



CKJ REVIEW

HIV and kidney diseases: 35 years of history and consequences

Pedro Campos¹, Alberto Ortiz^{2,3} and Karina Soto^{1,3,4}

¹Nephrology Department, Hospital Fernando Fonseca, Lisbon, Portugal, ²IIS-Fundación Jiménez Díaz, School of Medicine, UAM and IRSIN, Madrid, Spain, ³Iberoamerican CKD Research Network (IBERERC), Madrid, Spain, and ⁴Chronic Diseases Research Center-CEDOC-FCM, Nova Medical School, Lisbon, Lisbon, Portugal

Correspondence and offprint requests to: Karina Soto; E-mail: ksoto.nefro@gmail.com

Abstract

Kidney diseases in human immunodeficiency virus (HIV)-infected patients are often misdiagnosed. Despite reductions in morbidity and mortality owing to widespread use of highly effective combination antiretroviral therapy (cART), acute kidney injury (AKI) and chronic kidney disease (CKD) are still more common in these patients than in the general population, and are associated with poor health outcomes. HIV-associated nephropathy and HIV immune complex kidney diseases are the more recognizable HIV-related kidney diseases. However, a broad spectrum of kidney disorders related or not directly related with HIV infection can be observed, including cART-induced AKI, CKD, proximal tubular dysfunction, crystalluria and urolithiasis, among others. This review summarizes the major epidemiologic studies of kidney diseases in HIV-infected patients, discusses novel approaches that may potentially limit nephrotoxicity such as the use of tenofovir alafenamide, and outlines current screening measures for early diagnosis of kidney dysfunction or tubular damage, and for accurate detection of increased risk for acute or chronic kidney diseases.

Key words: acute kidney injury, antiretroviral, chronic kidney disease, HIV, nephropathy

Introduction

Human immunodeficiency virus (HIV) infection is the infectious disease of our time. The 2015 UNAIDS report estimates that 36.9 million people are infected and 2 million new cases are detected yearly [1]. In little more than two decades combination antiretroviral therapy (cART) has dramatically changed the HIV reality, from a fatal disease to a chronic controlled condition, improving survival and allowing patients to lead long productive lives [2]. Despite this, HIV infection was a leading cause of death worldwide in the past 23 years [3]. In this regard, HIV-infected patients are still at higher risk for both acute kidney injury (AKI) and chronic kidney disease (CKD), which are interconnected syndromes responsible for a heavy burden of mortality [4]. However,

key changes have occurred in past 35 years regarding the aetiology of kidney disease, i.e. a decrease in glomerular disease and an increase of nephrotoxicity, diabetes mellitus and nephroangiosclerosis [5–7]

Kidney disease in HIV-infected patients

The first description of severe proteinuria with a rapid loss of kidney function in HIV-infected patients with advanced acquired immune deficiency syndrome (AIDS) was published in 1984 [8]. The histopathological pattern corresponded to collapsing focal segmental glomerulosclerosis (FSGS), a condition, later known as HIV-associated nephropathy (HIVAN), that usually presents

Received: April 29, 2016. Accepted: September 15, 2016

© The Author 2016. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

high-grade proteinuria and rapid progression to end-stage renal disease (ESRD). Although HIVAN is the best known example of HIV-associated kidney disease, a large spectrum of kidney syndromes is now known to occur in HIV-infected patients, as outlined in Table 1 [9, 10].

HIVAN and HIVICK

Kidney damage in HIVAN results from a variety of mechanisms including direct viral cell injury and host susceptibility factors [5]. Viral infection of podocytes and tubular epithelial cells induces dedifferentiation, proliferation and apoptosis. Different viral gene products are key determinants for these processes [11]. Infiltrating leukocytes express two HIV co-receptors [12], meaning that HIV also infects infiltrating lymphocytes and macrophages, which release inflammatory mediators promoting further kidney injury. Recent data suggest a genetic host susceptibility to HIVAN [13]. Two recessive variants of the APOL1 gene,

present mainly in Africans, provide protection against *Trypanosoma brucei rhodesiensis* infection, but play a critical role in the development of FSGS in response to diverse kidney insults, conferring susceptibility to HIVAN in the African American population [14]. Both HIVAN and HIV immune complex kidney disease (HIVICK) were observed predominantly in African Americans [15], although in Europe HIVICK was mainly observed in non-Africans [16]. The main histologic patterns of glomerulopathy in Black South Africans were the 'classic HIVAN' (27%) and 'HIVICK' (21%) [17].

Both HIVAN and HIVICK are more frequent in individuals of African ancestry. Compared with HIVAN, HIVICK patients have more antiretroviral therapy exposure, lower viral loads, and higher CD4 and eGFR [10, 15, 18, 19]. Indeed, HIVICK is far less likely to progress to ESRD than HIVAN [15].

HIV infection is commonly associated with repeated infections and polyclonal immunoglobulin expansion, generating a susceptibility to immune complex formation with subsequent

Table 1. Differential diagnosis of kidney disease in HIV-infected patients [5, 9, 13]

Acute kidney injury
Common HIV non-specific causes
Opportunistic infections ^a
Kidney hypoperfusion and ischaemia
Acute interstitial nephritis
Rhabdomyolysis
Urinary tract obstruction: blood clots, fungus balls or crystalluria ^b
HIV-specific glomerulopathies ^a
Drugs ^b
Chronic kidney disease
HIV-specific glomerulopathies ^a
HIV-associated nephropathy (HIVAN)
HIV immune complex kidney disease (HIVICK)
Immune complex-mediated glomerulonephritis
Post-infectious glomerulonephritis
Immunoglobulin A nephritis
Mixed sclerotic/inflammatory disease
Membranous glomerulopathy
Lupus-like disease
Thrombotic microangiopathy
Common HIV non-specific glomerulopathies ^b
HCV-related membranoproliferative glomerulonephritis/cryoglobulinemia
Amyloidosis
Classic FSGS
Diabetic nephropathy
Minimal change disease
Nephroangiosclerosis
Drugs ^c
Fluid and electrolyte disorders
Disorders of osmolality
Potassium disorders
Acid-based disorders
Antiretroviral nephrotoxicity ^c
AKI: abacavir, atazanavir, didanosine, indinavir, ritonavir, saquinavir, tenofovir
CKD: abacavir, atazanavir, indinavir, lopinavir, tenofovir
Acute interstitial nephritis: abacavir, atazanavir, indinavir
Fanconi syndrome: tenofovir, didanosine, abacavir
Renal tubular acidosis: lamivudine, stavudine,
Crystalluria, lithiasis: indinavir, atazanavir and (rare): nelfinavir, amprenavir
Nephrogenic diabetes insipidus: didanosine, tenofovir
Others

HIV, human immunodeficiency virus; HCV, hepatitis virus C; FSGS, focal segmental glomerulosclerosis; AKI, acute kidney injury; CKD, chronic kidney disease.

