

Update on current management of chronic kidney disease in patients with HIV infection

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Abstract: The prevalence of HIV-associated chronic kidney disease (CKD) varies geographically and depends on the definition of CKD used, ranging from 4.7% to 38% globally. The incidence, however, has decreased with the use of effective combined antiretroviral therapy (cART). A wide variety of histological patterns are seen in HIV-associated kidney diseases that include glomerular and tubulointerstitial pathology. In resource-rich settings, there has been a plateau in the incidence of end-stage renal disease secondary to HIV-associated nephropathy (HIVAN). However, the prevalence of end-stage renal disease in HIV-positive individuals has risen, mainly due to increased longevity on cART. There is a disparity in the occurrence of HIVAN among HIV-positive individuals such that there is an 18- to 50-fold increased risk of developing kidney disease among HIV-positive individuals of African descent aged between 20 and 64 years and who have a poorer prognosis compared with their European descent counterparts, suggesting that genetic factors play a vital role. Other risk factors include male sex, low CD4 counts, and high viral load. Improvement in renal function has been observed after initiation of cART in patients with HIV-associated CKD. Treatment with an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker is recommended, when clinically indicated in patients with confirmed or suspected HIVAN or clinically significant albuminuria. Other standard management approaches for patients with CKD are recommended. These include addressing other cardiovascular risk factors (appropriate use of statins and aspirin, weight loss, cessation of smoking), avoidance of nephrotoxins, and management of serum bicarbonate and uric acid, anemia, calcium, and phosphate abnormalities. Early diagnosis of kidney disease by screening of HIV-positive individuals for the presence of kidney disease is critical for the optimal management of these patients. Screening for the presence of kidney disease upon detection of HIV infection and annually thereafter in high-risk populations is recommended.

Keywords: chronic kidney disease, HIV infection, current management

Background

Approximately 36.9 million people worldwide were living with HIV infection in 2014,¹ during which 2 million (1.9–2.2 million) new infections with HIV had occurred. Sub-Saharan Africa is the most affected region, with 25.8 (24–28.7) million people with HIV and ~70% of new infections.

Prevalence of HIV-associated chronic kidney disease

The prevalence of HIV-associated chronic kidney disease (CKD) varies geographically and depends on the definition of CKD used. In North America and Europe, HIV-associated CKD prevalence ranges from 4.7%–9.7% (CKD being defined as

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estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m²).²⁻⁴ The prevalence increases with a change in definition to include a reduced eGFR and/or proteinuria.^{5,6} Using this definition, the prevalence of CKD in the US was reported at 15.5%.⁷ Approximately 16.8% of HIV-positive Chinese patients from Hong Kong were reported to have CKD (defined as eGFR <60 mL/min per 1.73 m² and/or proteinuria for >3 months).⁸ Screening studies defining persistent proteinuria as an indicator of CKD revealed prevalence rates of 27% in India, 12.3% in Iran, and 5.6% in Brazil.⁹⁻¹¹ In HIV-positive individuals in Africa, the prevalence of renal disease is widely variable: 38% in Nigeria,¹² 33.5% in Zambia,¹³ 26% in Cote d'Ivoire,¹⁴ 20% in Uganda,¹⁵ 11.5% in Kenya,¹⁶ and 5.5%–6% in South Africa.^{17,18} This variation is attributed to genetic heterogeneity and inconsistency in access to care, initiation of combined antiretroviral therapy (cART), reporting methods, and CKD definition.

While the incidence of end-stage renal disease (ESRD) in HIV-positive individuals has decreased over time, they are still more likely than HIV-negative individuals to develop ESRD.¹⁹ There is a twofold to 20-fold greater risk of ESRD compared with the general population, with incidence rates in the US and Europe of three to ten per 1,000 person-years in HIV-positive individuals versus 0.5 per 1,000 person-years in HIV-negative individuals.²⁰⁻²³ There is also a significant racial disparity in the burden of ESRD, with a six times higher risk borne by individuals of African origin.^{19,22,24}

Spectrum of HIV-associated CKD

A wide variety of histological patterns are seen in HIV-associated kidney diseases that include glomerular and tubulointerstitial pathology (Table 1).

