Recent developments in HIV and the kidney
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Introduction
After HIV infection, the dramatic reduction in the incidence of opportunistic infections as a result of highly active antiretroviral therapy (HAART) has resulted in a shift of health concern toward chronic morbidities including renal dysfunction. The traditional problems of HIV-associated nephropathy (HIVAN), HIV-associated immune complex kidney disease (HIVICK), and thrombotic microangiopathy (TMA) remain important due to late diagnosis of HIV infection, or unavailability or nonresponse to HAART. In this review, we will highlight the changing patterns of HIV-related renal disease in the HAART era.

Acute renal failure
Prior to the availability of HAART, acute renal failure (ARF) was common, largely related to opportunistic infections, and often heralded a poor outcome [1]. A study from New York suggested that the incidence of ARF in hospitalized HIV-infected patients might have increased in the HAART era, from 2.9% in 1995 to 6% in 2003. However, the incidence of ARF also increased in HIV negative patients during this period. Thus, it is possible the disease severity of patients admitted to hospital has changed, or that ARF is now increasingly recognized [2].

ARF is mostly due to acute tubular necrosis (ATN) [3]. Risk factors for developing ARF include advanced HIV infection and hepatitis C co-infection [4]. These observations were confirmed in a recently published study from London, UK. This large, single-center cohort study showed an ARF incidence of 5.7%. The cohort comprised 6% intravenous (i.v.) drug users and a 10% prevalence of hepatitis C. The majority of ARF episodes occurred within 3 months of initiating HIV care, typically before HAART was commenced or took full effect. After 3 months of treatment, the incidence of ARF was around 15-fold lower and averaged 1.1 per 100 person-years. Drugs and reduced renal blood flow each contributed to acute renal injury in some 70% of patients [5].

Chronic kidney disease
Chronic kidney disease (CKD) is an important complication of HIV infection. In biopsy series, HIVAN, noncollapsing focal and segmental glomerulosclerosis...
(FSGS), and HIVICK predominate [6–8]. HIVAN is characterized by heavy proteinuria and high rates of progression to end-stage renal disease (ESRD). On the contrary, patients with early HIVAN lesions may have normal renal function, microalbuminuria, or mild proteinuria [9], and renal function may remain stable for many years following HAART initiation [10]. HIVAN and other forms of severe CKD, however, are likely to be overrepresented in renal biopsy series.

Several recent studies have defined the prevalence of CKD in the HAART era. In five cross-sectional cohort studies from Europe, Asia, and North America, 406 of 7362 patients (5.5%, range 4.7–8.7%) had stages 3–5 CKD [estimated glomerular filtration rate (eGFR) < 60 ml/min for more than 3 months] [11]. In the largest study, patients with CKD were older, had lower CD4 cell count nadirs, and had more often been diagnosed with AIDS, diabetes, or hypertension. In multivariate analysis, any use of indinavir (IDV) [odds ratio (OR) 2.49] or tenofovir (TFV) (OR 2.18) and cumulative exposure to IDV (OR 1.15 per year of exposure) or TFV (OR 1.60) were associated with increased odds of CKD [11**].

When proteinuria, defined as having at least 1+ on dipstick [12,14], or urine protein/creatinine ratio (PCR) of more than 0.3 mg/mg (~30 mg/mmol) [13], and reduced eGFR were combined to define CKD, 346 out of 2034 (17.0%, range 15.5–21.1%) patients had evidence of CKD [12–14]. Multivariate analysis identified older age, lower CD4 cell count, and use of IDV among Chinese [13] and older age, lower CD4 cell count, African–American ethnicity, hepatitis C infection, and hypertension as independent predictors of CKD among North American HIV-infected patients [12,14]. However, the nature of the association between hepatitis C infection and CKD remains unclear, and this association was not observed in European patients [11**] and neither in cross-sectional analysis (OR 0.69) nor in longitudinal analysis [hazard ratio (0.90) of 13 139 American HIV-infected patients [16].