^aLess common since combination antiretroviral therapy (cART) introduction.

^bMore common since cART introduction.

^cIncluding antiretroviral drugs listed in Antiretroviral nephrotoxicity.

kidney deposition, giving rise to HIVICK. Viral replication and the immune responses to viral proteins and other infection-related antigens are thought to contribute to the spectrum of immune-mediated glomerulonephritis that encompasses HIVICK [15].

Acute kidney injury in HIV-infected patients

AKI is more frequent in HIV-infected individuals than in the non-infected general population [20]. HIV infection is an independent risk factor for AKI in hospitalized and community-dwelling patients. The incidence of AKI is variable according to different literature sources and comparisons are difficult, as most studies were retrospective and used diverse AKI diagnosis criteria, mainly based on clinical judgment [20]. However, incidence of AKI appears to have decreased with widespread cART use, when AKI is diagnosed by using the new classification criteria [21, 22]. In any case, AKI remains common.

In the developed world and in the cART era, the incidence of AKI in ambulatory HIV-infected patients was reported to range from 2.7 to 6.9 per 100 person-years [21, 23–25]. The incidence differed between early and late-onset AKI, being more than 10-fold lower after the initial 3 months of HIV care [23]. This suggests that cART and control of opportunistic infections are associated with decreased risk of AKI.

Among hospitalized patients AKI occurs at 2–3 times the rate observed in uninfected controls [20] and the incidence ranges between 6 and 18% [20, 22, 26]. The highest AKI incidence, as expected, was observed in intensive care unit settings, ranging from 47 to 66%. The main risk factors were previous comorbidities such as CKD and illness severity [27, 28].

In general, AKI in HIV-infected individuals is more frequently related to severe opportunistic infections than to direct cART toxicity [20–22, 29].

In the pre-cART era, volume depletion, sepsis and nephrotoxicity were the leading causes, with 38% of AKI cases being pre-renal [30]. Vascular or glomerular diseases and drug-induced microtubular obstruction were common findings in biopsies among patients with AKI [30]. In the cART-era, the decrease in opportunistic infections and mortality and the increase in non-HIV comorbidities changed the incidence of AKI [23]. However, the aetiology remains diverse and mainly multifactorial, with most of the cases caused by more than two contributing factors [21]. Pre-renal causes such as volume depletion, sepsis and liver disease remain important factors, especially in severe AKI cases [21].

In different settings nephrotoxicity accounted for up to 30% of AKI episodes [28]. Medications frequently used to treat HIV-related infections have been associated with AKI, such as aminoglycosides, pentamidine, amphotericin and trimethoprim/sulfamethoxazole, and antivirals such as acyclovir and fos-carnet, among others. Roe and colleagues showed that cART toxicity may account for 14% of late-onset AKI [21], as discussed in detail below. Nonsteroidal anti-inflammatory drugs or iodinated contrasts may also cause AKI. Urinary obstruction-induced AKI is relatively rare and causes include nephrolithiasis and medication-induced crystalluria [20, 31, 32]. Many other factors may contribute to the susceptibility for developing AKI in HIV patients [24, 31, 33–35] and individual antiretroviral drug toxicity is rarely implicated as the sole cause of AKI [21, 24].

Risk factors for AKI did not differ substantially between the pre-cART and cART era. Among ambulatory patients, underlying CKD, AIDS and HCV co-infection are major risk factors [21, 23, 24, 29, 36]. In comparison, among hospitalized patients AKI has been associated with older age, previous CKD, diabetes and also with HCV co-infection [20, 22]. In a prospective analysis, 35% of HIV/

HCV co-infected individuals developed AKI compared with 17% of mono-infected HCV subjects, suggesting that HIV-related factors such as cART could play a more significant role in AKI risk than HCV infection per se [36].

Short- and long-term mortality is increased in AKI-HIV patients, as shown by a 5-fold increased in-hospital mortality in those patients [20]. In a Portuguese cohort of 489 HIV hospitalized patients, mortality was 27.3% in AKI versus 8% for non-AKI patients [26]. Moreover, long-term mortality is higher in HIV patients with AKI, the cumulative probability of death at 5 years being 31.3% compared with 16.5% in non-AKI HIV [37]. Recent data suggest that the incidence of dialysis-requiring AKI among hospitalized HIV patients has increased from 0.7 to 1.36% between 2002 and 2010, and severe AKI remains a significant predictor of in-hospital mortality [38]. Additionally, AKI in HIV-infected patients is associated with a high risk of adverse outcomes beyond mortality, including heart failure and ESRD [39].

Chronic kidney disease in HIV-infected patients

In the contemporary era of cART, CKD has emerged as a cause of morbidity and mortality in HIV patients [40]. Both HIV infection and the adverse effects of cART have been linked to CKD. However, the global burden of CKD in the HIV population remains difficult to estimate [5, 16, 41] due to differences in the studied populations, historic periods, settings, and also in the estimated glomerular filtration rate (eGFR) equations used [18, 42, 43]. The reported prevalence of CKD (eGFR <60 mL/min/1.73 m²) among HIV-infected persons in North America and Europe ranges from 4.7 to 9.7%, but was as high as 33% when defined by either reduced GFR or pathological proteinuria [44, 45]. CKD was higher when combining HIV related with traditional risk factors, such as diabetes and hypertension [41, 46]. In HIV-infected African populations the reported prevalence of CKD ranges between 3.5 and 48.5% [47].

Studies in Brazil have reported CKD prevalence rates from 3.8 to 8.4% [48, 49]. In a prospective Portuguese study, the prevalence of CKD was 5.9% in a cohort of 1281 patients using the creatinine (SCr)-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate GFR [50]. In a subsequent assessment of 966 patients from the same cohort, CKD prevalence was 3.9%, 4.4% and 6.1% when assessed by SCr-based CKD-EPI or Modification of Diet in Renal Disease (MDRD) and serum Cystatin C-based CKD-EPI equations, respectively [51].

In longitudinal studies the reported incidence of kidney function decline among HIV patients ranges from 3.3 to 11.2 per 1000 person-years [41, 46, 52]. In cross-sectional studies the prevalence of declining kidney function ranges from 4% to 17% in different populations [52, 53].

Recently, the EuroSIDA study reported that only 0.64% of 9044 patients developed advanced CKD/ESRD/renal death during a median follow-up of 5.0 years, with an incidence rate of 1.32 per 1000 person-years follow-up. At 6 years from baseline, 0.83% were estimated to have experienced the endpoint overall. Predictors of the endpoint included any cardiovascular event and lower eGFR or CD4 count [54].

The prevalence of CKD defined by eGFR and/or proteinuria among cART-naïve patients was 6.2% in a recent study [55], mostly accounted for by the isolated proteinuria CKD criterion, being only 0.5% due to eGFR <60 mL/min/1.73 m² [55].