HIV-associated nephropathy (HIVAN) is best defined. HIVAN characteristically presents with heavy proteinuria, reduced eGFR, and echogenic kidneys on ultrasound.²⁵⁻²⁷ Histologically, HIVAN is characterized by collapsing focal segmental glomerulosclerosis (FSGS), microcystically dilated tubules, and tubulointerstitial inflammation (typically comprising macrophages and T cells; Figure 1).²⁸⁻³² It usually occurs in states of advanced immunosuppression and in young adults of African ancestry. There is an 18-fold increased risk of developing HIVAN in people of African descent compared with those of European descent.³³ In the US, it has been reported in 3.5%–10% of HIV-positive individuals. The prevalence in African biopsy series varies greatly: 5%–27% in Johannesburg,^{18,34,35} 55%–57.3% in Cape Town,^{36,37} 70% in Nigeria,¹² and 83% in Durban.¹⁷ Prior to the use of cART, it progressed rapidly to ESRD. The incidence, however, has decreased with the use of effective cART.³⁸⁻⁴⁰

Table 1 Patterns of renal disease in HIV infection

Renal disorder	Association/subtype
Glomerular lesion	
HIV FSGS or "classic"	APOL1 risk variants
HIVAN	Mixed variant (HIV FSGS in combination with a proliferative glomerulonephritis)
HIVICD (these patients may be coinfectd with hepatitis B or C)	Mesangial proliferative Membranoproliferative (types I and II) Lupus like Exudative proliferative Crescentic Immunoglobulin A Membranous
Various glomerulonephropathies (heterogeneous group with various etiologies)	Minimal change disease Immunotactoid nephropathy Amyloidosis
HIV TTP/HUS	TTP HUS
Tubulointerstitial disease	
Proximal tubular injury	Tenofovir, adefovir, cidofovir, didanosine
Chronic tubular injury	Amphotericin, tenofovir, adefovir, cidofovir
Diabetes insipidus	Amphotericin, tenofovir, didanosine, abacavir
Crystal nephropathy	Indinavir, atazanavir, sulfadiazine, ciprofloxacin, acyclovir (IV)
Interstitial nephritis	Infections (including HIV, BK virus) Immune reconstitution inflammatory syndrome following cART Allergy to β -lactam, rifampicin, proton pump inhibitors, allopurinol, phenytoin, and drugs causing crystal nephropathy (listed in this table)

Comorbid illness

Diabetic nephropathy

Hypertensive nephrosclerosis

Autoimmune disease (lupus nephritis)

Note: Adapted from Naicker S, Rahmanian S, Kopp JB. HIV and chronic kidney disease. *Clin Nephrol*. 2015;83(7 Suppl 1):32–38, with permission.¹³⁷ Adapted from *Comprehensive Clinical Nephrology*. Johnson RJ, Feehally J, Floege J, editors. Human immunodeficiency virus infection and the kidney. Kopp JB, Naicker S. Philadelphia: © Elsevier Saunders; 2015.¹³⁸

Abbreviations: cART, combined antiretroviral therapy; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; HIVICD, HIV immune complex disease; HUS, hemolytic uremic syndrome; IV, intravenous; TTP, thrombotic thrombocytopenic purpura.

HIV-associated immune complex disease (HIVICD) occurs predominately in European and Asian populations.³⁹ It is a diverse group including immune complex glomerular disease (membranous nephropathy, membranoproliferative, and mesangial proliferative glomerulonephritis), IgA nephropathy, and lupus-like proliferative glomerulonephritis.⁴¹⁻⁴³ HIVICD is characterized histologically by immune complex deposits in the capillary loops and mesangium, mesangial cell expansion, and tubulointerstitial inflammation (predominately macrophages,

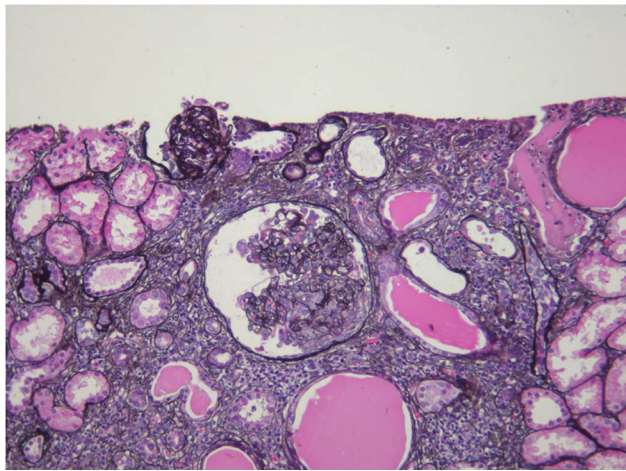


Figure 1 HIVAN (silver methenamine, ×200).

Note: Collapsing glomerulopathy with tubular microcysts and interstitial inflammation and scarring (Courtesy of Dr Pulane Mosiane, Department of Anatomical Pathology, University of the Witwatersrand, Johannesburg, South Africa).

Abbreviation: HIVAN, HIV-associated nephropathy.

