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Review article

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The changing landscape of HIV-associated kidney disease

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Abstract

The HIV epidemic has devastated millions of people globally, with approximately 40 million deaths since its start. The availability of antiretroviral therapy (ART) has transformed the prognosis of millions of individuals infected with HIV such that a diagnosis of HIV infection no longer automatically confers death. However, morbidity and mortality remain substantial among people living with HIV. HIV can directly infect the kidney to cause HIV-associated nephropathy (HIVAN) — a disease characterized by podocyte and tubular damage and associated with an increased risk of kidney failure. The reports of HIVAN occurring primarily in those of African ancestry led to the discovery of its association with *APOL1* risk alleles. The advent of ART has led to a substantial decrease in the prevalence of HIVAN; however, reports have emerged of an increase in the prevalence of other kidney pathology, such as focal segmental glomerulosclerosis and pathological conditions associated with co-morbidities of ageing, such as hypertension and diabetes mellitus. Early initiation of ART also results in a longer cumulative exposure to medications, increasing the likelihood of nephrotoxicity. A substantial body of literature supports the use of kidney transplantation in people living with HIV, demonstrating significant survival benefits compared with that of people undergoing chronic dialysis, and similar long-term allograft and patient survival compared with that of HIV-negative kidney transplant recipients.

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Key points

- The widespread use of antiretroviral therapy has led to a change in the histological pattern of kidney disease in people living with HIV (PLWH) away from HIV-associated nephropathy and towards comorbid diseases of ageing and antiretroviral therapy-related nephrotoxicity.
- Biopsy remains crucial for the appropriate management of an array of kidney diseases in PLWH; the current classification of kidney histology is based on the major tissue compartments affected, and is aimed at reducing heterogeneity in the biopsy definitions of HIV-related kidney disease and encouraging awareness of potential secondary causes of disease.
- The new race-neutral creatinine-based equation for estimating the glomerular filtration rate identified more Black individuals with a lower estimated glomerular filtration rate than previously recognized, and exposed a subgroup of Black individuals living with HIV who are at an increased risk of chronic kidney disease progression.
- The presence of *APOL1* risk alleles influences the pattern of kidney disease in PLWH, its response to therapy and its outcomes; clinical trials are investigating therapeutic options to reduce APOL1 protein and/or its activity, which may ameliorate its potential harm.
- Kidney transplantation in PLWH from both HIV-negative and HIV-positive donors is highly successful, and the donation of organs from PLWH may be an option for increasing the number of organs available for transplantation; however, this approach requires further evaluation before being adopted as standard clinical practice.

Introduction

Since the start of the HIV epidemic in 1981, over 84 million people have been infected with HIV and there have been 40 million deaths[1]. Four decades on, HIV continues to be a major cause of morbidity and mortality. HIV-associated nephropathy (HIVAN) was originally described as the typical renal pathology associated with HIV infection[2,3]. However, the availability of antiretroviral therapy (ART) has led to a transformation in the spectrum of kidney diseases associated with HIV infection, with a reduction in the prevalence of HIVAN and increases in other kidney pathology, such as focal segmental glomerulosclerosis (FSGS) and histological patterns associated with hypertension and diabetes mellitus[4,5]. Immediate initiation of ART at the time of HIV diagnosis has reduced AIDS-related morbidity and mortality. Early ART initiation was also shown to result in modestly higher estimated glomerular filtration rate (eGFR) and reduced proteinuria compared with delayed ART initiation[6]. However, prolonged life expectancy, the presence of comorbid diseases of ageing and longer cumulative exposure to potentially nephrotoxic ART have led to an increase in the prevalence of chronic kidney disease (CKD) in people living with HIV (PLWH). The widespread availability of ART has also resulted in excellent kidney transplant outcomes in recipients with HIV[7] and enabled the transplantation of organs from HIV-positive deceased donors into HIV-positive recipients[8]. Kidney transplants from live donors with HIV, including ABO-incompatible live donor transplants, and the potential to transplant kidneys from HIV-positive donors into HIV-negative recipients are areas of exploration to expand the donor pool and alleviate the growing burden of kidney failure.

This Review describes the changing pattern of kidney diseases associated with HIV infection and the risk factors associated with the different forms of histopathology. We discuss methods of evaluating kidney function in PLWH, including the potential role of biomarkers, and describe current therapeutic approaches to HIVAN as well as measures to reduce the nephrotoxicity of ART. The long-term outcomes of kidney transplantation for both recipients and donors with HIV are also reviewed, together with future options to expand HIV organ donation.