End-stage renal disease

African–American patients with advanced HIV infection are at increased risk of developing ESRD, and an ‘epidemic’ of ESRD has long been recognized in this population [17]. The cause of CKD and severity of kidney disease at renal diagnosis are likely to be of major importance in predicting renal outcome in HIV patients [6,8,10]. Patients with HIVAN, compared with those with other renal diagnoses, have more rapid progression to ESRD [6,8], and early HAART initiation may reduce the incidence of HIVAN [18]. Among African–Americans, the risk of requiring permanent renal replacement therapy (RRT) was 16.2-fold higher for those with AIDS and 6.7-fold higher for HIV patients without AIDS, compared with those without HIV infection. As patient survival improved in the HAART era, more patients developed ESRD and initiated RRT (5.8 per 1000 person-years in the pre-HAART era, 9.7 per 1000 person-years in the HAART era) [19**]. However, median survival for those who initiated dialysis in the HAART era remained poor and unchanged from that in the pre-HAART era (19.9 vs. 22.4 months, $P = 0.94$) [20].

Among African–Americans, HIV and diabetes mellitus confer similar risk of developing ESRD (hazard ratios 4.56 and 4.15) compared with white patients, in whom HIV infection is not associated with an increased risk of ESRD (hazard ratio 0.76) [21]. Among patients with stages 3–5 CKD, the incidence of ESRD was 71.1 for black and 11.3 per 1000 person-years for white HIV positive patients. Black patients with baseline eGFR measurements of 30–60 ml/min experienced significantly more rapid declines in renal function compared with white patients [22]. In the United States, patients with CKD more often have diabetes mellitus, cardiovascular complications, dementia, hepatitis C, and AIDS, and they are less likely to receive HAART compared with patients without CKD. When HAART is administered, dosing errors are frequent. Patients with CKD are at increased risk of death, which may be partly explained by reduced HAART use [23].

Renal transplantation in HIV-infected patients

Successful renal transplantation in HIV-infected patients is now well established. Two recent studies, comprising 26 HIV-infected renal allograft recipients, have added to this experience [24**,25]. In the largest study, 18 patients were followed for a median of 4 years. Three-year patient survival was 94%, with no deaths attributable to immunodeficiency or malignancy, and 3-year graft survival was 84%. Half of all patients experienced delayed graft function, and four grafts were lost to severe acute rejection (day 8), vascular thrombosis (day 8), and chronic rejection (days 1174 and 1773). Both patient and graft survival were similar to the results obtained in (older) non-HIV-infected US transplant recipients. The 1-year, 2-year, and 3-year cumulative incidences of rejection were 52, 64, and 73%, respectively, with 78% of episodes due to acute cellular rejection [24**]. The other study followed eight patients for a median of 15 months. At the end of this period, 100% of patients were alive, 88% with functioning grafts. A single patient sequentially developed BK nephropathy, cytomegalovirus infection, and acute rejection before losing graft function 11 months after transplantation. No opportunistic infections or malignancies were observed, and all patients maintained viral suppression and CD4 cell counts more
than 200 cells/μl [25]. The complexities of coadministration of antiretroviral and immunosuppressive regimens are well recognized and highlighted in a study of 97 pharmacokinetic evaluations in 35 HIV-infected kidney and liver transplant recipients [26*].

**Effects of highly active antiretroviral therapy on renal function**

Patients who initiate HAART may experience improvement in renal function, no change or modest decline in renal function, or overt renal toxicity. The effects of HAART on eGFR were recently examined in a large cohort study. Patients with no CKD had stable renal function following HAART initiation (annual eGFR decline of 0.2 ml/min), whereas patients with stage 1 CKD experienced a decline of 2.9 ml/min/year, whereas eGFR improved at a rate of 2.8 ml/min/year in patients with stage 2 CKD. Renal function improved most in patients with impaired eGFR and CD4 cell counts less than 200 cells/μl at baseline [27]. In two African cohorts, improvements in eGFR were observed during the first 2 years of HAART. Renal function improved most in patients with abnormal renal function at baseline [28,29]. The clinical significance of these generally small or modest changes in renal function remains unclear.