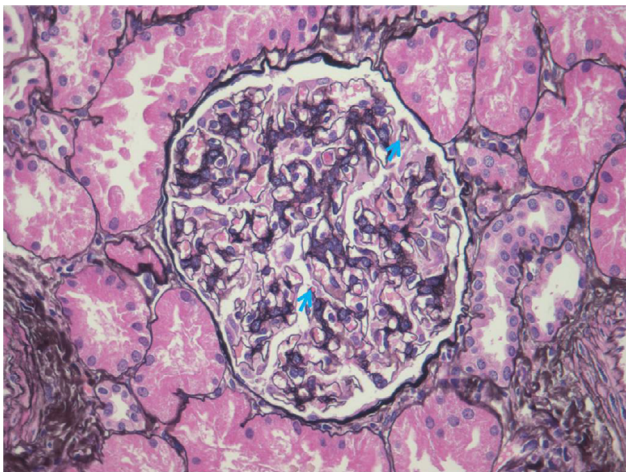


Figure 2 HIVICD (silver methenamine, ×400).

Note: Mild mesangial expansion and subepithelial immune complex deposits with a basement membrane reaction (blue arrows) (Courtesy of Dr Pulane Mosiane, Department of Anatomical Pathology, University of the Witwatersrand, Johannesburg, South Africa).

Abbreviation: HIVICD, HIV immune complex disease.

eosinophils, and B cells; Figure 2).^{41–43} Subepithelial immune deposits, described as a “ball-in-cup” basement membrane reaction, are also seen.³⁴ The prevalence in African biopsy series is 17%–40%.^{18,34,35} HIVICD has not been extensively studied, and the direct role of HIV infection in its pathogenesis is not known.^{44,45} Booth et al⁴⁶ recently reported on a multicentre study describing the clinical characteristics and outcomes of HIVICD in renal biopsies between 1998 and 2012. Of 265 biopsies, 92 revealed immune complex disease (ICD). They excluded biopsies with features of IgA nephropathy (n=27) and lupus nephritis (n=6) and classified the remaining ICD as HIVICD (n=59). Black ethnicity ($P=0.021$) and HIV viremia ($P=0.0009$) were associated with the biopsy diagnosis of

HIVICD. Renal outcomes were better in patients with HIVICD than those with IgA nephropathy or HIVAN. Improvement in eGFR and significant reduction in proteinuria were observed in patients with HIVICD who initiated cART, suggesting that this subgroup of patients may benefit from fully suppressive cART. No significant association between HIVICD and hepatitis B/C viral infection was observed in this series.

Individuals coinfecting with HIV and hepatitis C virus (HCV) are at increased risk of developing, or progression of, CKD.⁴⁷ While the histologic patterns of renal disease have not been studied in large populations of coinfecting patients, membranoproliferative glomerulonephritis is most common.⁴⁸ The classic clinical associations with cryoglobulinemia and hypocomplementemia are less frequent in coinfecting patients. In the cART era in coinfecting patients, there has been a decline in immune complex-related glomerulonephritis and an increase in non-collapsing FSGS.⁴⁹

Other more common patterns of HIV-associated renal disease include HIV-associated thrombotic microangiopathy (TMA), HIV-associated comorbidities (HCV infection, diabetes mellitus, and hypertension), and cART nephrotoxicities.

Widespread use of potent cART and the consequent increased lifespan of HIV-positive individuals have led to the appearance of new patterns of HIV-associated kidney disease, reflecting an increasing burden of comorbid disease and nephrotoxicity related to cART use.^{50,51}

In resource-rich settings, there has been a plateau in the incidence of ESRD secondary to HIVAN, with an annual incidence of 800–900 cases in the US.⁵² However, the prevalence of ESRD in HIV-positive individuals has risen, mainly due to increased longevity on cART.⁵² In biopsy series, there has been a shift from a predominance of HIVAN to an increased frequency of non-collapsing FSGS.^{26,53} An individual chronically infected with HIV is now more likely to have CKD due to non-HIVAN kidney disease. With increased survival and continued exposure to cART, a greater number of HIV-positive individuals are developing comorbid CKD risk factors, such as diabetes and hypertension. HIV may have an additive effect in promoting CKD progression in diabetics,^{54,55} possibly as a result of HIV-induced upregulation of inflammation.⁵⁶

In resource-limited settings such as Africa, little data exist on the effect of comorbid disease on the epidemiology of CKD in HIV-positive individuals. Fabian et al¹⁸ performed a prospective cohort study in HIV-positive South Africans screened for kidney disease. Kidney biopsies were performed before and after initiation of antiretroviral therapy (ART) to assess the clinical and histological response to treatment. This study demonstrated a rapid virological and renal response to cART in HIV-positive individuals with

histologically documented HIV-associated kidney disease; follow-up biopsies, however, showed a variable histological response to treatment.