Epidemiology of HIV infection

Of the 39 million PLWH globally, 25.6 million are in Africa, largely in sub-Saharan Africa (Fig. 1). In 2022, a total of 29.8 million PLWH accessed ART (an increase from 7.8 million in 2012), equating to 76% of all PLWH; 71% of all PLWH were virally suppressed (representing 92% of people on ART)[1]. The COVID-19 pandemic disrupted access to and provision of HIV prevention and treatment programs. This disruption probably contributed to the 1.5 million new infections in 2021 and 650,000 deaths. Eastern Europe, central Asia, the Middle East and North Africa, and Latin America have all seen increases in annual HIV infections over this period[1].

Despite increased awareness, many individuals still present late in the course of HIV infection, with severe immunosuppression and advanced comorbidities such as kidney disease and HIV-associated malignancies. Co-infection with *Mycobacterium tuberculosis* remains a major cause of death among patients with HIV. Despite the availability of ART, HIV-associated kidney diseases (such as HIVAN and immune complex-mediated glomerular disease) remain a considerable cause of morbidity among PLWH, in part because of the late presentation and diagnosis of HIV infection.

Kidney pathology with HIV infection

Prior to the availability of ART, HIVAN was the typical kidney pathology reported in HIV infection, resulting from the direct viral infection of kidney cells[9]. The widespread use of ART led to an evolution in the spectrum of HIV-associated kidney disease. The existence of kidney disease in patients with HIV infection now largely reflects a comorbid illness in an ageing HIV population and/or ART-related nephrotoxicity[10] (Table 1; Fig. 2).

A consensus classification of kidney histology in the setting of HIV infection, based on the major tissue compartments affected, has been proposed with the aim of reducing heterogeneity in the biopsy definitions of HIV-associated kidney disease[11]. This classification recommends that classic HIVAN is differentiated from focal segmental glomerulosclerosis not otherwise specified (FSGS (NOS)) in the setting of HIV. It also recommends that the term HIV immune complex kidney (HIVICK) disease is replaced with a specific depiction of the immune complex-mediated disease 'in the setting of HIV'. This change encourages identification of potential secondary causes of kidney disease, such as hepatitis B and/or C, which may be treatable.

Glomerular-dominant diseases

Glomerular-dominant diseases in the setting of HIV are divided into two main subcategories: podocytopathies and immune complex-mediated glomerular diseases. The podocytopathy group includes five main subtypes: classic HIVAN, FSGS (NOS), minimal change disease, diffuse mesangial hypercellularity and other podocytopathies in the setting of HIV. All of these entities are characterized by extensive foot process