The prevalence of CKD in the general population has been reported to be close to 10%, as exemplified by the Spanish EPIRCE study [56]. Some studies show a lower CKD prevalence in HIV patients than in the general population. However, at least

three reasons may explain this apparent contradiction: (i) mean prevalence rates in the general population are mainly driven by the elderly, who are generally not well represented in HIV cohorts; (ii) SCr-based equations may overestimate eGFR in HIV patients with decreased muscle mass; and (iii) the very sensitive urinary albuminuria/creatinine ratio (uACR) >30 mg/g criterion was used in general population studies, following KDIGO CKD diagnostic criteria [57], whereas albuminuria was not considered for CKD diagnosis in several HIV cohort studies.

Traditional risk factors for CKD are becoming increasingly prevalent in HIV-infected populations, including aging, diabetes mellitus, hypertension, cardiovascular disease, previous AKI and race/ethnicity [55]. Risk factors for CKD in HIV-persons are therefore a combination of traditional and HIV-related factors including low CD4 counts, high viral load, intravenous drug use, HCV co-infection and also cART, mainly tenofovir, indinavir, lopinavir/ritonavir, atazanavir/ritonavir and abacavir [44, 47, 48, 58–60]. In this regard, a quarter of HIV-infected patients are co-infected by HCV and co-infection with HCV may cause specific immune complex-mediated kidney disease [61–63]. Multiple concurrent risk factors for CKD may have a cumulative effect in HIV-infected individuals [64]. In this regard, diabetic nephropathy and nephroangiosclerosis are becoming important causes of CKD. In a German renal biopsy study, immune complex-mediated glomerulonephritis (26.1%), hypertensive (20.3%) and diabetic nephropathy (20.3%) were the most frequent causes of CKD in HIV patients and the latter two accounted for over 50% of cases in more recent years [65], while arterionephrosclerosis was the most common kidney diagnosis in a post-mortem American series [7]. Diabetic nephropathy was the cause of ESRD in 14% of HIV-positive patients in Spain [6]. Indeed, nephropathy was more common in HIV-infected than uninfected diabetic patients [66], and expression of an HIV transgene aggravated kidney injury in diabetic mice [67].

The increasing prevalence of age-associated nephropathies is not surprising. On one hand, as HIV patients are living longer, they are also getting older. In 2010, individuals older than 55 years old comprised ~20% of the people living with HIV in the USA. The CDC estimates that by 2015, >50% of individuals infected with HIV in the USA will be over 50 years old. On the other, chronic HIV infection is associated with accelerated aging despite apparent viral control, and therefore is associated with early onset of diseases linked to aging, including CKD [68]. As an example, HIV infection is associated with a significant increase in DNA methylation in brain tissue and blood, as an epigenetic biomarker of aging [69].

An HIV-specific CKD risk model score (D:A:D score) has been proposed to calculate the long-term risk of developing CKD using readily available clinical factors [70]. This model includes both traditional and HIV-related risk factors and could be used for identifying patients at high risk of CKD, estimating the increased risk when a new potential nephrotoxic drug is added to the cART regimen, and thus aiding in decision-making in daily clinical practice.

The nephrotoxicity of antiretroviral therapy

The introduction of cART completely changed HIV disease progression and life expectancy. However, some cART drugs require dose adjustment or are contraindicated in advanced CKD stages. As an example of a very widely used drug with nephrotoxic potential, tenofovir disoproxil fumarate dose should be adjusted when baseline creatinine clearance is below 50 mL/min and combinations of tenofovir with emtricitabine are not recommended

when creatinine clearance is below 30–50 mL/min, depending on the specific combination [71]. In addition, there is increasing evidence that cART can lead to a wide variety of nephrotoxic effects, including both AKI and CKD [24, 33, 34]. The potential insidious long-term kidney toxicity of cART leading to CKD progression is probably underappreciated. The cART drugs usually associated with CKD include indinavir, atazanavir, tenofovir disoproxil fumarate and lopinavir/ritonavir [33, 72]. Mechanisms of nephrotoxicity are summarized in Table 2 and risk factors in Table 3.

AKI related to cART is more frequent in the first year of therapy, but severe kidney dysfunction is rare [33]. The incidence of AKI decreased 10-fold after the first 3 months of cART but on the other side, cART toxicity causes 14% of all AKI episodes occurring at least 3 months after cART initiation [21]. Of note, in that study, indinavir contributed to 50% of cART-related AKI. The use of indinavir has decreased dramatically in more developed countries.

Since HIV patients are frequently exposed to multiple drug regimens, deleterious interactions can be difficult to define and AKI is frequently defined as multifactorial. Nevertheless, besides AKI and CKD, cART can cause an array of nephrotoxic effects (summarized in Table 2).

The incidence of advanced-stage CKD associated with cART toxicity is low, most likely because close monitoring of eGFR in most cohort allows cART discontinuation as soon as GFR decline is detected.

Protease inhibitors. Nephrotoxicity due to protease inhibitors (PIs), mainly indinavir and atazanavir, is related to the formation of urinary crystals, and development of nephrolithiasis, acute or chronic interstitial nephritis, crystal-induced nephropathy, AKI or CKD [20, 21, 32, 34, 73–75].

Although indinavir is now less frequently used in high income countries because of its potential for crystalluria (67%) and kidney stones (3%), it is still used in resource-limited settings [34, 74]. Low indinavir solubility in alkaline urine is the primary cause leading to intratubular crystals and stones. Risk factors for crystalluria include volume depletion, warm and/or alkaline urine, low BMI, high drug concentrations and co-administration with another nephrotoxic drug [76].

Atazanavir has largely replaced indinavir in cART as it has a better safety profile. However, approximately 7% of atazanavir is excreted unchanged in urine and due to its poor solubility, has the potential for crystalline precipitation at physiologic urine pH: the frequency of lithiasis ranges from 7.3 to 23.7 per 1000 person-years [73, 77]. Ritonavir-boosted atazanavir exposure has also the potential to cause crystalluria and urolithiasis, and acute, chronic or granulomatous interstitial nephritis [32, 73, 74]. The overall prevalence of symptomatic urolithiasis due to atazanavir crystals has been estimated at 0.97% [78]. In epidemiological studies, exposure to atazanavir was associated with a higher incidence of renal stones than other PI-based regimens [79]. In medium- and long-term therapy, crystalluria and nephrolithiasis are commonly associated with high atazanavir concentrations [80].

Ritonavir toxicity is most likely a result of drug interactions rather than a direct kidney effect. Other PIs such as nelfinavir, amprenavir, saquinavir, ritonavir and darunavir have also been reported to cause urolithiasis or to crystallize in urine [74].