Pathogenesis of HIV CKD

Viral factors

HIV infection of renal cells

How HIV infection induces chronic kidney injury leading to the pathologic syndrome of HIVAN is not well understood. Direct viral infection of podocytes, renal parenchymal cells particularly the visceral epithelial cells of the glomerulus, and the tubular epithelial cells, resulting in cytopathic effects (including proliferation and apoptosis), are implicated in the pathogenesis of HIVAN. Two main HIV co-receptors, the chemokine receptors *CCR5* and *CXCR4* that mediate entry of HIV-1 strains into susceptible cells, are not expressed by intrinsic renal cells.^{57,58} Infection of dendritic cells and podocytes and tubular epithelial cells by receptors of the CD209 (DC-SIGN) antigen and lymphocyte antigen 75 (DEC-205), respectively, may have a contributory role.⁵⁹ Release of inflammatory lymphokines or cytokines following HIV infection of lymphocytes and macrophages may promote injury and fibrosis, as demonstrated in circulating and infiltrating leukocytes at sites of tubulointerstitial inflammation.^{60,61}

There are two major types of HIV: HIV type 1 and HIV type 2. HIV-1 is the most common and pathogenic strain of the virus and is subdivided into groups. HIV-1 group M is the most frequent group and is further divided into subtypes. HIV-1 subtypes are unevenly disseminated throughout different geographical locations.⁶² Western Europeans and North Americans are predominantly infected with HIV-1 subtype B. In Africa, there are several different subtypes and recombinant forms of HIV-1. Subtype C predominates in Southern and Eastern Africa, whereas other subtypes and recombinant forms of HIV-1 are found in Western and Central Africa. HIV-2 is found in some areas of Western Africa. The infecting HIV type or subtype may determine the rate of progression of HIV disease.⁶³ Thus, different types or subtypes of HIV may result in differences in the replication abilities within the renal reservoir and thus lead to a variety of clinical expressions.⁶³

The HIV-1 subtype C is highly virulent and accounts for up to 98% of HIV infections in South Africa, with corresponding higher viral loads and lower CD4 cells with the development of HIVAN.⁶⁴ Late initiation of ART in resource-limited settings also has a part to play in predisposing at-risk individuals to HIVAN; studies have shown that effective rollout of ART could reduce the occurrence of HIVAN.^{65,66}

Viral proteins

Studies in transgenic mice expressing viral proteins have suggested that *vpr* and macrophage-specific expression of HIV proteins may play a role in the evolution of FSGS.⁶⁷ Some suggest that *nef* may affect the severity of interstitial nephritis, but not the glomerular changes seen in HIVAN.⁶⁸ Podocyte-restricted expressions of *vif*, *nef*, *tat*, *vpr*, and *rev* have been shown to induce many of the features of HIVAN in *nef:vpr* double transgenic mice models.⁶⁹ In HIVAN specimens, apoptosis of renal epithelial cells mediated by caspase activation and *Fas* upregulation has been seen.⁷⁰

Host factors

Genetic variations in the apolipoprotein L1 (*APOL1*) and myosin heavy 9 chain (*MYH9*) genes have been found to have a strong association with HIV-associated kidney disease in African-Americans.^{71,72}

It has been suggested that through activation of cytokine pathways, disease phenotype could affect the host response to viral infection. It has been shown that upregulation of many genes that mediate the inflammatory response in renal epithelial cells such as chemokines, cytokines, and adhesion molecules occurs in patients with HIV-associated kidney disease. A number of such upregulated genes are targets of nuclear factor- κ B and interleukin (IL)-6. Tumor necrosis factor (TNF) and IL-6 expression by tubular and mesangial epithelial cells increase HIV-1 expression by entering monocytes and further driving cytokine production. The part played by inflammatory mediators in the pathogenesis of HIVAN is not yet entirely understood.⁷³ Chronic HIV infection is associated with high levels of immunoglobulins. It is suggested that immune complexes circulating in the systemic circulation are deposited in the microvasculature of the kidney, leading to HIVICD.⁷⁴ A recognized feature of HIV infection includes deposition of platelets and thrombi in the vessel wall and endothelial dysfunction caused by abnormalities of the clotting cascade. How HIV affects renal vasculature is important in understanding the pathogenesis of TMA and other HIV-associated renal diseases. The expression of TNF and IL-1 is upregulated in HIV infection of the kidney. This further drives renal inflammation and can contribute to changes in regulation of the clotting cascade. *Fas*-mediated apoptosis of endothelial cells is triggered by HIV proteins. Downregulation of von Willebrand factor is a primary component of TMA by antibodies against the ADAMTS13 protease.⁷³

Genetic susceptibility

There is a disparity in the occurrence of HIVAN among HIV-positive individuals such that there is an 18- to 50-fold

increased risk of developing kidney disease among HIV-positive individuals of African descent aged between 20 and 64 years and who have a poorer prognosis than their European descent counterparts, suggesting that genetic factors play a vital role.⁷⁵ Other risk factors include male sex, low CD4 counts, and high viral load.

