HIV and the kidney

Kidney disease is an important complication of HIV infection. Antiretroviral therapy has dramatically improved the life expectancy of HIV-infected patients with end-stage renal disease. Renal replacement therapy, including kidney transplantation, should be offered to HIV-positive patients.

Highly active antiretroviral therapy (HAART) has revolutionized the management of HIV infection. HAART suppresses HIV replication, improves immune function, reduces the risk of opportunistic infections, and improves life expectancy as well as quality of life of HIV-infected patients. Opportunistic infections continue to cause significant morbidity and mortality among late presenters (patients with newly diagnosed, advanced HIV infection) and those declining or without access to HAART. Opportunistic infections are infrequently encountered in patients who respond to HAART, particularly when HAART is initiated before severe CD4+ T-lymphocytopaenia (CD4 count <200 cells/mm^3) has occurred.

Up to 30% of HIV-infected patients have some evidence of renal disease (proteinuria or reduced glomerular filtration rate). Renal disease, including proteinuria, acute renal failure and chronic kidney disease, is associated with CD4+ T-lymphocytopaenia. Consequently, initiation of HAART before CD4 counts drop below 200 cells/mm^3 reduces the risk of developing renal disease as well as opportunistic infections. As the life expectancy of HIV-infected patients on HAART increases to decades, it becomes important to monitor the long-term effects of HIV infection and HIV therapies on kidney function. This review discusses recent insights in the renal complications of HIV infection.

Proteinuria

Proteinuria, measured ≥1+ on dipstix, may be detected in ~30% of HIV-infected patients (Szczech et al, 2002; Gupta et al, 2004), and 18% of HIV-infected women may have or develop ≥2+ proteinuria (Gardner et al, 2003). Proteinuria is a risk factor for developing renal failure (Szczech et al, 2002) and death (adjusted hazard ratio 2.9) (Gardner et al, 2003). Risk factors for proteinuria among women are black ethnicity (odds ratio 2.0), CD4 count <200 cells/mm^3 (odds ratio 1.4), hepatitis C (HCV) co-infection (odds ratio 1.3), and high plasma HIV RNA load. CD4 count <200 cells/mm^3 and detectable viral load are important risk factors (hazard ratio 3.6 and 2.3 respectively) for renal failure in proteinuric women (Szczech et al, 2002). HIV-associated nephropathy (HIVAN) is a collapsing form of focal glomerulosclerosis with tubulo-interstitial injury and an important cause of moderate to severe proteinuria (>0.5 g/day). Formal diagnosis of HIVAN can only be made by renal biopsy. It is also important to remember that hypertension and diabetic nephropathy are relatively common causes of proteinuria in HIV-infected patients and these diseases should be excluded in all HIV-positive patients.

Acute kidney disease in HIV-infected patients

Patients with HIV infection are at high risk of developing acute renal failure. Almost one in ten HIV-infected patients experience ≥1 episode of acute renal failure (incidence rate 5.9 per 100 person years) (Franceschini et al, 2005). Risk factors for acute renal failure include CD4 count <200 cells/mm^3, plasma HIV RNA level >10 000 copies/ml, AIDS-defining conditions (opportunistic infections and malignancies), intravenous drug use and HCV co-infection. Acute renal failure is often the result of pre-renal causes or acute tubular necrosis, and associated with opportunistic infections and their therapies (*Table 1*), and with liver disease in patients co-infected with hepatitis virus (Franceschini et al, 2005). Acute renal failure in HIV-infected patients is an important risk factor for in-hospital mortality (adjusted odds ratio 5.8) (Wyatt et al, 2006).

In the authors' centre, >40% of all episodes of acute renal failure occur in late presenters hospitalized for serious (opportunistic) infections within the first 3 months of HIV diagnosis. These patients are typically not (yet) on HAART, and drug toxicity contributes significantly to the development of acute renal failure (*Table 1*). Patients who do not take or who poorly respond to HAART remain susceptible to infections and are consequently at high risk of developing acute renal failure, whereas patients who have experienced a favourable immunological and virological response to HAART are at much reduced risk of acute renal failure (Roe et al, 2007).

Since severe (opportunistic) infections, drug toxicity and dehydration are important factors that contribute to acute renal failure, careful monitoring of renal function in hospitalized patients, cautious administration of potentially nephrotoxic agents, and avoiding dehydration and non-steroidal analgesics which may precipitate acute renal failure by interfering with the autoregulation of glomerular perfusion, may be important measures to reduce the risk of acute renal failure. Drug dosing should be carefully adjusted for renal function in all patients with acute renal failure.