Nucleoside analogue reverse transcriptase inhibitors (NRTI). Nucleoside analogues such as lamivudine, stavudine and didanosine are excreted in urine and dose adjustment is required in presence

Table 2. Manifestations of antiretroviral toxicity [10, 13, 33, 34, 73]

Antiretroviral group	Kidney damage mechanism	Kidney manifestations
NRTI		
Abacavir	Inhibition of mitochondrial DNA polymerase; oxidative phosphorylation and endogenous nucleotide kinases	AKI, AIN (case report)
Didanosine		Fanconi or Fanconi-like syndrome
Lamivudine		Type B lactic acidosis
Stavudine		Nephrogenic diabetes insipidus (case reports)
Zidovudine		
NtRTI		
Tenofovir	Direct proximal tubular epithelial cells toxicity Intracellular accumulation Mitochondrial depletion	Fanconi syndrome Nephrogenic diabetes insipidus AKI Osteomalacia
NNRTI		
Efavirenz	Unknown	Minimal change disease (case report)
Nevirapine	Hypersensitivity	Urolithiasis (case report) AKI (case reports)
Protease inhibitors		
Indinavir	Intratubular drug precipitation due to poor solubility (mainly for indinavir, atazanavir)	AKI and CKD
Atazanavir		Acute and chronic interstitial nephritis
Nelfinavir		Nephrolithiasis, asymptomatic crystalluria, crystal nephropathy
Amprenavir		Papillary necrosis
Saquinavir		
Lopinavir		
Ritonavir		
Integrase inhibitors		
Raltegravir	Skeletal muscle toxicity	Rhabdomyolysis and AKI (case reports)

NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase; NNRTI, non-nucleoside reverse transcriptase inhibitor; AKI, acute kidney injury; AIN, acute interstitial nephritis; CKD, chronic kidney disease.

Table 3. Predisposing factors for kidney impairment in HIV-infected patients [18, 70]

Factors associated with kidney impairment
Previous kidney disease
Uncontrolled HIV infection
Time under ART
Older age
Female gender
African background: APOL1 genetic variants
CD4 count <200 cells/mm ³
Use of nephrotoxic drugs

HIV, human immunodeficiency virus; ART, antiretroviral therapy.

of decreased GFR, but direct nephrotoxicity is rare. However, their chronic use may cause mitochondrial dysfunction leading to type B lactic acidosis by inhibiting DNA polymerase- γ [81]. This effect in proximal tubular cells could explain the generalized proximal tubule dysfunction (Fanconi syndrome) associated with stavudine and lamivudine [82]. The prevalence and severity of lactic acidosis related with long-term NRTIs toxicity can increase in the presence of coexistent hepatocellular injury and reduced lactate metabolism, which can be more frequent in HIV patients because of co-infections or hepatotoxicity [81].

Nucleotide reverse transcriptase inhibitors (NtRTI). Tenofovir, adefovir and cidofovir are NtRTI capable of inducing renal tubular injury. Tenofovir is usually used as disoproxil fumarate and we will discuss this formulation in this section, only briefly mentioning the potential for lower nephrotoxicity with a novel formulation, tenofovir alafenamide. The most common nephrotoxic

effect is tenofovir-induced proximal tubular cell damage. Tenofovir is a first-line treatment of HIV infection and is currently used in approximately half of all cART regimens [33, 34]. Although large prospective trials support the general renal safety of tenofovir disoproxil fumarate [83], its safety profile is still debated, since cases of AKI, proximal tubular dysfunction and CKD have been frequently reported when using tenofovir disoproxil fumarate in clinical practice settings [84]. Tenofovir is excreted unchanged in the urine and it is cleared by a combination of glomerular filtration and proximal tubular secretion. Active transport is required for its uptake through basolateral human organic ion transporter-1 and for secretion to the tubular lumen through the apical transporter MRP4 (multidrug resistance-associated protein 4) [85]. Dysfunction of efflux transporters leads to drug accumulation into the proximal tubular cells resulting in mitochondrial injury [86] by a mechanism distinct from NRTIs, as it does not inhibit DNA polymerase- γ [87]. In recent case series inhibition of basolateral uptake of tenofovir seemed to protect against tubular injury [88].

Tenofovir disoproxil fumarate-induced AKI has been reported in 0.7–10% of patients and subclinical proximal tubular dysfunction developed in 22–81% of cases [89, 90]. Tubular toxicity was associated with higher tenofovir plasma concentrations [91] and with cumulative exposure to atazanavir and tenofovir [92]. Evidence of tenofovir-induced kidney tubular dysfunction includes Fanconi syndrome, increased excretion of tubular proteins, hyperphosphaturia/hypophosphataemia, glycosuria, metabolic acidosis and hypokalaemia [93]. Biopsy-proven AKI cases revealed toxic acute tubular necrosis, with distinctive proximal tubular eosinophilic inclusions representing giant mitochondria visible by light microscopy and mitochondrial enlargement, depletion and dysmorphic changes by electron

microscopy [87]. These are also the major ultrastructural findings in tenofovir-induced proximal tubular toxicity [94].

Case reports and more recently epidemiological studies observed that tenofovir disoproxil fumarate decreases eGFR at rates comparable to diabetic nephropathy [86]. The number of proximal tubular abnormalities was linearly associated with eGFR decline since tenofovir initiation [95]. Tenofovir disoproxil fumarate also causes chronic tubulointerstitial nephritis, which may account for the lack of reversibility in some individuals [96]. Therefore, concern exists about the long-term safety of tenofovir disoproxil fumarate, especially in patients with prior kidney abnormalities and/or concomitant exposure to nephrotoxic agents. In a recent retrospective analysis of a prospective French HIV cohort of patients starting ART with baseline eGFR >60 mL/min/1.73 m², CKD incidence was 9.6 per 1000 patient-years. The incidence was highest in patients treated with boosted PI including tenofovir disoproxil fumarate and having a high D:A:D risk score for CKD, but no impact was observed in patients with a low risk score [97]. In HIV individuals with normal baseline kidney function, the association between exposure to cARTs and CKD development appears to be cumulative, as shown by the D:A:D study [75]. In a median follow-up of 7.2 years, the incidence of CKD was 1.76 per 1000 patient-years and significantly increased with each additional year of exposure to tenofovir disoproxil fumarate, atazanavir/ritonavir and lopinavir/ritonavir. Although the absolute number of new CKD cases was modest, treatment with these cARTs appeared to result in an increasing and cumulative risk of CKD.