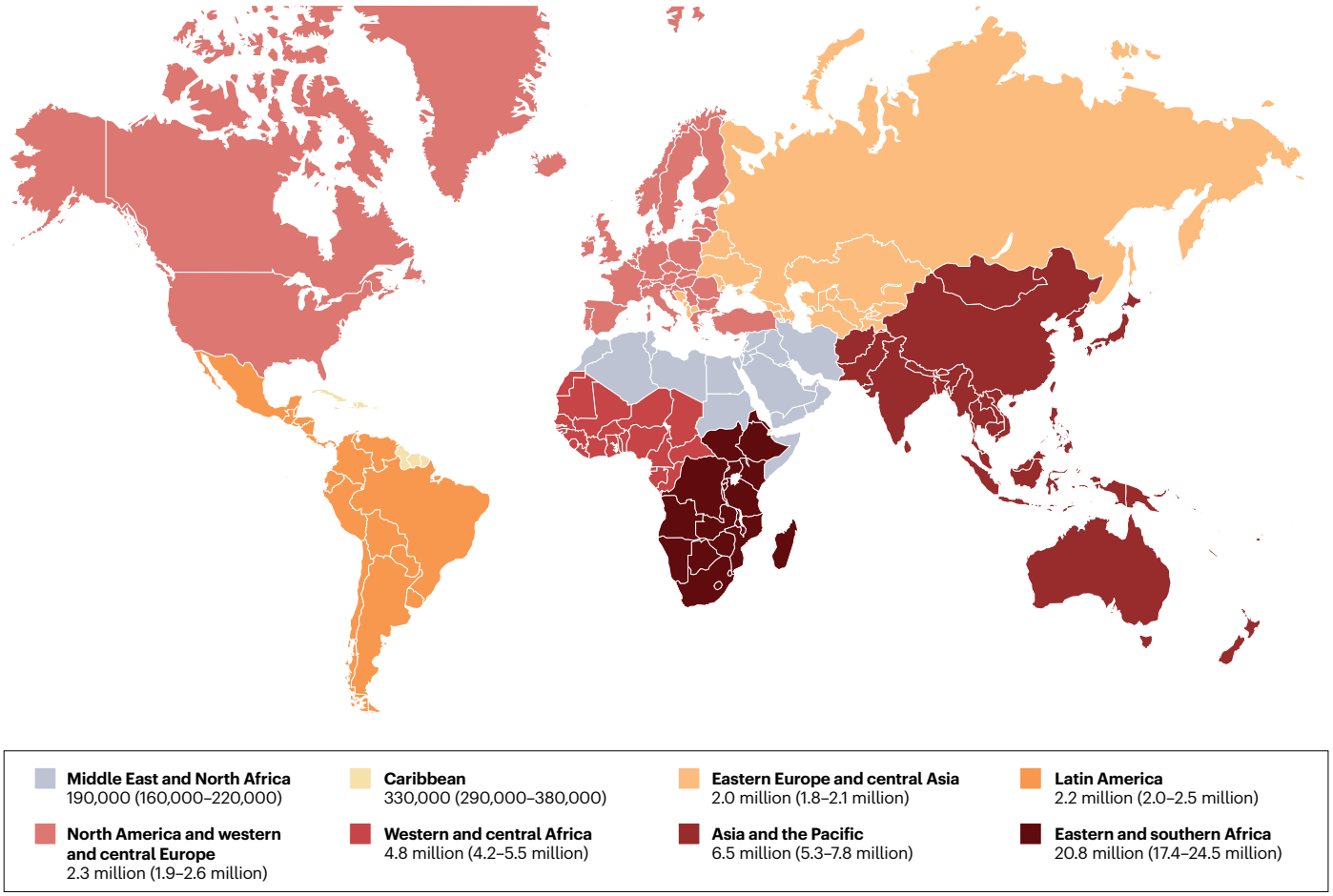

Fig. 1 | Global HIV prevalence amongst adults and children in 2022. Of the 39 million people living with HIV in 2022, two-thirds reside in Africa. The highest prevalence of HIV is seen in sub-Saharan Africa. Reprinted with permission from ref. 1, UNAIDS.

effacement and proteinuria with minimal or absent immune complex deposition.

Biopsy series have confirmed that the prevalence of classic HIVAN has decreased since the introduction of ART. An analysis of kidney biopsy series interpreted at Columbia University, USA, between 2011 and 2018, found that classic HIVAN accounted for 14% of diagnoses; in the same institution in 1987, HIVAN constituted 76% of kidney biopsy diagnoses[4]. Similarly, a series from Cape Town, South Africa, found a significant decline in the histological diagnoses of HIVAN in biopsies performed during 2016–2020 compared with those performed during 2005–2009 (29% versus 45%)[12]. Likewise, our comparison of histological diagnoses within a cohort of PLWH from Johannesburg, South Africa, demonstrated a significant decrease in the frequency of classic HIVAN diagnosis following the availability of ART (from 43.4% to 22.8%)[5].

Although the prevalence of classic HIVAN has been significantly reduced, it has not been eradicated. Reasons include undiagnosed HIV infections, incomplete ART coverage, potential non-adherence to ART and the genetic diversity of PLWH.

Non-HIVAN podocytopathies. In contrast to HIVAN, the proportion of histological diagnosis of FSGS (NOS) has increased in the setting of HIV on ART[10,13]. We reported an increase in FSGS (NOS) among PLWH from 4% prior to the rollout of ART to 15.6% after the introduction of ART ($P < 0.01$)[5]. Whether FSGS (NOS) lies on the same disease spectrum as HIVAN or is a separate entity is unclear. It may represent a partially treated or attenuated form of HIVAN, with a potential pathogenic contribution of age-related factors[14]. Patients who develop FSGS (NOS) are older and more likely to have undetectable viraemia than those with a histological diagnosis of HIVAN. HIV is presumed to be the causative factor when secondary causes of FSGS — including other viral causes of FSGS (cytomegalovirus, parvovirus, simian virus 40 infection), drug-induced disease and pathological conditions related to structural adaptations to certain diseases (hypertension, diabetes or obesity) — have been excluded[15]. Differentiating HIV-related FSGS from secondary FSGS — which arises secondary to hypertension, diabetes or obesity — is challenging. Molecular approaches that have been used in research settings to differentiate these entities are not yet available in clinical practice[16,17].

Immune complex-mediated glomerular diseases. Immune complex-mediated glomerular diseases in the setting of HIV are defined by their morphological appearance and link to HIV as a potential underlying aetiology. However, evidence of a direct causative role of HIV