Dr Frank A Post *is Clinical Lecturer in HIV Medicine in the Academic Department of HIV/Genitourinary Medicine and* **Professor Bruce M Hendry** *is Professor of Renal Medicine in the Academic Department of Renal Medicine, King's College London, London SE5 9RJ*

Correspondence to: Dr FA Post

Table 1. Infections and drugs associated with developing acute renal failure in HIV-infected patients

Infections caused by	*Cryptococcus neoformans*	
	Pneumocystis jerovecii	
	Cytomegalovirus	
	Herpes simplex	
	Toxoplasmosis	
	Mycobacterium tuberculosis	
	Mycobacterium avium complex	
	Staphylococcus aureus	
	Streptococcus pneumoniae	
	Salmonella spp.	
Drugs	Antimicrobials	Amphotericin B
		Co-trimoxazole
		Sulfadiazine
		Aminoglycosides
		Capreomycin
		Rifampicin
		Oxacillin/flucloxacillin
		Vancomycin
		Aciclovir
	Antiretrovirals	Indinavir
		Tenofovir
	Other	Non-steroidal anti-inflammatory drugs
		Cyclooxygenase-2 inhibitors

From Franceschini et al (2005) and personal observations (2007)

Chronic kidney disease in HIV-infected patients

Compared to the general, age-matched population, chronic kidney disease is common in HIV-infected patients. The prevalence of chronic renal failure (chronic kidney disease stage 3 or greater (estimated glomerular filtration rate <60 ml/min)) in HIV-infected patients is 2–4%. Risk factors for chronic kidney disease include CD4 T-lymphocytopaenia, proteinuria, hypertension, diabetes and HCV co-infection (Gupta et al, 2004; Krawczyk et al, 2004). HAART markedly reduces the risk of developing chronic kidney disease (odds ratio 0.5) (Krawczyk et al, 2004). In the authors' centre, most patients who are diagnosed with chronic kidney disease have evidence of renal disease (glomerular filtration rate <60 ml/min and/or proteinuria) at the time of HIV diagnosis. The incidence of new stage 3–5 chronic kidney disease in patients who do not have renal disease at HIV diagnosis is approximately 1 per 1000 person years (Campbell et al, 2007).

HIVAN is the most common aetiology in patients with chronic kidney disease who underwent renal biopsy (Szczech et al, 2004; Gerntholtz et al, 2006). HIVAN affects black patients, in whom the prevalence of HIVAN may be 3.5% (Ahuja et al, 1999). HIVAN is associated with advanced HIV infection, heavy proteinuria and severe renal failure (Szczech et al, 2004; Atta et al, 2006), although patients with mild proteinuruia (microalbuminuria) and normal glomerular filtration rate may have HIVAN on renal biopsy (Han et al, 2006).

Before the availability of HAART, progression to end-stage renal failure was common, and survival was measured in weeks (Carbone et al, 1989). The incidence of HIVAN has declined in the HAART era (Lucas et al, 2004), and several reports have documented improvement of renal function, amount of proteinuria and/or renal histology in patients who initiated HAART (Chemlal et al, 2000; Winston et al, 2001; Szczech et al, 2004; Atta et al, 2006). In the UK, the 5-year-survival rate of HIVAN patients exceeds 90%. Nevertheless, most HIVAN patients progress to end-stage renal failure (Szczech et al, 2004; Atta et al, 2006). It remains to be determined if angiotensin-converting enzyme inhibitors or corticosteroids slow the progression of renal disease in HIVAN patients receiving HAART.

Another form of chronic kidney disease that may affect HIV-infected patients is immune complex glomerulonephritis (Haas et al, 2005; Gerntholtz et al, 2006). A study from the USA described 14 predominantly black patients whose renal histology resembled lupus nephritis with diffuse or focal mesangial proliferation, crescent formation, and immunoglobulin and complement deposition. Patients had severe proteinuria, advanced renal failure, and the majority of patients progressed to end-stage renal failure within 1 year (Haas et al, 2005). Patients with immune complex kidney disease generally have advanced HIV infection, and are clinically indistinguishable from those who have HIVAN (Gerntholtz et al, 2006) (*Table 2*). Other glomerulopathies, including focal glomerulosclerosis, immunoglobulin A nephropathy, membranous nephropathy (which may relate to hepatitis B virus or syphilis co-infection) and mesangiocapillary glomerulonephritis (which may relate to HCV co-infection) have also been documented in HIV-infected patients (Gerntholtz et al, 2006). It is unclear whether these pathologies are more common in HIV infection, and whether HIV infection affects their natural history. Co-morbidities, such as hypertension, diabetes mellitus and reno-vascular disease, are important causes of chronic kidney disease in HIV-infected patients (Szczech et al, 2004). The adverse metabolic effects of HAART, including dyslipidaemia and insulin resistance, may unfavourably affect the natural history of these conditions as well as contribute to accelerated atherosclerosis in patients with chronic kidney disease.

