HIV and the kidney: a UK perspective

Kidney disease remains an important complication of HIV infection. This review provides an update on the burden of end-stage kidney disease, the cardiovascular morbidity associated with chronic kidney disease, and the effects of antiretroviral drugs on the kidney.

In the UK, approximately 98 000 people are estimated to be living with human immunodeficiency virus (HIV), of whom over 77 000 are engaged in care (Aghaizu et al, 2013). Since the introduction of combination antiretroviral therapy in 1996, the treatment of people living with HIV has changed from short interventions aimed at delaying death to the management of a chronic disease. Antiretroviral therapy controls HIV replication, improves immune function and reduces the immune activation, inflammation and coagulation that are associated with infectious and non-infectious comorbidities (Kuller et al, 2008). However, combination antiretroviral therapy needs to be provided life-long, and may have adverse effects on the cardiovascular system, liver, kidney and bone.

In the 6 years since we last discussed HIV and the kidney in this journal (Post and Hendry, 2008), many new insights have been gained in terms of the epidemiology of acute kidney injury and chronic kidney disease, the cardiovascular complications of chronic kidney disease, and the effects of antiretroviral drugs on the kidney. This article discusses the UK perspective of HIV and the kidney, a setting with widespread combination antiretroviral therapy coverage and high rates of HIV suppression among those on treatment. Nevertheless, some 22% of those infected remain unaware of their HIV status and just under half of patients with newly diagnosed HIV present 'late', i.e. with an acquired immunodeficiency syndrome (AIDS) diagnosis or a CD4 cell count <350/mm^3 (Aghaizu et al, 2013). Immunodeficiency is an important risk factor for acute kidney injury and chronic kidney disease, and earlier HIV diagnosis coupled with the provision of combination antiretroviral therapy is paramount in reducing the risk of renal complications.

Acute kidney injury

Acute kidney injury may result from diminished kidney perfusion, the toxic effects of drugs and other substances, infection, or obstruction of the renal tract. It is seen frequently in HIV, and an incidence of 5.9 cases per 100 person years was found in a large American cohort of ambulant patients. Acute kidney injury was associated with being male, having a CD4 count <100/mm^3, and a viral load >10 000 copies/ml. The majority of cases were pre-renal, caused by diarrhoea, hepatic disease (particularly in patients with hepatitis C co-infection) and infections; other mechanisms included intrinsic renal pathology from drug toxicity (Franceschini et al, 2005). In this study, more than half of acute kidney injury cases were infection-related, of which AIDS-defining conditions were the majority. *Table 1* shows factors commonly associated with acute kidney injury.

In the UK, acute kidney injury is particularly common within the first 3 months of initiating HIV care, when complications of immunodeficiency are most frequent. Treatment of opportunistic infections commonly involves medications that have nephrotoxic potential, such as trimethoprim-sulfamethoxazole, sulfadiazine, amphotericin B, rifampicin, aciclovir and ganciclovir. Most patients who experience acute kidney injury are not on combination antiretroviral therapy or have a history of combination antiretroviral therapy exposure without HIV suppression. Dehydration is also common and should be alleviated; non-steroidal analgesics should be avoided, and renally cleared drugs should be dose-adjusted for the degree of renal impairment (Roe et al, 2008). In patients who have attained viral suppression on combination antiretroviral therapy, infectious and

Table 1. Factors associated with the development of acute kidney injury

Acquired immunodeficiency syndrome (AIDS)-defining conditions
Low nadir CD4 <100 cells/mm^3
Injecting drug use
Hepatitis C co-infection
Infections, liver disease and malignancy
Dehydration
Exposure to nephrotoxic medications

From Roe et al (2008)

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other complications are infrequent, and acute kidney injury does not appear to be more frequent with exposure to tenofovir or atazanavir (Ibrahim et al, 2010), two commonly used antiretrovirals that have been linked to acute kidney injury in case reports (Zimmerman et al, 2006; de Silva et al, 2007), and with chronic kidney disease and chronic kidney disease progression in cohort studies (Mocroft et al, 2010). However, acute kidney injury may be the initial presentation of chronic kidney disease, especially in those with HIV-associated nephropathy (Post et al, 2008).