Genetic susceptibility to HIVAN had originally been attributed to genetic variations within non-muscle *MYH9* and now considered to be due to *APOL1*.^{71,72}

An association has been shown between the *APOL1* gene on chromosome 22 (seen in African-Americans) and FSGS and hypertension-attributed ESRD. A subsequent study revealed 17-fold higher odds for FSGS and 29-fold higher risk for HIVAN in those with the *APOL1* variant.⁷⁶ A recent South African study showed 89-fold odds for HIVAN in HIV-positive individuals carrying two *APOL1* risk alleles.⁷⁷ Untreated HIV-positive patients with the *APOL1* risk allele have a 50% risk of developing HIVAN. High-risk *APOL1* variants G1 and G2 have been strongly associated with HIVAN. The G1 allele (rs73885319) frequency is reported to be ~7.3% in South Africa, which is much lower than that reported in West Africa, in whom the frequencies are ~50% for Yoruba and 23.3% for Igbo or in African-Americans where the G1 frequency is ~20%.^{76–78} HIV-infected individuals of Ethiopian origin who did carry the high-risk *APOL1* genetic variants were reported to not have HIVAN.⁷⁹

It has been postulated that *APOL1* mediates kidney injury via autophagic and apoptosis pathways.^{80–83}

There could also be the possibilities of other environmental exposures and nutritional and genetic factors, coupled with other infections, which may modify the effects of *APOL1* variants on the kidney.

Management

Antiretroviral therapy

Improvement in renal function has been seen after initiation of cART in patients with HIV-associated CKD. In the DART study from Zimbabwe and Uganda, eGFR improved by 1.9–6.0 mL/min per 1.73 m² after 4–5 years of cART.⁸⁴ Peters et al¹⁵ also reported a 21% improvement in median eGFR after 2 years on cART in patients with HIV-associated CKD from Uganda. Improvement in renal function with a median period of cART of 2 years was reported in a Tanzanian study; there was a decrease from 76% to 29.2% in the number of patients with eGFR <90 mL/min per 1.73 m².⁸⁵

Lescure et al⁵⁰ documented the change in histological patterns of renal disease in HIV-positive patients since the

introduction of cART to France. Non-collapsing forms of FSGS have overtaken HIVAN as the most common glomerular lesion, which were seen in 47% of biopsies between 2004 and 2007.

HIVAN is an indicator for the initiation of cART irrespective of CD4 lymphocyte count.⁸⁶ Rapid progression to ESRD is seen in patients with HIVAN, but not in those on cART.⁸⁷ With the increased use of cART, there has been a decline in the incidence of HIVAN and HIV-associated ESRD.^{19,50,51,88} The US Renal Data System reports a 60% reduction in the risk of HIVAN-associated ESRD after the introduction of cART.⁸⁹ There have also been sporadic case reports of recovery of renal function following initiation of cART.^{90,91} Patients who develop HIVAN despite being on cART are more likely to develop ESRD.⁸⁷

There is inconclusive evidence for initiating cART in HIVICD; it seems appropriate to do so, given the benefits seen in HIV-associated CKD. A study by Szczech et al³⁹ revealed no benefit with cART in patients with HIVICD. However, two South African studies revealed improved renal function with cART in patients with HIVICD.^{18,37} In the series from Cape Town, 16 of 221 biopsies revealed HIVICD. The patients receiving cART over a 3-year period showed stabilization in eGFR and an improvement in proteinuria, but these findings were not statistically significant. Booth et al⁴⁶ recently reported an observed significant reduction in proteinuria and improvement in eGFR in patients with HIVICD initiated on cART.

The widespread use of cART has resulted in a decline in the incidence of HIV-associated TMA. cART initiation also resulted in clinical remission in these patients.^{92–94}

Dose adjustment of cART is necessary in patients on antiretroviral agents eliminated by the kidney (Table 2).⁸⁶ Incorrect dosing has been associated with higher mortality.⁹⁵ Fixed-dose combinations should be avoided once eGFR is <60 mL/min per 1.73 m².⁸⁶

Nephrotoxicity of cART

Specific cART agents have been associated with an increased risk of developing CKD or CKD progression. Two drugs with confirmed potential to cause nephrotoxicity are tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor, and indinavir, a protease inhibitor. Both drugs show a strong association between cumulative exposure and development of CKD.^{96,97} Prolonged use of atazanavir, a newer protease inhibitor, has been associated with renal stones and a decline in eGFR, but not proteinuria or CKD.⁹⁷ Wever et al⁹⁸ observed stabilization or improvement in eGFR in individuals who discontinued TDF with a eGFR of <60 mL/min per 1.73 m²; however, there was incomplete recovery to