A small but significant proportion of HIV-infected patients develop end-stage renal failure. In the authors' centre, 0.7% of patients developed end-stage renal failure. These patients had severe renal failure at HIV diagnosis (median estimated glomerular filtration rate 27 ml/min). HIVAN, and therefore black ethnicity, is an important

risk factor for developing end-stage renal failure (Campbell et al, 2007). HAART has improved the prognosis of HIV-infected patients maintained on chronic dialysis (Ahuja et al, 2002). HIV-positive patients with end-stage renal failure, CD4 counts >200 cells/mm^3 and complete suppression of HIV replication on HAART should now be considered for kidney transplantation (Bhagani et al, 2006). Early results suggest that HIV-positive patients have similar graft and overall survival rates as HIV-negative patients (Qiu et al, 2006). However, patients require careful monitoring since HIV treatments (protease, nucleoside and non-nucleoside reverse transcriptase inhibitors) may significantly interact with many of the drugs used as immunosuppressants after transplantation including calcineurin inhibitors (ciclosporin and tacrolimus) and mycophenolate (Izzedine et al, 2004).

HAART nephropathy

Although most antiretroviral drugs may cause renal injury, indinavir and tenofovir have been most frequently associated with nephrotoxicity. Crystallization of indinavir in the urinary tract, which can result in nephrolithiasis or tubulo-interstitial nephritis, may affect up to 30% of patients (Gagnon et al, 2000; Herman et al, 2001). Both acute and chronic renal failure have resulted from indinavir administration. Although most episodes resolve with rehydration and drug discontinuation, gradual loss of renal function, and progressive or irreversible renal failure have also been reported. Given the range of alternative protease inhibitors, indinavir is now infrequently used.

Of greater interest to HIV physicians is the nephrotoxic potential of tenofovir, a widely used nucleotide reverse-transcriptase inhibitor. Tenofovir has been associated in case reports with acute and chronic renal injury, renal tubular acidosis, Fanconi syndrome, nephrogenic diabetes insipidus, hypokalaemia, hypophosphataemia, and urinary concentration defects. In randomized clinical trials, tenofovir use was not associated with renal injury (Staszewski et al, 2005; Moreno et al, 2006). The prevalence of tenofovir-associated renal toxicity in cohort studies has generally been quite low (0.3–2%). Patients who receive tenofovir as part of (ritonavir-boosted) protease inhibitor-containing HAART appear to be at increased risk (Zimmermann et al, 2006). Other risk factors include advanced HIV infection, old age, low body mass, pre-existing renal failure, and co-administration of didanosine. The risk of renal injury in patients without chronic renal failure who receive tenofovir as part of non-nucleoside reverse transcriptase inhibitor-containing HAART is very low (<1%).

Several reports of Fanconi syndrome (Malik et al, 2005; Davies et al, 2006), an otherwise extremely rare condition, in patients receiving tenofovir are strongly suggestive of a causal link. Patients on tenofovir should be monitored regularly (every 3 months) for features of tubular dysfunction. The combination of proteinuria, hypophosphataemia and glycosuria (with normal blood glucose) are strongly suggestive of Fanconi syndrome. Suspected cases should be referred for nephrological review. The proteinuria of Fanconi syndrome is tubular and will not be detected by measurement of urinary albumin:creatinine ratio or by use of an albumin-based urine stick test. Discontinuation of tenofovir usually leads to resolution of the renal abnormalities.

Assessment of renal function and prevention of kidney disease

In accordance with American guidelines (Gupta et al, 2005), all HIV-infected patients should be screened for the presence of chronic renal disease at the time of HIV diagnosis and/or before commencing antiretroviral therapy. This screening should include estimation of glomerular filtration rate and stick test for proteinuria. Estimation of glomerular filtration rate can be performed by measurement of serum creatinine and application of the Modification of Diet in Renal Disease formula, which requires the patient's age, gender and ethnicity (Gupta et al, 2005). It should be repeated annually thereafter in patients at risk of developing kidney disease (black patients and patients with diabetes mellitus, hypertension, viral hepatitis or proteinuria >1 g/day at baseline, and those not receiving or not responding to antiretroviral therapy). Those HIV patients who have ≥1+ proteinuria should be further assessed by measurement of urine protein/creatinine ratio and in some cases 24-hour urine protein assay (*Figure 1*). Detection and management of hypertension and diabetes is vital. Patients with stage 3 (or worse) chronic kidney disease or with urinary protein/creatinine ratio of >30 mg/mmol should be considered for nephrological review. As most nucleos(t)ide reverse transcriptase inhibitors are renally excreted, these drugs may require dose adjustment in patients who develop renal failure.