Chronic kidney disease

In the UK, approximately 2% of HIV-positive patients have chronic kidney disease as defined by an estimated glomerular filtration rate <60 ml/min/1.73m^2 (Campbell et al, 2009; Ibrahim et al, 2012), although this is set to increase as the HIV population ages. A further 11–17% of patients have microalbuminuria (Szczech et al, 2007; Campbell et al, 2012b) and thus satisfy the Kidney Disease: Improving Global Outcomes (KDIGO) definition of chronic kidney disease, although progression to severe chronic kidney disease (stages 4/5 chronic kidney disease, defined by estimated glomerular filtration rate <30 ml/min/1.73m^2 for >3 months) remains uncommon, especially in non-black HIV-positive populations (Ibrahim et al, 2012; Ryom et al, 2013) (*Table 2*).

HIV-associated nephropathy is the most severe form of kidney disease affecting HIV-positive patients. It is characterized by a collapsing glomerulopathy, severe proteinuria, echogenic kidneys on ultrasound and, in the absence of combination antiretroviral therapy, high rates (>50% at 5 years) of progression to end-stage kidney disease (Post et al, 2008). HIV-associated nephropathy almost exclusively affects black patients, which may be explained by polymorphisms in the APOL1 gene that are more commonly encountered in this population (Kopp et al, 2011). If diagnosed before extensive kidney damage and advanced kidney failure are established, combination antiretroviral therapy may improve kidney function and/or slow the progression to end-stage kidney disease (Post et al, 2008).

Table 2. Aetiology of chronic kidney disease

HIV-associated nephropathy*
Immune-complex kidney disease
Non-HIV pathology
Diabetes mellitus
Hypertension
Atherosclerosis
Diseases of the urinary tract (reflux, obstruction)
Drug toxicity
Non-antiretrovirals
Antiretrovirals – tenofovir, indinavir

* HIV-associated nephropathy was seen exclusively in patients of black ethnicity.
Adapted from Campbell et al (2009)

In the era of widespread combination antiretroviral therapy use, the incidence of HIV-associated nephropathy has declined (Lucas et al, 2004) and immune complex kidney disease has become the commonest group of pathologies in renal biopsy series (Booth et al, 2013). It remains unclear whether some or all of types of immune complex kidney disease are caused by or, indeed, associated with HIV. Preliminary evidence suggests that some forms of immune complex kidney disease, including membranous and mesangio-capillary glomerulonephritis, are associated with viral replication. This may imply a pathogenetic role for HIV or the immune activation that results from viral replication in these pathologies. The natural history of immune complex kidney disease in terms of progression to end-stage kidney disease is more benign than that of HIV-associated nephropathy, with 25% of patients requiring renal replacement therapy at 5 years (Booth et al, 2013).

Similar to the general nephrology population, HIV-positive patients may also present with chronic kidney disease secondary to diabetes mellitus, hypertension, atherosclerotic vascular disease or urological pathology. In addition, impaired renal function may result from exposure to potentially nephrotoxic medications including non-steroidal anti-inflammatory drugs and the antiretrovirals indinavir or tenofovir (see below). Multiple risk factors for chronic kidney disease frequently co-exist in these patients (Campbell et al, 2009). As in the general population, chronic kidney disease is an important risk factor for cardiovascular morbidity and mortality (Choi et al, 2010; Campbell et al, 2012a); the risk of death in patients with mild-moderately advanced chronic kidney disease exceeds the risk of kidney disease progression (Ibrahim et al, 2012). Accordingly, cardiovascular risk factors such as smoking and dyslipidaemia should be aggressively managed and, whenever possible, nephrotoxic medications avoided (Williams et al, 2012).

End-stage kidney disease affects approximately 1% of black patients with HIV infection in the UK, and 0.15% of those from other ethnicities (Bansi et al, 2009). This racial disparity is at least in part explained by the genetic susceptibility of black patients to developing HIV-associated nephropathy via the APOL1 gene. Favourable long-term outcomes in patients with end-stage kidney disease have increased the number of patients requiring renal replacement therapy (Bansi et al, 2009) and kidney transplantation is actively pursued in HIV-positive patients with end-stage kidney disease who have achieved HIV viral load suppression, CD4 cell counts above 200/mm^3 and no contraindications in terms of current or past comorbidities (Stock et al, 2010; Gathogo et al, 2014). Patient and graft survival and the risk of infectious complications in these carefully selected patients appear simi-

lar to those in non-HIV-infected recipients. By contrast, the incidence of acute graft rejection is markedly increased (cumulative incidence approximately 45% at 1 year). Interactions between ritonavir-boosted protease inhibitors and calcineurin inhibitors require careful dose adjustment of the latter (with reductions up to 99%) when these drugs are co-administered, and frequent monitoring is advised until the desired concentrations have been achieved (Gathogo et al, 2014).