has been difficult to establish owing to the absence of molecular and immunochemical analyses, and has also not been extensively studied, possibly because of a lack of appropriate animal models. In a small human study of PLWH and immune complex-mediated kidney disease, HIV antigens and specific HIV antibodies were demonstrated in glomerular immune deposits, suggesting a causative role of HIV in some cases of immune complex-mediated kidney disease in the setting of HIV[18,19]. A 'ball-in-cup' subepithelial glomerular immune deposit has been observed in kidney biopsy series from South Africa, but is not specific to HIV immune complex-mediated glomerular disease[5,12,20]. IgA nephropathy can coexist in patients with HIV; however, whether this kidney pathological condition is due to the deposition of IgA directed against HIV antigens or is co-incidental remains uncertain[18]. Ethnic differences may account for the higher prevalence of IgA nephropathy in US cohorts compared with South African cohorts, as IgA nephropathy is less common in Black individuals[21,22]. In one US cohort, half of the patients with IgA nephropathy were co-infected with HCV, potentially indicating that liver disease resulted in the reduced hepatic clearance of IgA[4]. An aggregation of longitudinal studies that included more than 8 million patients showed that the risk of reduced GFR was higher among patients co-infected with HIV and HCV than among patients with HIV infection alone (adjusted HR 1.64; 95% CI 1.28–2; $P < 0.001$)[23]. HIV and HBV co-infection is also associated with an increased risk of kidney disease progression[24]. Newer methods are now available to assist in subtyping immune complex-mediated kidney disease, such as anti-phospholipase A2 receptor antibodies (AntiPLA2R Ab) and guide management[11]. Cases without a likely aetiology may represent true HIV-related immune complex-mediated glomerular disease, rather than a co-incidental disease in PLWH.

Tubulointerstitial-dominant disease

Tubulointerstitial-dominant disease in the setting of HIV occurs predominantly in classic HIVAN (including hyaline droplet tubulopathy, tubular microcysts and tubulointerstitial inflammation), acute tubular

Table 1 | Spectrum of kidney histology findings in people living with HIV

Study details and biopsy findings			South Africa		USA
			Johannesburg (2022)[5]	Cape Town (2023)[12]	New York (2020)[4]
Study details and demographics					
Age in years (IQR)			35 (29–41)	36 (31–44)	53 (45–60)
Black ethnicity (%)			97.5	85[a]	41[b]
Number of biopsy samples			690	671	437
Renal histology (%)					
Glomerular dominant	Total		76.2	63.5	44
	Podocytopathies	Total	44.5	46.5	27
		Classic HIVAN	25.8	43.7	14
		FSGS (NOS)	13.9	2.1	12
		Other podocytopathy in the setting of HIV	4.8	0.7	2
	Immune complex-mediated glomerular disease	Total	31.7	17	17
		Uncharacterized ICGN with no other aetiology than HIV	11.2	NR	2
		Membranous nephropathy in the setting of HIV	6.5	2.2	3
		Membranoproliferative glomerulonephritis in the setting of HIV	6.4	5.2	NR
		IgA nephropathy in the setting of HIV	0.7	0.5	5
		Other	6.9	9.1	5
Tubulointerstitial dominant		Total	10.5	24.7	26
		Tubulo-interstitial nephritis	7	16	3
		Acute tubular injury	3	3.1	8
		Tenofovir nephrotoxicity	NR	3.6	13
		Other	0.5	2.0	2.0
Vascular dominant		Total	1.4	0.3	2
Other		Total	11.9	11.6	28
		Hypertensive nephrosclerosis	6.2	4.0	NR
		Diabetic kidney disease	3.6	4.0	16
		Other	2.1	3.6	12

Data are from the three largest biopsy series utilizing the new KDIGO classification[11] and demonstrate the large variety of kidney histology described in PLWH. FSGS (NOS), focal segmental glomerulosclerosis (not otherwise specified); HIVAN, HIV-associated nephropathy; ICGN, immune complex-mediated glomerulonephritis; IQR, interquartile range; NR, not reported. [a]A majority of non-black individuals were of mixed race. [b]30% of the cohort's ethnicity was unknown.

injury or necrosis (for example, in response to a toxin or ischaemia), drug-induced tubulointerstitial nephritis (secondary to antibiotics, antivirals, proton pump inhibitors, NSAIDs or other agents) or direct renal parenchymal infection (by bacterial, viral, fungal or protozoal pathogens). Less commonly, immune dysfunction-related tubulointerstitial inflammation in the setting of HIV can result from diffuse infiltrative lymphocytosis syndrome or immune reconstitution inflammatory syndrome. Diffuse infiltrative lymphocytosis syndrome is a hyperimmune reaction against HIV antigens whereas immune reconstitution inflammatory syndrome is seen in patients who have initiated ART and subsequently develop an immune response to an infectious aetiology in the kidney parenchyma due to recovery of the immune system.

In the three largest histology series in PLWH from the current era, tubulointerstitial-dominant disease constituted a notable percentage of kidney diagnoses: 26%, 24.7% and 10.5% in the USA and two South African cohorts respectively[4,5,12]. We reported a significant increase in diagnoses of tubulointerstitial-dominant disease from 3% pre-ART rollout to 11.7% after the introduction of ART ($P = 0.009$)[5]. Similarly, the Cape Town series reported an increase from 13% to 33% between 2005–2009 and 2016–2020, with a prominence of granulomas attributed to *M. tuberculosis*. Exposure to ART containing tenofovir was associated with an increased risk of tubulointerstitial disease[12].