Drug-induced renal dysfunction has been reported with nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine), the nucleotide reverse transcriptase inhibitor TFV, protease inhibitors (IDV, atazanavir, nelfinavir, ritonavir, and saquinavir), and the fusion inhibitor enfuvirtide. The complexities of coadministration of antiretroviral and immunosuppressive regimens are well recognized and highlighted in a study of 97 pharmacokinetic evaluations in 35 HIV-infected kidney and liver transplant recipients [26*].

Although the exact cause of TFV-associated tubular dysfunction remains unclear, it is likely to be multifactorial and dependent upon a complex interaction of genetic, environmental, and pharmacological effects. Increased nephrotoxic potential may result from higher systemic TFV exposure, for example, TFV clearance is reduced by 17% in patients who take lopinavir/ritonavir [41], and there may be an interaction between ritonavir and tubular efflux of TFV mediated through multidrug resistant proteins 2 or 4 or both (MRP2/ABCC2 and MRP4/ABCC4) [42]. In addition, polymorphisms exist for the genes encoding these tubular efflux transporters [43], which may influence intracellular levels of TFV (Fig. 1). Intracellular concentrations of TFV may determine the degree of mitochondrial disruption as measured by mitochondrial DNA depletion and respiratory chain enzyme dysfunction, an effect that may be enhanced by didanosine [44]. Of note, in-vitro studies have not confirmed a straightforward dose-related effect of TFV on proximal tubular injury results in Fanconi syndrome, with phosphaturia, glycosuria, and aminoaciduria. Boosted protease inhibitors appear to increase the nephrotoxic potential of TFV, as Fanconi syndrome is almost exclusively observed in patients who receive TFV with (boosted) protease inhibitors [37], and patients who take TFV with boosted protease inhibitors experience greater decline in renal function compared with patients in whom TFV is used together with nonnucleoside reverse transcriptase inhibitors (NNRTI) [38–40].

TFV is widely used in the management of HIV infection and has an excellent safety profile, with serious renal adverse events reported in 0.5% and elevations in serum creatinine in 2.2% of patients. Older age, reduced renal function at baseline, low body weight, low CD4 cell count, and concomitant nephrotoxic medications may predispose to nephrotoxicity [35]. TFV is excreted through glomerular filtration and active secretion in the proximal tubule. Proximal tubular dysfunction, which may result in reduced phosphate reabsorption, hypophosphatemia and/or renal tubular acidosis, may be observed in one-third of patients [36]. However, tubular function may be affected by other drugs, HIV infection itself, and the endocrine environment. In its most severe form, proximal tubular injury results in Fanconi syndrome, with phosphaturia, glycosuria, and aminoaciduria. Boosted protease inhibitors appear to increase the nephrotoxic potential of TFV, as Fanconi syndrome is almost exclusively observed in patients who receive TFV with (boosted) protease inhibitors [37], and patients who take TFV with boosted protease inhibitors experience greater decline in renal function compared with patients in whom TFV is used together with nonnucleoside reverse transcriptase inhibitors (NNRTI) [38–40].

There are four organic anion transporters (OATs) of which OAT 1 and 3 appear to be most important for tenofovir (TFV) uptake. TFV excretion is through a family of 14 multidrug resistance-associated proteins (MRPs), the most important of which are MRP2 (also known as ABCC2: ATP-binding cassette, subfamily C member 2) and MRP4 (ABCC4). Of note, MRP2 activity is inhibited by ritonavir (RTV). Genetic polymorphisms in ABCC2 or ABCC4 may also affect the function of these transporters, potentially resulting in increased intracellular TFV concentrations.

**Figure 1 Simplified diagram of tenofovir transport through proximal tubular cells**

![Diagram of tenofovir transport through proximal tubular cells](https://example.com/diagram)

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The potential effects of TFV or proximal tubular dysfunction on bone mineralization are of concern. Several cross-sectional studies have documented low bone mass in patients with HIV infection [47]. Hypophosphatemia due to renal tubular phosphate wasting could worsen this problem. However, serum phosphate levels are difficult to interpret as they vary with diet and time of sampling, and hypophosphatemia is common in routinely collected blood samples irrespective of TFV use [48]. In randomized clinical trials of patients who received TFV as part of NNRTI-based HAART, bone mineral density has remained stable following an initial decline of approximately 2.5% [49].