Table 2 Dose adjustments and renal effects of cART in CKD and ESRD

cART name	CKD (adjusted according to CrCl by eGFR)	Dialysis	Renal effect
Nucleoside or nucleotide analogs			
Abacavir	No adjustment	No adjustment HD: dosing independent of dialysis sessions	AIN (case report) Fanconi syndrome (case report)
Azidothymidine (AZT), zidovudine	CrCl ≥ 15 mL/min: no adjustment CrCl < 15 mL/min: 100 mg po q6-8h	HD: 100 mg po q6-8h or 300 mg po qd PD: no data	None reported
Didanosine (ddi)	Weight > 60 kg CrCl 30–59 mL/min: 200 mg po qd CrCl 10–29 mL/min: 150 mg po qd CrCl < 10 mL/min: 75 mg po qd Weight < 60 kg CrCl 30–59 mL/min: 150 mg po qd CrCl 10–29 mL/min: 100 mg po qd CrCl < 10 mL/min: 75 mg po qd	HD: dosing as per CrCl < 10 mL/min, dosing after HD session PD: dosing as per CrCl < 10 mL/min	Fanconi Syndrome AKI Lactic acidosis Nephrogenic diabetes insipidus (case reports)
Emtricitabine	CrCl > 50 mL/min: no adjustment CrCl 30–49 mL/min: 200 mg po q48h CrCl 15–29 mL/min: 200 mg po q72h CrCl < 15 mL/min: 200 mg po q96h	HD: 200 mg po q96h, dosing after HD session PD: no data	
Lamivudine (3TC)	CrCl > 50 mL/min: no adjustment CrCl 30–49 mL/min: 150 mg po qd CrCl 15–29 mL/min: 150 mg first dose, then 100mg po qd CrCl 5–14 mL/min: 150 mg first dose, then 50mg po qd CrCl < 5 mL/min: 50 mg first dose, then 25mg po qd	HD: 50 mg first dose, then 25 mg po qd, dosing after HD session	Renal tubular acidosis Hypophosphatemia (case report)
Stavudine (d4T)	CrCl > 50 mL/min: no adjustment CrCl 26–50 mL/min: 15–20 mg po bid CrCl ≤ 25 mL/min: 15–20 mg po qd	HD: 20 mg po qd, dosing after HD session PD: has been used safely	Renal tubular acidosis Hypophosphatemia (case report)
Tenofovir	CrCl > 50 mL/min: no adjustment CrCl 30–49 mL/min: 300 mg po q48h CrCl 10–29 mL/min: 300 mg po q72h	300 mg po every 7 days, dosing after HD session	Proximal tubular dysfunction with Fanconi syndrome Nephrogenic diabetes insipidus AKI CKD
Zalcitabine	CrCl > 40 mL/min: no adjustment CrCl 10–40 mL/min: 0.75 mg po q12h CrCl < 10 mL/min: 0.75 mg po q24h	HD: dosage for CrCl < 10 mL/min, dosing after HD session PD: no data	
Non-nucleoside reverse transcriptase inhibitors	No adjustment	No adjustment	Efavirenz: nephrolithiasis
Protease inhibitors	No adjustment	No adjustment	Atazanavir: AIN (case report) Indinavir: AKI (AIN), CKD (AIN), nephrolithiasis, intratubular drug precipitation, papillary necrosis, hypertension, renal atrophy Nelfinavir: nephrolithiasis (case report) Ritonavir: AKI Saquinavir: AKI in association with ritonavir
Entry or fusion inhibitor			
Enfuvirtide	CrCl ≥ 35 mL/min: no adjustment CrCl < 35 mL/min: unknown, use with caution	Unknown, use with caution	Membranoproliferative glomerulonephritis (case report)

cART name	CKD (adjusted according to CrCl by eGFR)	Dialysis	Renal effect
CCR5 antagonist			
Maraviroc	No dosage recommendations CrCl <50 mL/min: patients should only receive maraviroc and CYP3A inhibitor if potential benefit outweighs risk	No data	None reported
Integrase inhibitor			
Raltegravir	No adjustment	No adjustment	None reported

Note: Adapted from *Comprehensive Clinical Nephrology*. Johnson RJ, Feehally J, Floege J, editors. Human immunodeficiency virus infection and the kidney. Kopp JB, Naicker S. Philadelphia: © Elsevier Saunders; 2015.¹³⁸

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; cART combined antiretroviral therapy; CKD, chronic kidney disease; CrCl, creatinine clearance; ESRD, end stage kidney disease; HD, hemodialysis; PD, peritoneal dialysis; po, orally; q24h, every 24 hours; q48h, every 48 hours; q72, every 72 hours; q6-8h, every 6 to 8 hours; qd, daily.