In the US series, the most common causes of tubulointerstitial-dominant disease were tenofovir nephrotoxicity and acute tubular injury. The significant increase seen in the Johannesburg series was attributed to the use of co-trimoxazole as prophylaxis and the introduction of tenofovir disoproxil fumarate (TDF) as first-line ART in 2010. A rise in granulomatous interstitial nephritis in the setting of HIV has also been reported in South Africa; in one study, 45 (14.2%) of 361 biopsies from PLWH showed granulomatous interstitial nephritis with *M. tuberculosis* (60%) noted as the leading cause, followed by drugs (20%) including co-trimoxazole, antibiotics, NSAIDs and diuretics[25]. This high prevalence of biopsy-proven *M. tuberculosis* mirrors the tuberculosis epidemic in South Africa.

Other pathological conditions in the setting of HIV

The introduction of ART has transformed HIV into a chronic disease, and with the longevity of PLWH, kidney disease is increasingly associated with age-associated comorbidities, such as the metabolic syndrome, obesity, diabetes mellitus, chronic inflammation and arterionephrosclerosis. Hypertension, type 2 diabetes and vascular disease are now common causes of CKD in these individuals. Clinical evidence shows that activation of the immune system by HIV infection and inflammation drive an increase in atherosclerosis-associated cardiovascular risk, even among PLWH who achieve viral suppression[26]. The exact mechanisms underlying this increased risk remain unknown; however, they may involve chronic macrophage-mediated inflammation[27–29], increased oxidative stress, endoplasmic reticulum stress, inflammasome activation and dysregulation of autophagy[30–32]. Data on the association between HIV infection and type 2 diabetes are contradictory, probably because of differences in study design[33,34]. In a large Danish cohort study from 2021, the adjusted odds ratio of type 2 diabetes in PLWH was 1.77 (95% CI 1.23 – 2.54; $P = 0.002$) compared with matched uninfected controls[35]. Risk factors included higher age and BMI. HIV-specific risk