In conclusion, it is prudent to limit exposure to tenofovir disoproxil fumarate in patients with risk factors for nephrotoxicity and to replace the drug in case of early features of nephrotoxicity. A new formulation of tenofovir, tenofovir alafenamide, appears to have reduced kidney toxicity as assessed by serum creatinine and proteinuria, although hard end-points were not assessed [98–100]. Indeed, switching to a tenofovir alafenamide-containing regimen from one containing tenofovir disoproxil fumarate led to higher eGFR and improved bone mineral density [101]. Tenofovir alafenamide favours drug-uptake into immune cells at low plasma concentrations, and not being a substrate for renal

organic anion transporters, does not accumulate in proximal tubular cells. Initial results showed slight declines in eGFR and small increase in proximal tubular dysfunction markers. An ongoing open-label study is evaluating the safety of tenofovir alafenamide in patients with creatinine clearance between 30 and 69 mL/min. However, whether tenofovir alafenamide may lead to nephrotoxicity under specific circumstances is unknown; there is no 'real-world' experience, which is where tenofovir disoproxil fumarate nephrotoxicity became apparent, and tenofovir alafenamide renal safety in patients with CKD has not been addressed in randomized controlled trials (RCTs) [102]. In this regard, a recent RCT comparing the two tenofovir formulations did not find any case of proximal tubular dysfunction with either drug [103].

Other factors associated to kidney disease in the HIV-infected population

Increased survival of HIV patients under cART has led to complex interactions of HIV infection with prevalent chronic diseases of the developed world. Some of these prevalent diseases may lead to kidney disease. Despite a progressive decrease in the rate of HIV-specific kidney diseases with widespread use of cART, the incidence of CKD [5, 10, 18, 41] and the geographical differences appear to remain stable, pointing to the role of other environmental factors or genetic susceptibility in the pathogenesis of the disease. Diabetes, metabolic syndrome, hypertension and atherosclerosis may synergize with HIV infection or cART to accelerate the loss of kidney function, leading to CKD presenting as decreased eGFR, increased urinary protein excretion or other abnormal urinary findings.

Therefore, it remains challenging to distinguish cART-related nephrotoxicity from direct effects of HIV or non-HIV-related kidney diseases.

Monitoring kidney dysfunction

In general, kidney function in HIV-infected patients declines slowly, being clinically unapparent. Therefore, a baseline

Table 4. Recommended approach to kidney injury screening in HIV-infected patients [104, 105]

Approach to kidney screening	Abnormality	Actions ^a twice yearly in stable patients
Blood pressure measurement	>140/90 mmHg	Revise therapy
Glomerular filtration rate	<60 mL/min/1.73 m ² or rapid decrease	Search cause, including nephrotoxicity
Serum creatinine based eGFR (CKD-EPI equation)		Nephrology referral
Serum cystatin C based eGFR (CKD-EPI equation)		Change to quarterly evaluation
Glomerular injury		
uACR	>30 mg/g	Search for kidney disease (consider biopsy)
uPCR	>150 mg/g	Search for glomerular disease
uAPR	>0.4	Consider tubulopathy, search for specific protein lost in urine
Urinary sediment (check also for crystals!)	Crystalluria Hematuria	Search for cART toxicity Search for glomerular disease
Proximal tubulopathy		
Urine dipstick	Abnormal	If proteins: quantify uACR/uPCR If blood: sediment If leukocytes: sediment, culture
Glycosuria	Present	Check for Diabetes Mellitus or cART toxicity
FePi	>10%	Search for cART toxicity
FeUrate	>20%	Search for cART toxicity

HIV, human immunodeficiency virus; eGFR, estimated glomerular filtration rate; uPCR, urinary protein creatinine ratio; uACR, urinary albumin creatinine ratio; uAPR, urinary albumin protein ratio; FePi, fractional excretion of phosphate; FeUrate, fractional excretion of urate; cART, combined antiretroviral therapy.

^aValues should be confirmed.

assessment of glomerular and tubular function should be made at the time of diagnosis and on initiation or change of cART. Regular screening for nephrotoxicity should be performed at least yearly in stable patients using the same eGFR estimation method to identify changes over time. CKD or at-risk patients must be monitored more frequently. Different guidelines have been proposed recently [104, 105]. Our recommended approach is shown in Table 4.

SCr and eGFR based on SCr must be interpreted with care in HIV patients. Despite standardization of SCr assays, GFR estimation by the SCr-based MDRD or CKD-EPI equations is still fairly imprecise, especially in patients with muscle mass different from expected for sex and age. HIV-infected patients often present with muscle wasting, which can lower SCr and falsely suggest the presence of normal kidney function [106]. Cystatin C is a new filtration biomarker generated at a fairly constant rate in nucleated cells, freely filtered in the glomerulus and totally excreted. The CKD-EPI group has developed equations based on Cystatin C and on its combination with SCr, which appear more suitable for estimating GFR in this population [107]. Nephrotoxicity is mainly presented as tubular injury, therefore to assess tubular function urinary albumin/creatinine (uACR) and urinary protein/creatinine (uPCR) ratios allows the calculation of the uACR/uPCR ratio (uAPR). A uAPR <0.4 suggests the excretion of low molecular weight proteins that arise from tubular failure to reabsorb filtered low molecular weight proteins such as light chains [108]. A uAPR <0.4 in association with increased uric acid and phosphorus excretion fractions appears to be highly sensitive and specific for proximal tubular injury. The presence of crystalluria may also point to potential nephrotoxicity, although the value of crystalluria to predict development of CKD has not been tested.

Implementation of risk score models as part of routine care would allow graded consideration of the safest drugs when initiating and switching antiretrovirals, as well as identifying individuals who require more intensive kidney monitoring [70]. The D:A:D risk score helps to individualize the risk for cART-nephrotoxicity and CKD development. Nevertheless, it still lacks accurate biomarkers of early tubular toxicity associated to the HIV-specific risk score for CKD to be applied at the point of care. Fractional excretion of phosphate showed a good performance as an early marker of tubular dysfunction, and should be incorporated as a tool of CKD prediction. Urinary phosphate wasting was a sensitive marker for tenofovir-induced proximal tubular dysfunction and was associated with unrecognized and permanent kidney function decline [109]. However, prediction risk models are not yet broadly implemented in routine clinical practice, although implementation has the potential to increase the safety of ART [110].

If there is suspicion of cART-induced proximal tubular injury, the following tests should be performed if not already available in the setting of routine monitoring: glycosuria and blood glucose, uAPR, and uric acid and phosphorus excretion fractions.

Therapeutic approach to the patient with CKD and HIV infection

Standard therapies for CKD applied to the general population are recommended to prevent CKD progression in HIV patients, including appropriate management of cardiovascular risk factors like albuminuria, diabetes, dyslipidemia and blood pressure control. Avoiding nephrotoxic agents is also recommended to preserve kidney function [104, 105].

Nephrologist referral is recommended when eGFR decreases by more than 25% from baseline, to less than 60 mL/min/

1.73 m² or if there is evidence of glomerular or tubular damage [105]. In case of CKD progression to ESRD, HIV patients on renal replacement therapies have similar survival rates to other kidney disease patients and the choice of haemodialysis or peritoneal dialysis does not appear to impact survival. Selected ESRD HIV-infected patients can be recipients of kidney transplant with good graft survival if eligibility criteria are met [111].