baseline eGFR in more than half of the individuals. The use of a TDF-based cART regimen has been associated with a greater eGFR decline compared with a non-TDF-based regimen; the clinical importance of this association is not known. TDF nephrotoxicity may be enhanced by the coadministration of the following drugs: acyclovir, cidofovir, valacyclovir, ganciclovir, valganciclovir, dipyridamole, nonsteroidal anti-inflammatory drugs, probenecid, and ritonavir.⁹⁹

Guidelines recommend the avoidance of TDF if eGFR <60 mL/min per 1.73 m². In patients already on TDF who experience a >25% decline in eGFR from baseline and an eGFR <60 mL/min per 1.73 m², a substitution to an alternate antiretroviral is recommended.

Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

No randomized trials of renin–angiotensin inhibitors in patients with HIV-related CKD have been conducted. Most studies concerning the use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) in HIV-positive CKD patients were undertaken in patients with HIVAN in the pre-cART era. ACE inhibitor use was associated with a lower risk of ESRD and longer time to ESRD.^{100–102}

In a single-center prospective cohort study by Wei et al,¹⁰¹ 44 patients with biopsy-proven HIVAN were included. A total of 28 patients received fosinopril 10 mg/day. The study period was 5.1 years. Median renal survival of treated patients was significantly improved after receiving fosinopril. The risk of renal failure was also reduced with ACE inhibitors (relative risk [RR] =0.003, $P<0.0001$). Survival was improved in the ACE inhibitor treatment group ($P<0.001$).

The use of reverse transcriptase inhibitors and captopril was independently associated with a longer mean renal survival before ESRD in 18 cases of biopsy-proven HIVAN before 1996.¹⁰²

Treatment with an ACE inhibitor/ARB is recommended, when clinically indicated in patients with confirmed or suspected HIVAN, or clinically significant albuminuria (in diabetic mellitus patients with >30 mg albumin/day and nondiabetic patients with >300 mg albumin/day).⁸⁶

Immunosuppression

Corticosteroids are not considered to be standard treatment in HIVAN. Retrospective observational studies and uncontrolled trials in the pre-cART era suggested modest, short-lived benefits. Eustace et al¹⁰³ included 21 patients in a retrospective cohort study, where 13 received corticosteroids (prednisone 60 mg/day for 1 month). At 6 months, one patient from the nonsteroid group and seven patients who received steroids remained dialysis free. In a retrospective cohort of 102 biopsy-confirmed cases of HIVAN from 18 hospitals in France between 1984 and 1996, delay in the initiation of hemodialysis was seen in patients receiving prednisone at 1 mg/kg for 2–6 weeks (RR=0.29 for progression to dialysis with prednisone).¹⁰⁴ Sothinathan et al¹⁰⁵ reported a case study of a single patient whose creatinine remained stable but proteinuria increased after 2 years. There was no associated increase in opportunistic infections but a significant increase in avascular necrosis.^{106–108} Wearne¹⁰⁹ is currently conducting a prospective randomized control study with the aim of assessing whether corticosteroids preserve/improve renal function and proteinuria or histological features in patients with biopsy-proven HIVAN. Patients receive 1 mg/kg of prednisone for 1 month, and the dose is thereafter tapered by 10 mg/month. Interim data presented at the World Congress of Nephrology 2015 showed promising improvement in eGFR but not proteinuria. Patients receiving steroids had a greater risk of herpes zoster, but mortality was not significantly higher. Corticosteroids are recommended as a possible adjunct to cART and ACE inhibitors/ARB in biopsy-proven HIVAN.⁸⁶ There are no published data of corticosteroid use in renal disease other than HIVAN.

Data on cyclosporine efficacy in children with HIVAN to reduce proteinuria are limited.¹¹⁰

Blood pressure control

Optimal blood pressure targets have not been specifically evaluated in HIV-positive patients with CKD. The Eighth Joint National Committee guidelines recommend a target blood pressure of $\leq 140/90$ mmHg for patients with CKD.¹¹¹ KDIGO (Kidney Disease Improving Global Outcomes) 2012 guideline recommends a target blood pressure of $\leq 130/80$ mmHg for patients with CKD with moderate to severely increased albuminuria.¹¹²

Other standard management approaches for patients with CKD are recommended. These include addressing other cardiovascular risk factors (appropriate use of statins and aspirin, weight loss, cessation of smoking), avoidance of nephrotoxins and management of serum bicarbonate and uric acid, anemia, calcium, and phosphate abnormalities.