Conclusions

Renal complications are common in HIV infection. All patients should be assessed for proteinuria and impaired renal function at the time of HIV diagnosis. Patients with chronic kidney disease should be managed to prevent progressive renal failure and cardiovascular complications. Renal replacement therapy and transplantation are appropriate treatments for HIV-positive patients. BJHM

Table 2. Aetiology of chronic kidney disease in HIV-infected patients

HIV-associated nephropathy
Immune complex glomerulonephritis
Other forms of immune-mediated kidney disease
Diabetes mellitus
Hypertension
Renovascular disease
Drug toxicity
Obstruction

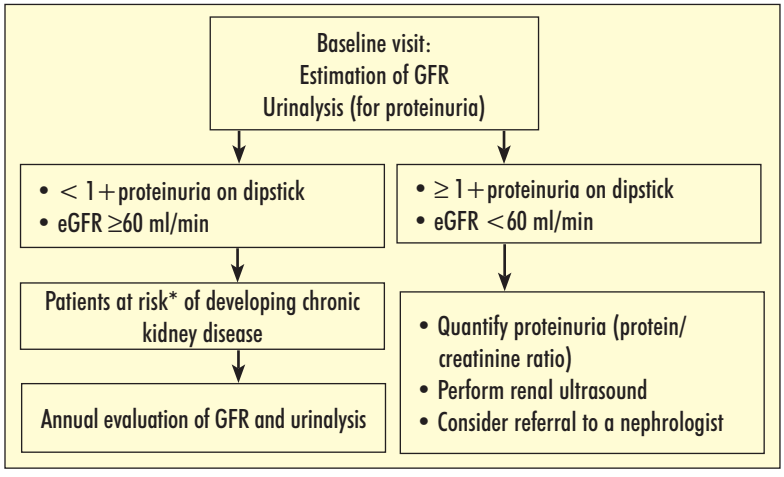

Figure 1. Renal screening algorithm for HIV-infected patients. From Gupta et al (2005). * Risk factors for chronic kidney disease include black ethnicity, diabetes, hypertension, hepatitis C infection, CD4 counts <200 cells/mm³, HIV RNA >4000 copies/ml. eGFR = estimated glomerular filtration rate.

Conflict of interest: Dr FA Post has received travel support, research grants, honoraria or consultancy fees from Boehringer-Ingelheim, Bristol Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, Roche and Tibotec.

Ahuja TS, Borucki M, Funtanilla M, Shahinian V, Hollander M, Rajaraman S (1999) Is the prevalence of HIV-associated nephropathy decreasing? *Am J Nephrol* **19:** 655–9

Ahuja TS, Grady J, Khan S (2002) Changing trends in the survival of dialysis patients with human immunodeficiency virus in the United States. *J Am Soc Nephrol* **13:** 1889–93

Atta MG, Gallant JE, Rahman MH et al (2006) Antiretroviral therapy in the treatment of HIV-associated nephropathy. *Nephrol Dial Transplant* **21:** 2809–13

Bhagani S, Sweny P, Brook G (2006) Guidelines for kidney transplantation in patients with HIV disease. *HIV Med* **7:** 133–9

Campbell L, Tissingh E, Easterbrook PJ, Hendry BM, Post FA (2007) Prevalence, incidence and aetiology of chronic renal failure in a cohort of HIV infected patients. 13th Annual Conference of the British HIV Association (BHIVA) with the British Infection Society (BIS), Edinburgh, 25–28 April: Abstract O28

Carbone L, D'Agati V, Cheng JT, Appel GB (1989) Course and prognosis of human immunodeficiency virus-associated nephropathy. *Am J Med* **87:** 389–95

Chemlal K, Nochy D, Kenouch S, Joly V, Carbon C (2000) Dramatic improvement of renal dysfunction in a human immunodeficiency virus-infected woman treated with highly active antiretroviral therapy. *Clin Infect Dis* **31:** 805–6

KEY POINTS

- Proteinuria is present in up to 30% of HIV-infected patients and a risk factor for renal failure and death.
- Acute renal failure is common in hospitalized patients with opportunistic infections, intravenous drug users and patients co-infected with hepatitis C.
- Chronic kidney disease affects up to 2% of HIV-infected patients.
- Highly active antiretroviral therapy reduces the incidence of acute and chronic renal failure.
- All patients with newly diagnosed HIV infection should be screened for chronic kidney disease, and annually thereafter if at risk of developing chronic kidney disease.
- As life expectancy of HIV-infected patients has dramatically improved with highly active antiretroviral therapy, dialysis should be offered to those with end-stage renal failure.
- Kidney transplantation is an option for HIV-infected patients with completely suppressed HIV replication and CD4 counts >200/mm³.