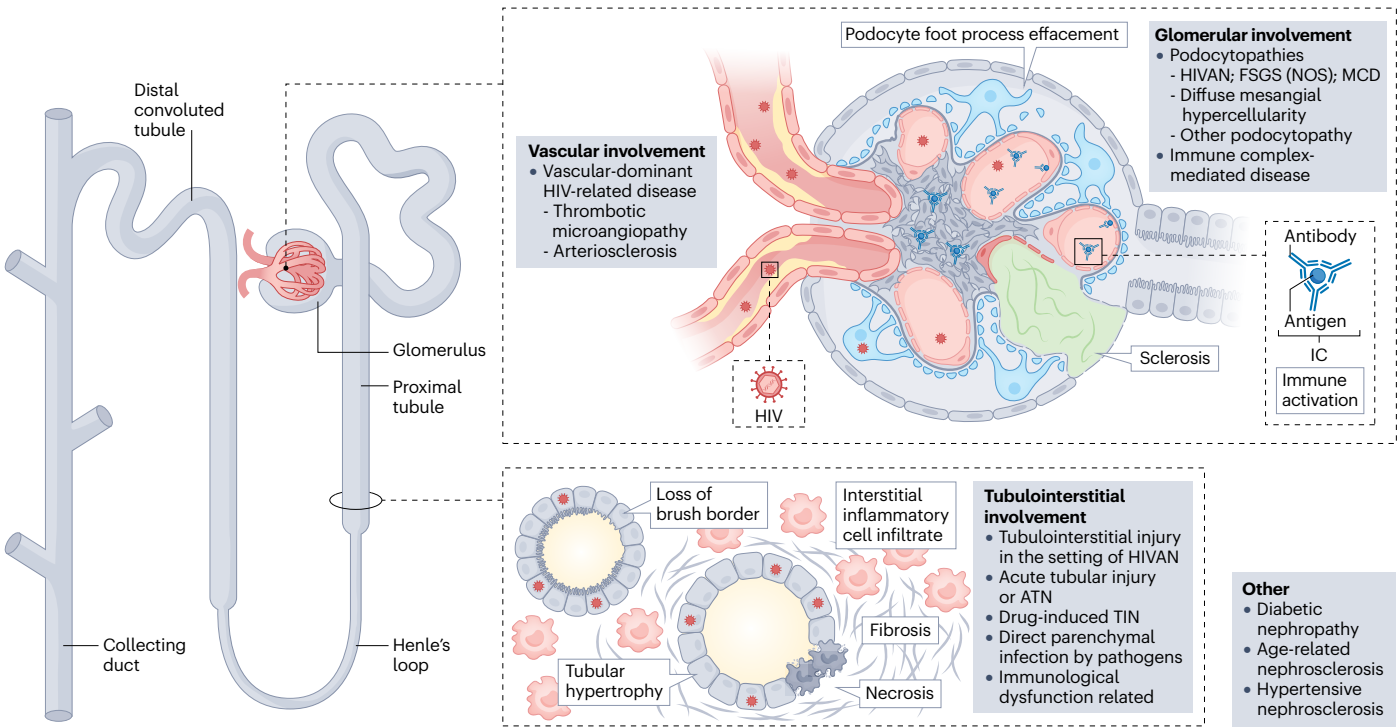

Fig. 2 | Pathological classification of HIV-associated kidney disease. HIV infection can affect all compartments of the kidney. The pathological classification of HIV-associated kidney diseases proposed by KDIGO is based on the major tissue compartment involved. The four main categories are: glomerular dominant, tubulointerstitial dominant, vascular dominant and other in the setting of HIV. The schematic view shows the location and subtypes in each main category. ATN, acute tubular injury; FSGS (NOS), focal segmental glomerulosclerosis (not otherwise specified); HIVAN, HIV-associated nephropathy; IC, immune complex; MCD, minimal change disease; TIN, tubulointerstitial nephritis.

factors, including CD4 count, duration on ART, use of older ART and previous AIDS-defining illnesses, were not associated with the increased risk of type 2 diabetes. However, type 2 diabetes in PLWH was associated with CKD (OR 2.8; 95% CI 1.29–6.09; $P = 0.009$)[35]. The proposed contributing mechanisms included the ART regimen, co-infection with HCV or tuberculosis, growth hormone deficiency, lipodystrophy and mitochondrial dysfunction, leading to insulin resistance[36]. In a mouse model of diabetic kidney disease, expression of an HIV transgene upregulated pro-inflammatory cytokines and worsened kidney injury[37].

The median age of patients in the US biopsy cohort was 53 years, and the prevalence of hypertension and diabetes was 57% and 31% respectively[4]. 16% of patients had diabetic kidney disease on biopsy. By contrast, the median age of patients in our Johannesburg cohort was 35 years and the prevalence of diabetic kidney disease only 3.6%[5]. This variance may support previous findings that HIV infection alone is not a risk factor for diabetic kidney disease. Global sclerosis (NOS), which is frequently associated with hypertension and obesity, was reported in 9% of kidney biopsy samples in the US biopsy series.

HIV has been suggested to accelerate the ageing process, with accelerated progression of comorbidities and onset of frailty. This proposal is supported by findings of a 2023 cohort study, which reported an increase in the burden of CKD over time among 8,880 PLWH compared with that of 8,880 matched controls, indicative of accelerated ageing in the PLWH group[38].

Diagnosis of kidney disease in HIV

The utility of the kidney biopsy

Estimating the prevalence of kidney histological diagnoses in the setting of HIV from biopsy data has its limitations. It is subject to selection bias, and many individuals with HIV and kidney disease do not undergo a kidney biopsy as the facility is not available or the risks are deemed to outweigh the potential benefit. Moreover, histological findings on the biopsy core may not be representative of the disease within the kidney. However, no clinical parameters, including genotyping for *APOL1*, can accurately predict histological diagnosis in HIV infection and biopsy therefore remains crucial for the appropriate management of an array of kidney diseases[4,5,12,39]. Histological diagnosis not only guides management but also assists in prognosticating kidney survival in patients with HIV-associated kidney diseases.

Biomarkers of kidney disease

Although kidney histology is the gold standard for diagnosis to aid therapy and prognostication of HIV kidney disease, serum and urinary biomarkers can be helpful. The most common and reliable biomarkers for CKD progression are GFR and proteinuria or albuminuria. Estimates (in the case of GFR) or measures of these biomarkers can be used to detect and monitor kidney disease progression and guide management. Biomarkers that are used predominantly in research settings and are increased in the urine of patients with HIV-associated kidney diseases include urine kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L-FABP), alpha-1-microglobulin (α1m), B2-microglobulin (B-2M), neutrophil gelatinase-associated lipocalin (NGAL), and N-acetyl-beta-D-glucosaminidase (NAG)[40–43]. Patients with HIVAN express four-fold higher levels of urinary NGAL than those with other glomerulopathies, reflecting the cystic tubular dilation that is a feature of HIVAN[41,42]. Some of these urinary biomarkers, including KIM-1, albumin, total protein, B2M, clusterin, trefoil factor-3 (TFF3), and cystatin C, have been used to detect potential glomerular and tubular dysfunction in clinical trials of ART[44,45].

Biomarkers associated with disease progression include increased urine albumin, IL-18 and KIM-1, which in one study, correlated with more rapid eGFR decline over 8 years of follow-up in women with HIV infection. The upper tertiles of IL-18 or KIM-1 were associated with a 7–8% faster rate of annual eGFR decline among women living with HIV[46].

Estimating kidney function

Accurate determination of kidney function is required for the staging and prognostication of CKD, to establish drug dosage regimens, and to facilitate prompt referral to nephrology services, enabling timely access to dialysis and listing for kidney transplantation. Direct measurement of GFR is complex and costly and thus, GFR is usually estimated from measured serum creatinine using an indirect laboratory-based calculation.