Conclusions

In summary, HIV infection may promote kidney injury due to direct infection of kidney cells or because of immune response to viral antigens or opportunistic agents. Additional risk for kidney injury results from cART, therapy for other infections and the concomitant presence of other chronic diseases associated with kidney injury. An improved understanding of the pathogenesis of these complex interactions may allow the development of novel tools to monitor kidney health, allowing early diagnosis of kidney dysfunction. As therapy for HIV continues to evolve, nephrologists must keep abreast of current developments in order to provide the best care to this population.

Acknowledgements

Grant support includes FEDER funds and FIS ISCIII-RETIC REDinREN RD12/0021, PI13/00047, Comunidad de Madrid (CIFRA S2010/BMD-2378), CYTED IBERERC, Programa Intensificación Actividad Investigadora (ISCIII/Agencia Laín-Entralgo/CM) to A.O., FCT (Fundação para a Ciência e Tecnologia) EXPL/DTP-FTO/1792/2013 to K.S. and P.C., and SPN2013 (Sociedade Portuguesa de Nefrologia) Fundos de Investigação de 2013 to K.S. and P.C.

Conflict of interest statement

None declared.

References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). *AIDS by the Numbers*. Joint United Nations Programme on HIV/AIDS (UNAIDS). http://www.unaids.org/sites/default/files/media_asset/AIDS-by-the-numbers-2016_en.pdf. 1211 Geneva 27, Switzerland, 2016
2. Selik RM, Byers RH, Dworkin MS. Trends in diseases reported on U.S. death certificates that mentioned HIV infection, 1987–1999. *J Acquir Immune Defic Syndr* 2002; 29: 378–387
3. Correction Naghavi M, Wang H, Lozano R et al. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 385: 117–171
4. Couser WG, Remuzzi G, Mendis S et al. The contribution of chronic kidney disease to the global burden of major non-communicable diseases. *Kidney Int* 2011; 80: 1258–1270
5. Rosenberg AZ, Naicker S, Winkler CA et al. HIV-associated nephropathies: epidemiology, pathology, mechanisms and treatment. *Nat Rev Nephrol* 2015; 11: 150–160
6. Saracho R, Martín Escobar E, Comas Farnés J et al. Clinical evolution of chronic renal patients with HIV infection in replacement therapy. *Nefrología* 2015; 35: 457–464
7. Wyatt CM, Morgello S, Katz-Malamed R et al. The spectrum of kidney disease in patients with AIDS in the era of antiretroviral therapy. *Kidney Int* 2009; 75: 428–434

8. Rao TK, Filippone EJ, Nicastrì AD *et al*. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1984; 310: 669–673
9. Bigé N, Lantermier F, Viard J-P *et al*. Presentation of HIV-associated nephropathy and outcome in HAART-treated patients. *Nephrol Dial Transplant* 2012; 27: 1114–1121
13. Mallipattu SK, Wyatt CM, He JC. The new epidemiology of HIV-related kidney disease. *J AIDS Clin Res* 2012; Suppl 4: 1–6.
10. Kumar N, Perazella MA. Differentiating HIV-associated nephropathy from antiretroviral drug-induced nephropathy: a clinical challenge. *Curr HIV/AIDS Rep* 2014; 11: 202–211
11. Canaud G, Dejuqç-Rainsford N, Avettand-Fenoël V *et al*. The kidney as a reservoir for HIV-1 after renal transplantation. *J Am Soc Nephrol* 2014; 25: 407–419
12. Eitner F, Cui Y, Hudkins KL *et al*. Chemokine receptor CCR5 and CXCR4 expression in HIV-associated kidney disease. *J Am Soc Nephrol* 2000; 11: 856–867
14. Kasembeli AN, Duarte R, Ramsay M *et al*. APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans. *J Am Soc Nephrol* 2015; 26:2882–90
15. Foy MC, Estrella MM, Lucas GM *et al*. Comparison of risk factors and outcomes in HIV immune complex kidney disease and HIV-associated nephropathy. *Clin J Am Soc Nephrol* 2013; 8: 1524–1532
16. Nochy D, Glotz D, Dosquet P *et al*. Renal-disease associated with HIV infection—a multicentric study of 60 patients from Paris hospitals. *Nephrol Dial Transplant* 1993; 8: 11–19
17. Gerntholtz TE, Goetsch SJW, Katz I. HIV-related nephropathy: a South African perspective. *Kidney Int* 2006; 69: 1885–1891
18. Naicker S, Rahmanian S, Kopp JB. HIV and chronic kidney disease. *Clin Nephrol* 2015; 83: 32–38
19. Booth JW, Hamzah L, Jose S *et al*. Clinical characteristics and outcomes of HIV-associated immune complex kidney disease. *Nephrol Dial Transplant* 2016; January 18, 2016 doi:10.1093/ndt/gfv436
20. Wyatt CM, Arons RR, Klotman PE *et al*. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. *AIDS* 2006; 20: 561–565
21. Roe J, Campbell LJ, Ibrahim F *et al*. HIV care and the incidence of acute renal failure. *Clin Infect Dis* 2008; 47: 242–249
22. Li Y, Shlipak MG, Grunfeld C *et al*. Incidence and risk factors for acute kidney injury in HIV infection. *Am J Nephrol* 2012; 35: 327–334
23. Kalim S, Szczech LA, Wyatt CM. Acute kidney injury in HIV-infected patients. *Semin Nephrol* 2008; 28: 556–562
24. Wikman P, Safont P, Del Palacio M *et al*. The significance of antiretroviral-associated acute kidney injury in a cohort of ambulatory human immunodeficiency virus-infected patients. *Nephrol Dial Transplant* 2013; 28: 2073–2081
25. Franceschini N, Napravnik S, Eron JJ *et al*. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. *Kidney Int* 2005; 67: 1526–1531
26. Lopes JA, Melo MJ, Viegas A *et al*. Acute kidney injury in hospitalized HIV-infected patients: a cohort analysis. *Nephrol Dial Transplant* 2011; 26: 3888–3894
27. Lopes JA, Fernandes J, Jorge S *et al*. An assessment of the RIFLE criteria for acute renal failure in critically ill HIV-infected patients. *Crit Care* 2007; 26: 915–21
28. Randall D, Brima N, Walker D *et al*. Acute kidney injury among HIV-infected patients admitted to the intensive care unit. *Int J STD AIDS* 2014; 26: 915–21
29. Ibrahim F, Naftalin C, Cheserem E *et al*. Immunodeficiency and renal impairment are risk factors for HIV-associated acute renal failure. *AIDS* 2010; 24: 2239–2244
30. Rao TKS, Friedman EA. Outcome of severe acute renal failure in patients with acquired immunodeficiency syndrome. *Am J Kidney Dis* 1995; 25: 390–398
31. Perazella MA. Acute renal failure in HIV-infected patients: a brief review of common causes. *Am J Med Sci* 2000; 319: 385–391
32. Coelho S, Aparicio SR, Manso R *et al*. Quiz page June 2012: kidney failure in an HIV-positive patient. *Am J Kidney Dis* 2012; 59: 3–6
33. Kalyesubula R, Perazella MA. Nephrotoxicity of HAART. *AIDS Res Treat* 2011; 2011: doi: 10.1155/2011/562790
34. Jao J, Wyatt CM. Antiretroviral medications: adverse effects on the kidney. *Adv Chronic Kidney Dis* 2010; 17: 72–82
35. Ortiz A, Justo P, Sanz A *et al*. Tubular cell apoptosis and didanosine-induced acute renal failure. *Antivir Ther* 2005; 10: 185–190
36. Garg S, Hoenig M, Edwards EM *et al*. Incidence and predictors of acute kidney injury in an urban cohort of subjects with HIV and hepatitis C virus coinfection. *AIDS Patient Care STDs* 2011; 25: 135–141
37. Lopes JA, Melo MJ, Raimundo M *et al*. Long-term risk of mortality for acute kidney injury in HIV-infected patients: a cohort analysis. *BMC Nephrol* 2013; 14: 32
38. Nadkarni GN, Patel AA, Yacoub R *et al*. The burden of dialysis-requiring acute kidney injury among hospitalized adults with HIV infection: a nationwide inpatient sample analysis. *Aids* 2015; 29: 1061–1066
39. Choi AI, Li YM, Parikh C *et al*. Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int* 2010; 78: 478–485
40. Sackoff JE, Hanna DB, Pfeiffer MB *et al*. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* 2006; 145: 397–406
41. Lucas GM, Lau B, Atta MG *et al*. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. *J Infect Dis* 2008; 197: 1548–1557
42. Okparavero AA, Tighiouart H, Krishnasami Z *et al*. Use of glomerular filtration rate estimating equations for drug dosing in HIV-positive patients. *Antivir Ther* 2013; 18: 793–802
43. Mocroft A, Kirk O, Gatell J *et al*. Chronic renal failure among HIV-1-infected patients. *AIDS* 2007; 21: 1119–1127
44. Gupta SK, Mamlin BW, Johnson CS. Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients. *Clin Nephrol* 2004; 61: 1–6
45. Szczech LA, Gange SJ, Van der Horst C *et al*. Predictors of proteinuria and renal failure among women with HIV infection. *Kidney Int* 2002; 61: 195–202
46. Mocroft A, Kirk O, Reiss P *et al*. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS* 2010; 24: 1667–1678
47. Stanifer JW, Jing B, Tolan S *et al*. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* 2014; 2: 174–181
48. Santiago P, Grinsztejn B, Friedman RK *et al*. Screening for decreased glomerular filtration rate and associated risk factors in a cohort of HIV-infected patients in a middle-income country. *PLoS One* 2014; 9: e93748
49. Menezes AM, Torelly J Jr, Real L *et al*. Prevalence and risk factors associated to chronic kidney disease in HIV-infected patients on HAART and undetectable viral load in Brazil. *PLoS One* 2011; 6: e26042
50. Campos P, Batista J, Fidalgo P *et al*. Prevalence of chronic kidney disease in HIV patients. *Antiretroviral therapy and*