Markers of renal injury
Persistent proteinuria may be present in one-third of HIV positive patients [14,50,51], though most studies suggest a prevalence of approximately 10% across different populations [9,12,13,52–54]. Proteinuria is a risk factor for renal failure and death [50,55], and its presence should prompt exclusion of other causes such as diabetes mellitus, hypertension, or other glomerular diseases. Proteinuria in HIV infection may be predominantly of low molecular weight and tubular in origin, and its significance is not well understood. In order to distinguish glomerular proteinuria from tubular proteinuria, it may be useful to compare urinary albumin/creatinine ratio (ACR) with PCR [56]. Significant albuminuria reflects a high molecular weight protein leak due to glomerular injury, and renal biopsy may be helpful. HIV per se does not appear to confer additional risks to renal biopsy, which continues to be the gold standard investigation when the cause of proteinuria is unclear [57].

HIV infection is independently associated with microalbuminuria (OR 5.11). Older age, African–American ethnicity, insulin resistance, elevated systolic blood pressure, family history of hypertension, and presence of glycosuria are associated with microalbuminuria. The severity of microalbuminuria is inversely related to CD4 cell count [58]. A study of microalbuminuria in women found prior AIDS and greater HIV RNA level to be associated with higher ACR. Black ethnicity, higher ACR, and greater HIV RNA level at baseline predicted a greater ACR at 6–12 months’ follow-up, whereas the use of HAART was associated with decreased ACR at follow-up [59]. In the diabetic and hypertensive populations, microalbuminuria is seen as an endothelial ‘distress signal’ and signifies enhanced cardiovascular risk [60]. The factors associated with microalbuminuria in HIV infection suggest a similar relationship, though a pilot study of HIV-infected patients with albuminuria or proteinuria failed to show evidence of endothelial dysfunction as assessed by flow-mediated vascular dilatation [61].

As creatinine-based markers of renal function may be affected by muscle mass and antiretroviral-induced inhibition of tubular creatinine secretion, the usefulness of other markers is under investigation. Cystatin C is a low molecular weight cysteine proteinase produced by nucleated cells and cleared by glomerular filtration and is neither influenced by muscle mass nor liver function. One study found higher cystatin C levels in 1008 HIV-infected patients compared with HIV negative controls, despite similar serum creatinine levels and eGFR. HIV-infected patients were more likely to have cystatin C levels of more than 1.0 mg/l (OR 9.8), a threshold associated with increased risk for death, cardiovascular and kidney disease in HIV negative elderly patients [62]. Another study compared cystatin C to creatinine-based eGFR assessments in 250 HIV-infected patients on HAART and noted a greater proportion of patients (15.2 vs. 2.4%) to have impaired renal function (eGFR < 60 ml/min) when cystatin C was used to evaluate kidney function [63]. At present, cystatin C cannot be considered a useful measurement of kidney function in HIV-infected patients or as predictor of progression.

Conclusion
Over the past 18 months, our knowledge of HIV-associated kidney disease has advanced dramatically. HAART may reduce the incidence of HIVAN and the progression of CKD to ESRD. However, prolonged survival afforded by HAART allows more patients to develop CKD due to age-related decline in renal function, vascular and metabolic diseases, obstructive uropathy, or drug-associated renal injury. This will pose challenges in terms of the number of patients requiring renal evaluation and dialysis. Renal transplantation is likely to further develop as a treatment modality but remains restricted by the limited availability of donor organs.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
● of special interest
• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 95).


13. This fascinating 15-year study showed a 10-fold higher incidence of ESRD among HIV-infected African-Americans compared with uninfected patients. It describes the changing epidemiology of CKD in the HAART era, and that the incidence of CKD and mortality among patients with CKD has declined, whereas the prevalence of CKD and the incidence of RRT have increased.


21. In this article, protease inhibitors dramatically increase trough concentrations of cyclosporine, tacrolimus, and sirolimus.


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A US study looking at parameters associated with microalbuminuria in HIV-infected patients showed traditional risk factors for vascular disease were highly represented in the albuminuric group, and HIV infection conferred additional risk of albuminuria. However, it excluded proteinuric patients based on dipstick urinalysis, and such a cross-sectional study may be affected by survival bias.


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