Antiretrovirals and the kidney

Currently used antiretrovirals have been associated with alterations in kidney function, incident chronic kidney disease and kidney disease progression (*Table 3*). In addition, tenofovir may result in renal tubular disease and progressive or accelerated decline in renal function, while atazanavir may result in interstitial nephritis and the formation of kidney stones (Yombi et al, 2014).

Several antiretrovirals may affect trans-membrane transporters in the basolateral and apical membranes of proximal tubular cells. Inhibition of the transporters of creatinine (OCT2 on the basolateral membrane by rilpivirine and dolutegravir, MATE1 on the apical membrane by ritonavir and cobicistat) results in modest elevations of serum creatinine and thus reductions in calculated creatinine clearance and estimated glomerular filtration rate. The median reduction in creatinine clearance by these drugs is 5–15 ml/min, although the actual glomerular filtration rate is unaffected (Yombi et al, 2014). Use of lopinavir plus ritonavir has been associated with incident chronic kidney disease or chronic kidney disease progression (Mocroft et al, 2010), and darunavir plus ritonavir with crystalluria (de Lastours et al, 2013). Although six patients in each arm of a clinical trial developed kidney stones with lopinavir plus ritonavir and darunavir plus ritonavir (Orkin et al, 2013), no cases of kidney injury have been reported with either drug in clinical practice.

Tenofovir, a nucleotide reverse transcriptase inhibitor and the most commonly used antiretroviral, has activity against both HIV and hepatitis B. It is excreted via the kidney through glomerular filtration and tubular secretion. Tubular secretion is mediated via OCT1 and OCT3 on the basolateral membrane and MRP4 on the apical membrane. Inhibition of or polymorphisms in the gene encoding the apical transporter may result in increased intracellular tenofovir concentrations, leading to mitochondrial toxicity (Post and Hendry, 2008). In its most severe form, tenofovir toxicity results in an acquired Fanconi syndrome with excess loss of phosphate, glucose and low molecular weight proteins in the urine; osteomalacia may be present in 40% of patients and lead to pathological skeletal fractures (Woodward et al, 2009). Others have reported nephrogenic diabetes insipidus and acute renal failure with tenofovir exposure, or accelerated decline in estimated glomerular filtration rate during exposure to tenofovir (de Silva et al, 2007; Campbell et al, 2009).

Sub-clinical kidney dysfunction is common with tenofovir. A Spanish study reported a cumulative incidence of proximal tubular dysfunction of >50% at 5 years; tenofovir exposure was associated with a 21-fold increase in the likelihood of developing renal tubular dysfunction (Labarga et al, 2009). Polymorphisms in ABCC2, the gene encoding the tubular transporter MRP2, were associated with renal tubular dysfunction in patients who received tenofovir (Rodriguez-Novoa et al, 2009). The clinical significance of renal tubular dysfunction remains unclear; in particular, there is no evidence to suggest that patients with renal tubular dysfunction progress to severe, treatment-limiting renal tubular disease, or that they are more prone to developing osteomalacia and fractures. Tenofovir use has also been associated with the development or progression of chronic kidney disease (Mocroft et al, 2010; Scherzer et al, 2012), proteinuria (Gupta et al 2009; Scherzer et al, 2012) and rapid decline in estimated glomerular filtration rate in cohort studies (Scherzer et al, 2012). In clinical practice, the rate at which tenofovir is discontinued in clinical practice increases as the estimated glomerular filtration rate declines; in these patients, renal function, as assessed by estimated glomerular filtration rate, tends to improve after discontinuation of tenofovir, reaching pre-tenofovir values in the majority of patients (Jose et al, 2014).

Atazanavir is a protease inhibitor that is extensively metabolized in the liver; up to 8% is excreted via the kidney through glomerular filtration. Atazanavir is poorly soluble and thus prone to precipitate in the urinary tract. Case reports have described stones that contained pure atazanavir, while cohort studies have provided an estimate of the incidence of kidney stones, ranging from 7.3 to 23.7 episodes per 1000 person-years of follow up (Rockwood et al, 2011; Hamada et al, 2012). A Japanese study suggested that the propensity to form kidney stones was not a protease inhibitor class effect but specific to atazanavir (Hamada et al, 2012). In this study, no specific risk factors were identified. A further study from the UK noted that an estimated glomerular filtration rate <60 ml/min/1.73m^2 at the time of atazanavir initiation