- proteinuria as risk factors. Abstract presented at World Congress of Nephrology 2013
51. Campos P, Dias C, Batista J et al. Chronic kidney disease evolution in HIV-infected patients, two years of follow-up. *Nephrol Dial Transplant* 2014; 29 (Suppl 3): iii: 373
 52. Lucas GM, Mehta SH, Atta MG et al. End-stage renal disease and chronic kidney disease in a cohort of African-American HIV-infected and at-risk HIV-seronegative participants followed between 1988 and 2004. *AIDS* 2007; 21: 2435–2443
 53. Fernando SK, Finkelstein FO, Moore BA et al. Prevalence of chronic kidney disease in an urban HIV infected population. *Am J Med Sci* 2008; 335: 89–94
 54. Ryom L, Kirk O, Lundgren JD et al. Advanced chronic kidney disease, end-stage renal disease and renal death among HIV-positive individuals in Europe. *HIV Med* 2013; 14: 503–508
 55. Achhra AC, Mocroft A, Ross M et al. Kidney disease in antiretroviral-naïve HIV-positive adults with high CD4 counts: prevalence and predictors of kidney disease at enrolment in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV Med* 2015; 16: 55–63
 56. Otero A, de Francisco A, Gayoso P et al. Prevalence of chronic renal disease in Spain: results of the EPIRCE study. *Nefrologia* 2010; 30: 78–86
 57. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; 3: 4
 58. Jotwani V, Li Y, Grunfeld C et al. Risk factors for ESRD in HIV-infected individuals: traditional and HIV-related factors. *Am J Kidney Dis* 2012; 59: 628–635
 59. Ryom L, Mocroft A, Kirk O et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis* 2013; 207: 1359–1369
 60. Scherzer R, Estrella M, Li Y et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS* 2012; 26: 867–875
 61. Wyatt C, Malvestutto C. The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis. *AIDS* 2008; 22: 1799–1807
 62. Mocroft A, Neuhaus J, Peters L et al. Hepatitis B and C coinfection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults. *PLoS One* 2012; 7: 1–9
 63. George E, Nadkarni GN, Estrella MM et al. The impact of hepatitis C coinfection on kidney disease related to human immunodeficiency virus (HIV): a biopsy study. *Medicine (Baltimore)* 2011; 90: 289–295
 64. Ryom L, Mocroft A, Kirk O et al. Predictors of advanced chronic kidney disease and end-stage renal disease in HIV-positive persons. *AIDS* 2014; 28: 187–199
 65. Jung O, Haack HS, Brodt HR et al. Changing spectrum of renal disease in HIV infection. *Dtsch Med Wochenschr* 2013; 138: 1887–1891
 66. Pilay S, Aldous C, Mahomed F. A deadly combination—HIV and diabetes mellitus: where are we now? *S Afr Med J* 2016; 106: 54
 67. Mallipattu SK, Liu R, Zhong Y et al. Expression of HIV transgene aggravates kidney injury in diabetic mice. *Kidney Int* 2013; 83: 626–634
 68. High KP, Brennan-Ing M, Clifford DB et al. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *J Acquir Immune Defic Syndr* 2012; 60 (Suppl 1): S1–S18
 69. Horvath S, Levine AJ. HIV-1 infection accelerates age according to the epigenetic clock. *J Infect Dis* 2015; 212: 1563–1573
 70. Mocroft A, Lundgren JD, Ross M et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. *PLoS Med* 2015; 12: 1–31
 71. Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/44/arv-dosing-for-renal-or-hepatic-insufficiency>
 72. Flandre P, Pugliese P, Cuzin L et al. Risk factors of chronic kidney disease in HIV-infected patients. *Clin J Am Soc Nephrol* 2011; 6: 1700–1707
 73. Hara M, Suganuma A, Yanagisawa N et al. Atazanavir nephrotoxicity. *Clin Kidney J* 2015; 8: 137–142
 74. Izzedine H, Lescure FX, Bonnet F. HIV medication-based urolithiasis. *Clin Kidney J* 2014; 7: 121–126
 75. Mocroft A, Lundgren JD, Ross M et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. *Lancet HIV* 2016; 3: 23–32
 76. Salahuddin S, Kok DJ, Buchholz NN-P. Influence of body temperature on indinavir crystallization under loop of Henle conditions. *J Antimicrob Chemother* 2006; 59: 114–117
 77. Wood R. Atazanavir: its role in HIV treatment. *Expert Rev Anti Infect Ther* 2008; 6: 785–796
 78. Couzigou C, Daudon M, Meynard JL et al. Urolithiasis in HIV-positive patients treated with atazanavir. *Clin Infect Dis* 2007; 45: e105–e108
 79. Hamada Y, Nishijima T, Watanabe K et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis* 2012; 55: 1262–1269
 80. Gervasoni C, Meraviglia P, Minisci D et al. Metabolic and kidney disorders correlate with high atazanavir concentrations in HIV-infected patients: is it time to revise atazanavir dosages? *PLoS One* 2015; 10: 1–12
 81. Dagan T, Sable C, Bray J et al. Mitochondrial dysfunction and antiretroviral nucleoside analog toxicities: what is the evidence? *Mitochondrion* 2002; 1: 397–412
 82. Nelson M, Azwa A, Sokwala A et al. Fanconi syndrome and lactic acidosis associated with stavudine and lamivudine therapy. *AIDS* 2008; 22: 1374–1376
 83. Nelson MR, Katlama C, Montaner JS et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS* 2007; 21: 1273–1281
 84. Cooper RD, Wiebe N, Smith N et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010; 51: 496–505
 85. Imaoka T, Kusuhara H, Adachi M et al. Functional involvement of multidrug resistance-associated protein 4 (MRP4/ABCC4) in the renal elimination of the antiviral drugs adefovir and tenofovir. *Mol Pharmacol* 2006; 71: 619–627
 86. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat* 2011; 2011: 354908
 87. Herlitz LC, Mohan S, Stokes MB et al. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney Int* 2010; 78: 1171–1177

