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td>Prerenal</td>
<td>NSAIDs, PPIs, B-lactams, etc</td>
</tr>
<tr>
<td>Hypovolaemia, congestive heart failure</td>
<td>Hepatitis B and C virus–related disease</td>
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<tr>
<td>Acute tubular necrosis</td>
<td>Rhabdomyolysis</td>
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<td>Ischaemia, sepsis, drugs, intravenous contrast agents</td>
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<tr>
<td>Postrenal</td>
<td>Cocaine, heroin</td>
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<tr>
<td>Nephrolithiasis, prostate disease, cancer</td>
<td>Concomitant use of statins and protease inhibitors</td>
</tr>
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<td>Trauma</td>
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(FSGS) and IgA nephropathy. Other glomerular diseases include AA-amyloidosis, lupus nephritis, membranous nephropathy and postinfectious glomerulonephritis.5

- Altered lipid metabolism associated with HAART.6 The protease inhibitors cause accelerated atherosclerosis due to impairment of endothelial function, dyslipidaemia (with increased VLDL and triglycerides and lowered HDL) and insulin resistance and impaired glucose tolerance.7
- Direct effects of HIV on the kidney (HIV-associated nephropathy, HIV immune complex kidney disease).3,4,5,6

Apart from the well known risk factors for the development of chronic renal disease in the general population (e.g. diabetes, hypertension, family history, ethnicity, atherosclerosis, smoking), there are some HIV-specific risk factors, such as lower CD4 counts, high viral load, hepatitis C virus co-infection and cocaine abuse.4 Cocaine is frequently abused by the HIV population, and is a nephrotoxin linked to hypertensive renal changes. Hepatitis C-related kidney disease is common in injection drug users. Immune complex formation with HCV antigens may lead to HCV-associated glomerulonephritis, and may present with any combination of renal insufficiency, proteinuria and haematuria.3

### HIV-associated nephropathy (HIVAN)

HIVAN occurs almost exclusively in patients of African descent5,6 and is caused by direct infection of the epithelial cells of the nephron (glomerular podocytes and tubular epithelial cells) by HIV.4 The renal epithelial cells are capable of complete viral replication and collectively represent a separate compartment for HIV-1.4 The histopathologic lesion seen in HIVAN is a collapsing FSGS due to podocyte proliferation, accompanied by microcystic tubular dilatation with atrophy and flattening of the tubular epithelial cells, and interstitial oedema and inflammation (often with fibrosis).4,5 In the early HAART era, most cases of chronic kidney disease were attributed to HIVAN but, with viral suppression, non-HIVAN disease now predominates.5

Untreated HIVAN usually presents with a high serum creatinine and variable proteinuria (often in the nephrotic range of > 3 g/24 hours), with rapid progression to end stage renal disease within weeks to months. Oedema and hypertension may be absent, which often contributes to delayed diagnosis.5 Enlarged kidneys may be seen on renal ultrasound. The diagnosis is confirmed by renal biopsy.6 Early diagnosis is of utmost importance, as treatment may prevent progression to ESRD. HIVAN is treated with HAART, ACE-inhibitors or angiotensin receptor blockers, and corticosteroids.5,6

### HIV immune complex-mediated glomerulonephritis

Unlike HIVAN, HIV immune complex-mediated glomerulonephritis has no racial predilection. This disease entity can be divided into four categories:

- Immune complex-mediated glomerulonephritis
- IgA nephritis
- Mixed sclerotic/inflammatory disease
- Lupus-like disease5

The first two categories are characterised by the formation of immune complexes with HIV antigens, which can be detected in the circulation and renal tissue.5 IgA nephritis occurs most commonly in patients of European descent and is characterised by mesangial IgA deposits. With lupus-like disease,
immunoglobulin (IgG, IgA and IgM) and complement (C3, C1q) deposits are seen in the kidney in the absence of serologic markers for systemic lupus erythematosus. Treatment is with HAART, to reduce viral antigen and immune complex formation.

HIV-related thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is an uncommon disorder resembling thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome. The pathogenesis is not clear, but it is suggested that HIV proteins may mediate endothelial dysfunction, leading to platelet activation and deposition in the microvasculature of the kidney.

TMA involving the kidney may present with renal insufficiency, proteinuria, haematuria, haemolytic anaemia, thrombocytopenia, fever and neurological manifestations. Treatment includes HAART and therapies similar to that indicated for idiopathic TMA.

Drug-related toxicities

Drug-related toxicities may present in one of four ways:

- Acute tubular necrosis or tubular disorders
- Acute interstitial nephritis
- Crystalluria or renal stone formation;
- Rhabdomyolysis, which is seen with concomitant administration of protease inhibitors and statins

Acute interstitial nephritis

Acute interstitial nephritis (AIN) is most often due to drug hypersensitivity, and the drugs most commonly implicated in the HIV population are the NSAIDs, B-lactams, sulphas, fluoroquinolones, proton pump inhibitors and allopurinol. The time from drug exposure to presentation with AIN can range from a few days (especially with re-exposure) to months. The classic triad of fever, rash and eosinophilia, which was originally described with methicillin-induced AIN, is seen in only 5% of cases. It is therefore important to have a high index of suspicion for AIN if a patient presents with any form of renal insufficiency. Early discontinuation of the culprit drug is of utmost importance, as tubular atrophy and interstitial fibrosis can develop in as little as two weeks. This is easier said than done, as these patients often take multiple medications, many of which may have nephrotoxic potential.