Table 3. Potential renal complications associated with specific antiretrovirals in current clinical practice

Renal condition	Drugs
Acute kidney injury	Tenofovir, atazanavir
Chronic kidney disease	Tenofovir, atazanavir, lopinavir
Tubular dysfunction	Tenofovir, atazanavir
Crystalluria	Atazanavir, darunavir
Nephrolithiasis	Atazanavir
Fanconi syndrome	Tenofovir
Inhibition of creatinine secretion (no effect on overall renal function)	Cobicistat, ritonavir, dolutegravir, rilpivirine

was present in 42% of patients (Rockwood et al, 2011), suggesting that impaired renal function may pose considerable risk for subsequent stone formation. It is unclear whether crystalluria, which was present in 8.9% of patients who received ritonavir-boosted atazanavir (de Lastours et al, 2013), identifies patients at increased risk of nephrolithiasis.

Sub-clinical kidney dysfunction has also been noted with atazanavir. Apart from the crystalluria described above, atazanavir has been associated with the development of or progression to chronic kidney disease (Mocroft et al, 2010; Calza et al, 2013) and rapid decline in estimated glomerular filtration rate in cohort studies (Rasch et al, 2012; Scherzer et al, 2012). However, another study suggested that atazanavir plus ritonavir was associated with greater initial reductions in estimated glomerular filtration rate compared with lopinavir plus ritonavir, with stable values after 6 months (Young et al, 2012). Indeed, as atazanavir and tenofovir were co-administered in most studies, these abnormalities may in part reflect the effects of tenofovir or tenofovir plus ritonavir on the kidney.

Managing chronic kidney disease in HIV-positive patients and managing HIV in patients with chronic kidney disease

There are no evidence-based guidelines for the management of chronic kidney disease in HIV-positive patients. The authors suggest that the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) guidelines are applied to HIV-positive patients with chronic kidney disease. These guidelines recommend blood pressure control with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers when proteinuria is present, and the management of diabetes mellitus and dyslipidaemia. In addition, lifestyle interventions to stop smoking, reduce sodium intake and achieve a healthy weight should be encouraged. Patients with HIV-associated nephropathy should start life-long combination antiretroviral therapy as soon as possible, irrespective of CD4 cell count, to reduce the risk of kidney disease progression; a similar recommendation could be considered for those diagnosed with immune complex kidney disease. Dialysis should be offered to, and kidney transplantation considered in, all HIV-positive patients who develop end-stage kidney disease.

The optimal management strategy of HIV in the context of chronic kidney disease remains to be defined. Given that tenofovir and atazanavir may cause kidney injury and have been associated with chronic kidney disease and chronic kidney disease progression, it seems prudent to avoid these antiretrovirals in patients with chronic kidney disease, those at greatest risk of kidney disease progression, and in the setting of kidney transplantation. Tenofovir should be discontinued in patients who develop clinically-overt renal tubular disease.

KEY POINTS

- Long-term survival is the norm for patients with HIV infection on combination antiretroviral therapy; risk factors for renal disease will become more prominent in this aging cohort.
- Advanced and uncontrolled HIV infection is associated with acute kidney injury.
- The prevalence of chronic kidney disease is higher in the HIV population than the general population and is strongly influenced by ethnicity.
- HIV-positive patients with end-stage kidney disease should be considered for offered renal transplantation as many have good outcomes.
- Certain antiretrovirals have been associated with renal disease; renal function in patients on tenofovir and atazanavir should be monitored more closely.

Conclusions

Although the overall prognosis for HIV infection has improved, patients continue to experience renal disease as a result of HIV-associated nephropathy and AIDS-defining illnesses in those with advanced immunodeficiency, and as a result of renal pathology from other diseases and drug toxicity irrespective of CD4 cell count. Early diagnosis and treatment of HIV and related conditions, improved management of secondary causes, and judicious use of drugs with nephrotoxic potential may lead to better outcomes for patients with renal pathology. **BJHM**

Conflict of interest: Dr E Mabonga has received sponsorship to attend scientific conferences from Merck, Boehringer and Bristol-Myers Squibb; Dr E Cheserem has received sponsorship to attend scientific conferences from Gilead Sciences, Janssen Pharmaceuticals, Viiv Healthcare and Abbvie Ltd; Dr FA Post has received funding to attend conferences or educational meetings, honoraria and/or funding for research from Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ ViiV healthcare, and Merck.

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