The CKD Epidemiology Collaboration (CKD-EPI) equation has been evaluated in several populations and is considered to have greater accuracy in estimating GFR than other equations among PLWH[47,48]. Indeed, the CKD-EPI equation is the method recommended by the European AIDS Clinical Society guidelines[49]. The original creatinine-based CKD-EPI equation incorporated race (Black or non-Black) as a patient-specific variable[50] to account for the higher serum creatinine levels measured in patients who self-identified as Black in the original studies. However, in 2020, the National Kidney Foundation and American Society of Nephrology (NKF–ASN) formed a joint taskforce to scrutinize the use of race-based eGFR equations, arising from concerns that incorporation of the race co-efficient into eGFR equations lacks a biological basis and results in higher apparent GFRs in Black individuals, thereby exacerbating health inequities[51]. Their recommendations, released in September 2021, included the immediate implementation of the 2021 CKD-EPI Cr equation refit (CKD-EPIcr_R) without a race co-efficient, and the increased use of cystatin C as a confirmatory method, especially in patients at risk of CKD[52].

A subsequent observational study that reported on the consequence of adopting the new race-neutral CKD-EPIcr_R equation on racial differences in kidney disease progression among 69,125 PLWH in North America found that 15.9% of Black individuals were reclassified into a lower GFR at baseline[53]. These individuals also had a higher prevalence of CKD risk factors and a higher risk of CKD progression across all GFR stages than white participants. Use of the new race-neutral eGFR creatinine-based equation may therefore identify Black PLWH who are at an increased risk of CKD progression, enabling earlier diagnosis and providing an opportunity to address modifiable risk factors to slow CKD progression.

The extent to which eGFR equations are transferrable to individuals living in continental Africa was investigated by comparing creatinine and cystatin C-based equations to mGFR (slope-intercept method for iohexol plasma clearance) in 2,578 participants from Malawi, Uganda and South Africa[54]. Creatinine-based GFR estimation equations, including the CKD-EPIcr_R equation, underestimated prevalence of kidney disease in these African populations — a finding that has considerable implications for both individuals and public health systems. Cystatin C-based estimating equations outperformed creatinine-based equations overall and at all stages of mGFR, consistent with data from the USA[55]. The best method for estimating kidney function therefore remains unclear. Available data suggest that cystatin C might be the preferred biomarker for African populations; however, assays to measure this biomarker remain largely unavailable. Moreover, cystatin C concentrations are also affected by inflammation and HIV viraemia, which may be a confounder in PLWH[56].

Pathogenesis of kidney disease

The causal relationship between direct HIV infection of the renal epithelial cells and HIVAN has been established in animal and in vitro models, and in human studies of kidney biopsy samples[57–59]. Transgenic animal models of HIV infection suggest that the pathogenesis of HIVAN might be promoted by the renal expression of HIV genes, particularly *Nef* (which encodes negative factor) and *Vpr* (which encodes viral protein r)[60–63]. In vitro studies in human cells suggest that the HIV gene *Tat* (which encodes trans activator of transcription) might also contribute to the development of HIVAN[64]. HIV can infect all compartments of the kidney, resulting in classic HIVAN (characterized by collapsing glomerulopathy, microcystic tubular dilatation and tubulointerstitial inflammation). Prior to the availability of ART, HIVAN rapidly progressed to kidney failure. Initiation of ART results in the stabilization of kidney function, even in patients with established HIVAN[65] — a finding that is consistent with a direct causative role of HIV infection in HIVAN (Fig. 3).

The kidney can act as a reservoir for the virus even when viraemia is undetectable[66], as evidenced by the detection of HIV-1 nucleic acids and phylogenetic analyses of HIV-1 sequences in kidney biopsy samples from virally suppressed patients with HIVAN[57,58,67], and evidence of HIV-1 shedding and compartmentalization in urine of virally suppressed PLWH[68,69]. Further evidence that the kidney can act as a reservoir for HIV is provided by the finding that HIV-1 can infect podocytes and tubular epithelial cells of kidney allografts from HIV-negative donors following transplantation into virally suppressed recipients on ART[70]. Measuring DNA and RNA levels of HIV-1 in urine can be used as a non-invasive test of HIV-1 infection in kidney allografts. Detection of donor and recipient HIV-1 strains in urine, renal epithelial cells and an allograft kidney biopsy following transplantation of an HIV-positive donor kidney into an HIV-positive recipient has been reported, suggesting that kidney transplantation from an HIV-positive viraemic donor to an HIV-positive recipient can result in the transfer and transient detection (for up to 16 days) of the donor's viral strain in the recipient, despite administration of ART[71]. Of note, a 2023 autopsy study of two PLWH who had been virally suppressed for many years on ART showed the presence of HIV DNA in various tissues, including genetically intact proviruses in lymphoid organs, and multiple copies of identical HIV genomes in all sampled tissues with half of the tissue reservoirs showing evidence of clonal expansion. The findings from this study suggest that infected cells might expand, migrate and circulate between different tissues and anatomical sites despite prolonged ART[72].