88. Izzedine H, Thibault V, Valantin M. Tenofovir/probenecid combination in HIV/HBV-coinfected patients: how to escape Fanconi syndrome recurrence? *AIDS* 2010; 24: 1078–1079
89. Rodríguez-Nóvoa S, Labarga P, Soriano V et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. *Clin Infect Dis* 2009; 48: e108–e116
90. Labarga P, Barreiro P, Martin-Carbonero L et al. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. *AIDS* 2009; 23: 689–696
91. Ezinga M, Wetzels JFM, Bosch MEW et al. Long-term treatment with tenofovir: prevalence of kidney tubular dysfunction and its association with tenofovir plasma concentration. *Antivir Ther* 2014; 19: 765–771
92. Dauchy F-A, Lawson-Ayayi S, de La Faille R et al. Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy. *Kidney Int* 2011; 80: 302–309
93. Rifkin B, Perazella M. Tenofovir-associated nephrotoxicity: Fanconi syndrome and renal failure. *Am J Med* 2004; 15: 282–284
94. Cote H, Magil A, Harris M. Exploring mitochondrial nephrotoxicity as a potential mechanism of kidney dysfunction among HIV-infected patients on highly active antiretroviral therapy. *Antivir Ther* 2006; 11: 79–86
95. Casado JL, Banon S, Santiuste C et al. Prevalence and significance of proximal renal tubular abnormalities in HIV-infected patients receiving tenofovir. *AIDS* 2016; 30: 231–239
96. Perazella MA. Tenofovir-induced kidney disease: an acquired renal tubular mitochondriopathy. *Kidney Int* 2010; 78: 1060–1063
97. Flandre P, Pugliese P, Allavena C et al. Does first line antiretroviral regimen impact risk for chronic kidney disease whatever the risk-group? *AIDS* 2016; 30: 1433–8
98. Wyatt CM. Will a new tenofovir prodrug for the treatment of HIV reduce the risk of nephrotoxicity? *Kidney Int* 2016; 89: 5–6
99. Milburn J, Jones R, Levy JB. Renal effects of novel antiretroviral drugs. *Nephrol Dial Transplant* 2016. doi: 10.1093/ndt/gfw064
100. Sax PE, Wohl D, Yin MT et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2016; 385: 2606–2615
101. Mills A, Arribas JR, Andrade-Villanueva J et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis* 2016; 16: 43–52
102. Aloy B, Tazi I, Bagnis CI et al. Tenofovir: is tenofovir alafenamide safer than tenofovir disoproxil fumarate for the kidneys? *AIDS Rev* 2016; Jul 19; !8(4) [Epub ahead of print]
103. Gallant JE, Daar ES, Raffi F et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV* 2016; 3: e158–e165
104. Lucas GM, Ross MJ, Stock PG et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV medicine association of the infectious diseases society of America. *Clin Infect Dis* 2014; 59: e96–e138
105. Gorriz JL, Gutierrez F, Trullas JC et al. Consensus document on the management of renal disease in HIV-infected patients. *Nefrologia* 2014; 34 (Suppl 2): 1–81
106. Inker LA, Schmid CH, Tighiouart H et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; 367: 20–29
107. Seape T, Gouden V, Deventer H et al. Cystatin C- and creatinine-based equations in the assessment of renal function in HIV-positive patients prior to commencing highly active antiretroviral therapy. *Ann Clin Biochem* 2016; 53: 58–66
108. Wu MT, Lam KK, Lee WC et al. Albuminuria, proteinuria, and urinary albumin to protein ratio in chronic kidney disease. *J Clin Lab Anal* 2012; 26: 82–92
109. Waheed S, Attia D, Estrella MM et al. Proximal tubular dysfunction and kidney injury associated with tenofovir in HIV patients: a case series. *Clin Kidney J* 2015; 8: 420–425
110. Scherzer R, Shlipak MG. Risk factors: individual assessment of CKD risk in HIV-positive patients. *Nat Rev Nephrol* 2015; 11: 392–393
111. Ahuja TS, Collinge N, Grady J et al. Is dialysis modality a factor in survival of patients with ESRD and HIV-associated nephropathy? *Am J Kidney Dis* 2003; 41: 1060–1064