Vaccinations

Suboptimal response to vaccinations is likely, due to combined immunosuppression from HIV infection and CKD. The development of protective antibodies and the length of protection are likely to be reduced.¹¹³ The following vaccines are recommended in HIV-positive patients: influenza, hepatitis B, and pneumococcal.¹¹⁴

Renal replacement therapy

Dialysis

With the widespread use of cART, HIV-positive patients are at risk not only of HIV-related kidney disease but also of diseases associated with the aging process, such as hypertension and diabetes mellitus. HIV-positive patients are at increased risk of developing ESRD compared with the general population.¹¹⁵ Risk factors for the development of ESRD in HIV-positive patients include traditional risk factors (hypertension, diabetes mellitus, cardiovascular disease) and HIV-associated factors (low CD4 lymphocyte count, high HIV-RNA, coinfection with hepatitis C).²³

There is no evidence to suggest that either of the dialysis modalities is superior in HIV-positive patients.¹¹⁶ Survival rates on dialysis are comparable to those of HIV-negative dialysis patients.

HIV-positive patients on hemodialysis do not require isolation or dedicated machines.¹¹⁷ Retrospective data have documented a significant increase in arteriovenous graft thrombosis and infections, which is not seen in patients with native arteriovenous fistulae (AVF). Thus, AVF are

the access of choice, and early creation of AVF is recommended in HIV-positive patients approaching dialysis.^{118–120} While transmission of HIV in the dialysis unit is rare, precise use of standard infection control procedures ensures a reduced risk.¹¹⁶ Patient-to-patient HIV transmission has been documented in dialysis units in Argentina, Colombia, and Egypt.^{121–123} Dialyzer reuse by the same patient is not associated with increased risk of transmission to staff members.¹¹⁷

HIV survives in peritoneal dialysis drainage fluid and dry tubing and thus should be disposed of correctly.^{124,125} Dilutions of 50% Amikacin and 10% bleach are able to inactivate HIV in dialysate.¹²⁴ Variable rates of peritonitis have been reported. Some studies have reported increased incidence of pseudomonas and fungal peritonitis in HIV-positive peritoneal dialysis patients.^{126,127} Other studies show rates of peritonitis comparable with HIV-negative peritoneal dialysis patients.^{128,129}

Improved survival of HIV-positive patients on dialysis is seen with younger age, higher CD4 counts, cART use, and initiation of RRT at an earlier stage of HIV infection.^{129–132} There is an increased risk of cardiovascular disease in HIV-positive dialysis patients on long-term cART.

Renal transplantation

With the use of cART, HIV infection is no longer a contraindication to renal transplantation.¹³³ Stock et al¹³⁴ reported on a series of 150 renal transplants occurring between 2003 and 2009. Although there are higher rates of acute graft rejection in HIV-positive recipients, graft and patient survival rates are comparable to HIV-negative recipients. Outcomes of HIV-positive to HIV-positive kidney transplantation has been reported by Muller et al.^{135,136} A total of 27 HIV-positive patients received a cadaveric kidney from HIV-positive donors. Cumulative rates of graft survival, 93% at 1 year and 84% at 5 years, and cumulative rates of patient survival, 84% at 1 year and 74% at 5 years, are similar to outcomes reported in HIV-positive patients who received a graft from HIV-negative donors. There is a risk of HIVAN recurrence in the allograft.

Pharmacological interactions occur between antiretroviral agents and transplant medications. Dose adjustment and immunosuppressant drug monitoring is recommended.⁸⁶

Screening and early diagnosis of HIV CKD

HIV-positive individuals present with advanced stages of CKD in clinical practice in Africa. Early diagnosis of kidney disease by screening of HIV-positive individuals for the presence of kidney disease is critical for the optimal management of these patients. The HIV Medicine Association of the Infectious

Disease Society of North America recommends screening for the presence of kidney disease upon detection of HIV infection and annually thereafter in high-risk populations, similar to the recommendations for type 2 diabetes mellitus.^{75,86} Screening strategies include measurement of blood pressure, kidney function (serum creatinine; eGFR), and urine examination (proteinuria via spot urine protein creatinine ratios; hematuria). Referral to nephrology services is recommended when the eGFR is <60 mL per 1.73 m² or if it decreases by >25% from baseline. The role of kidney biopsy has been debated; there are no clear clinical diagnostic criteria for HIVAN; the decision for a kidney biopsy should be guided by the risks to the individual patient, the uncertainty of diagnosis, and the patient's preference.

Conclusion

The presence of advanced HIV-associated CKD is an important cause of mortality and morbidity. The recent World Health Organization recommendations to treat all individuals upon diagnosis of HIV infection, while causing huge concerns for overburdened health systems and constrained health budgets, may decrease the burden of HIV CKD. Screening and early diagnosis of kidney disease will improve outcomes in patients with HIV infection.

Disclosure

The authors report no conflicts of interest in this work.

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