Davies CLN, Hall AM, Williams IG et al (2006) Tenofovir-associated renal toxicity. Eighth International Congress on Drug Therapy in HIV Infection, Glasgow, 12–16 November: Abstract P149

Franceschini N, Napravnik S, Eron JJ, Jr., Szczech LA, Finn WF (2005) Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. *Kidney Int* **67:** 1526–31

Gagnon RF, Tecimer SN, Watters AK, Tsoukas CM (2000) Prospective study of urinalysis abnormalities in HIV-positive individuals treated with indinavir. *Am J Kidney Dis* **36:** 507–15

Gardner LI, Holmberg SD, Williamson JM et al (2003) Development of proteinuria or elevated serum creatinine and mortality in HIV-infected women. *J Acquir Immune Defic Syndr* **32:** 203–9

Gerntholtz TE, Goetsch SJ, Katz I (2006) HIV-related nephropathy: a South African perspective. *Kidney Int* **69:** 1885–91

Gupta SK, Mamlin BW, Johnson CS, Dollins MD, Topf JM, Dube MP (2004) Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients. *Clin Nephrol* **61:** 1–6

Gupta SK, Eustace JA, Winston JA et al (2005) Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* **40:** 1559–85

Haas M, Kaul S, Eustace JA (2005) HIV-associated immune complex glomerulonephritis with 'lupus-like' features: a clinicopathologic study of 14 cases. *Kidney Int* **67:** 1381–90

Han TM, Naicker S, Ramdial PK, Assounga AG (2006) A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. *Kidney Int* **69:** 2243–50

Herman JS, Ives NJ, Nelson M, Gazzard BG, Easterbrook PJ (2001) Incidence and risk factors for the development of indinavir-associated renal complications. *J Antimicrob Chemother* **48:** 355–60

Izzedine H, Launay-Vacher V, Baumelou A, Deray G (2004) Antiretroviral and immunosuppressive drug-drug interactions: an update. *Kidney Int* **66:** 532–41

Krawczyk CS, Holmberg SD, Moorman AC, Gardner LI, McGwin G Jr (2004) Factors associated with chronic renal failure in HIV-infected ambulatory patients. *AIDS* **18:** 2171–8

Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD (2004) Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS* **18:** 541–6

Malik A, Abraham P, Malik N (2005) Acute renal failure and Fanconi syndrome in an AIDS patient on tenofovir treatment--case report and review of literature. *J Infect* **51:** E61–5

Moreno S, Domingo P, Palacios R et al (2006) Renal safety of tenofovir disoproxil fumarate in HIV-1 treatment-experienced patients with adverse events related to prior NRTI use: data from a prospective, observational, multicenter study. *J Acquir Immune Defic Syndr* **42:** 385–7

Qiu J, Terasaki PI, Waki K, Cai J, Gjertson DW (2006) HIV-positive renal recipients can achieve survival rates similar to those of HIV-negative patients. *Transplantation* **81:** 1658–61

Roe J, Campbell L, Easterbrook PJ, Hendry BM, Post FA (2007) Acute renal failure in a cohort of HIV infected patients. 13th Annual Conference of the British HIV Association (BHIVA) with the British Infection Society (BIS), Edinburgh, 25–28 April: Abstract O27

Staszewski S, Pozniak AL, Lu B, Enejosa J, Cheng A (2005) Similar renal safety profile between tenofovir DF (TDF) and stavudine (d4T) using Modification of Diet in Renal Disease (MDRD) and Cockroft-Gault (CG) estimation of glomerular filtration rate (GFR) in antiretroviral-naive patients through 144 weeks. 10th European AIDS Conference (EACS) Dublin, Ireland, 17–20 November

Szczech LA, Gange SJ, van der Horst C et al (2002) Predictors of proteinuria and renal failure among women with HIV infection. *Kidney Int* **61:** 195–202

Szczech LA, Gupta SK, Habash R et al (2004) The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int* **66:** 1145–52

Winston JA, Bruggeman LA, Ross MD et al (2001) Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med* **344:** 1979–84

Wyatt CM, Arons RR, Klotman PE, Klotman ME (2006) Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. *Aids* **20:** 561–5

Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G (2006) Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* **42:** 283–90