Crystal nephropathy

This occurs when drugs precipitate as crystals in the renal tubular lumen. In the HIV-infected population, drugs that could cause this include ciprofloxacin, intravenous aciclovir, sulfadiazine, indinavir and atazanavir. Volume depletion (sluggish urine flow) and reduced GFR (leading to reduced drug clearance and excessive drug concentrations) predispose to the development of crystal nephropathy. Adequate hydration and dosage adjustment according to the GFR are important measures to reduce the occurrence of crystal nephropathy.

Tenofovir toxicity

Tenofovir (TFV) is widely used in the management of HIV infection and has an excellent safety profile. Clinical trials involving TFV originally failed to show any serious impairment of renal function, but later case reports and cohort studies indicated that TFV may adversely affect kidney function, and cases of acute renal failure and Fanconi syndrome were reported. In some cases renal function did not recover completely after discontinuation of TFV. A retrospective analysis demonstrated that there was a relative median reduction in GFR of 4% in patients who received TFV, compared to those who received another nucleoside reverse transcriptase inhibitor as part of a HAART regimen.

TFV is excreted through glomerular filtration and active secretion in the proximal tubule. Therefore, TFV toxicity manifests primarily as proximal tubular dysfunction with reduced phosphate reabsorption, hypophosphataemia and/or renal tubular acidosis. In its most severe form, it may result in Fanconi syndrome with phosphaturia, glycosuria and aminoaciduria. Acute tubular necrosis without glomerular or interstitial involvement is seen on biopsy. TFV toxicity is almost exclusively seen in patients treated with TFV with boosted protease inhibitors.

It is recommended that patients taking TFV with the following risk factors be monitored every three months: diabetes mellitus, hypertension, GFR < 90 ml/minute/1.73 m², and co-administration of other renally secreted drugs or boosted protease inhibitors. Monitoring should include an estimation of the GFR, a serum phosphate level and testing for urinary glucose. Persistent hypophosphataemia and glycosuria in a non-diabetic patient suggests proximal tubular dysfunction.

Cotrimoxazole toxicity

The effects of cotrimoxazole on the kidney may be summarised as:

- Acute interstitial nephritis
- Hyperkalaemia due to trimethoprim-induced blockade of the epithelial sodium channel in the distal tubule
- An increase in serum creatinine in patients with
existing abnormal renal function. These patients rely on higher rates of proximal tubular creatinine secretion, which is blocked by cotrimoxazole. In these patients, the increase in serum creatinine does not necessarily indicate a further decline in renal function.

**Screening for kidney disease**

It is recommended that risk factor assessment and screening for kidney disease be performed at the time of diagnosis of HIV. As mentioned before, apart from the well-known risk factors for chronic kidney disease in the general population, the HIV-specific risk factors include advanced HIV infection, use of antiretroviral treatment, hepatitis C co-infection and cocaine abuse. Screening includes testing for proteinuria and estimation of the GFR (eGFR). The Infectious Diseases Society of America (IDSA) guidelines recommend that patients having ≥ 1+ proteinuria on dipstick, or an eGFR < 60 ml/minute/1.73 m², should undergo further investigation, including a renal ultrasound examination, and referral to a nephrologist and renal biopsy should be considered. Patients with kidney disease risk factors only should be rescreened annually and those without risk factors should be followed up clinically. Fine and Atta recommend that a spot urine protein:creatinine ratio > 300 mg/g be used to test for proteinuria.

To calculate the eGFR, the Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) formula may be used. The MDRD formula is more accurate in the general population, but it may significantly overestimate the GFR in the small/wasted patient with a reduced muscle mass. Using the C-G equation may be more appropriate in the wasted HIV positive patient as weight is one of the variables in the equation. In a cachectic patient with very low muscle mass, creatinine generation may be so feeble that the serum creatinine level remains in the normal range even in the presence of a GFR < 25ml/min. The C-G equation is also the formula used by the pharmaceutical industry for drug dose administration. If the eGFR varies widely between these formulae, a 24-hour urine collection for creatinine clearance or assessment by nuclear imaging may be useful.

**Renal replacement therapy**

As patient survival improved in the HAART era, more patients developed ESRD requiring renal replacement therapy. Among African Americans, the risk of permanent RRT was 16.2-fold higher in those with AIDS and 6.7-fold higher in HIV patients without AIDS, compared to those without HIV infection. However, the prognosis remains dismal, with median survival for those whose dialysis was initiated in the HAART era unchanged from that in the pre-HAART era. Survival among haemodialysis patients with HIV is significantly lower than among uninfected dialysis patients.

**Renal transplantation**

In the pre-HAART era, HIV infection was an absolute contraindication to organ transplantation in most medical centres. Two recent studies, comprising 26 HIV infected renal allograft recipients, followed these patients for median 4 years and 15 months and found that kidney graft and patient survival rates were similar between HIV infected and uninfected patients. No opportunistic infections or malignancies were observed. Of major concern are the drug interactions that may occur between antiretroviral and immunosuppressant drugs.

**Conclusion**

HIV is a multisystem disease and the kidney is one of the organs affected by this disease. Anaesthesiologists should be aware of the increasing prevalence of renal disease in the HIV infected population. Preserving renal function is one of the goals of a successful anaesthetic. Therefore, it is prudent to assess risk factors for kidney disease, test for proteinuria, and calculate the GFR. Furthermore, in order to preserve kidney function intraoperatively, the patient’s condition should be optimised preoperatively by ensuring adequate hydration, treating infections, adjusting drug dosages according to the eGFR and discontinuing culprit drugs. Finally, maintaining adequate renal perfusion pressure should be the standard during any anaesthetic.

**References**