APOL1 and kidney pathological conditions in HIV infection

The reports of HIVAN occurring primarily in those of African ancestry led to the discovery of its association with the GI and G2 *APOL1* risk alleles[73,74]. These two *APOL1* variants evolved as a protective mechanism against human African trypanosomiasis and are widely dispersed, largely as a consequence of out-of-Africa migration and the transatlantic slave trade from West Africa, where these variants are present in over 40% of the population[75].

In PLWH, the presence of *APOL1* risk alleles influences the pattern of kidney disease, its response to therapy and its outcomes. The lifetime risk of HIVAN is 50% in African American individuals not receiving ART and with two *APOL1* risk alleles[76]. The *APOL1* risk variants are particularly associated with HIVAN[77–80] (Table 2). A cross-sectional study of 2,864 PLWH of African ancestry living in the UK reported increased odds of HIVAN among individuals with APOL1 risk genotypes (OR 30.16; 95% CI 12.48–72)[81]. The study also reported that an estimated 49% of kidney failure cases were attributable to the presence of *APOL1* risk genotypes[81]. The association between *APOL1* risk variants and HIVAN is further supported by a systematic review and meta-analysis, which reported that the prevalence of *APOL1* high-risk alleles significantly increased the risk of HIVAN (pooled OR 16.67; 95% CI 10.22–27.19; $n = 769$, $P < 0.001$)[82].

The *APOL1* risk variants are also associated with other forms of HIV-associated kidney diseases. An analysis of kidney biopsy samples from 98 African Americans with HIV, two *APOL1* risk alleles and non-HIVAN kidney disease found that the majority (76%) had FSGS whereas 10% had hypertensive nephrosclerosis. Among individuals with one *APOL1* risk allele, 47% had immune complex-mediated glomerulonephritis as the predominant lesion whereas only 23% had FSGS. By contrast, individuals with no *APOL1* risk allele, 40% had immune complex-mediated glomerulonephritis and 12% had FSGS. Individuals with two *APOL1* risk alleles had a nearly three-fold higher risk of kidney failure than those with one or zero risk alleles[83].

In children with perinatal HIV infection, the presence of *APOL1* risk genotypes was associated with 3.5-fold increased odds of developing CKD than that of children with low-risk genotypes (that is, in possession of zero or one risk allele; 95% CI; 1.2–10.0 in adjusted analyses)[84]. In a cross-sectional study from the Democratic Republic of Congo, 23 (5.7%) of 401 children living with HIV who carried two *APOL1* risk alleles had an almost 22-fold increased risk of elevated albuminuria compared with children with one or zero risk alleles[85].

Some reports have claimed that populations that do not express *APOL1* risk variants — in Ethiopia, for example — are protected from HIVAN[86,87]. However, these claims are based on clinical diagnoses of kidney function (that is, eGFR and proteinuria), rather than histological diagnoses.

Available evidence suggests that *APOL1* risk alleles are toxic, gain-of-function variants[88,89]. Several mechanisms have been linked to the pathogenesis of *APOL1*-mediated kidney disease, including mitochondrial damage, endoplasmic reticulum and lysosomal stress[75], and JNK–MAPK-mediated cytotoxicity, resulting in extrusion of intracellular potassium, cell lysis and death[90]. The mechanisms by which *APOL1* high-risk variants potentiate HIVAN are not yet clear. One proposal is that the expression of HIV-associated genes in kidney cells increases the expression of interferon and/or TNF within the kidney, possibly stimulating the expression of *APOL1* G1 and/or G2 transcripts[91]. Animal models and cell-based experiments have shown that the expression of *APOL1* risk variants is toxic to kidney cells and results in histological injury closely resembling HIVAN[92,93].

Rapid progression of HIVAN to kidney failure has been reported among patients with two *APOL1* risk alleles who receive no treatment or are under-treated[83,94]. In the Multicenter AIDS Cohort Study, the rate of annual eGFR decline was 2.5-fold faster among individuals with the high-risk *APOL1* genotype if viral suppression was poor[95]. This rapid decline in kidney function was not seen in individuals with the *APOL1* high-risk genotype, who maintained durable viral suppression.

'Second hits'

Not all individuals with the *APOL1* high-risk genotype develop *APOL1*-associated kidney disease, suggesting that 'second hits' that produce inflammatory or interferon responses are required to induce detrimental effects on kidney cells. Examples of such second hits include viruses (especially HIV or SARS-CoV-2), autoimmune diseases (systemic lupus erythematosus), ischaemia–reperfusion injury (sickle cell disease), kidney allograft rejection and exogenous interferon administration[96].

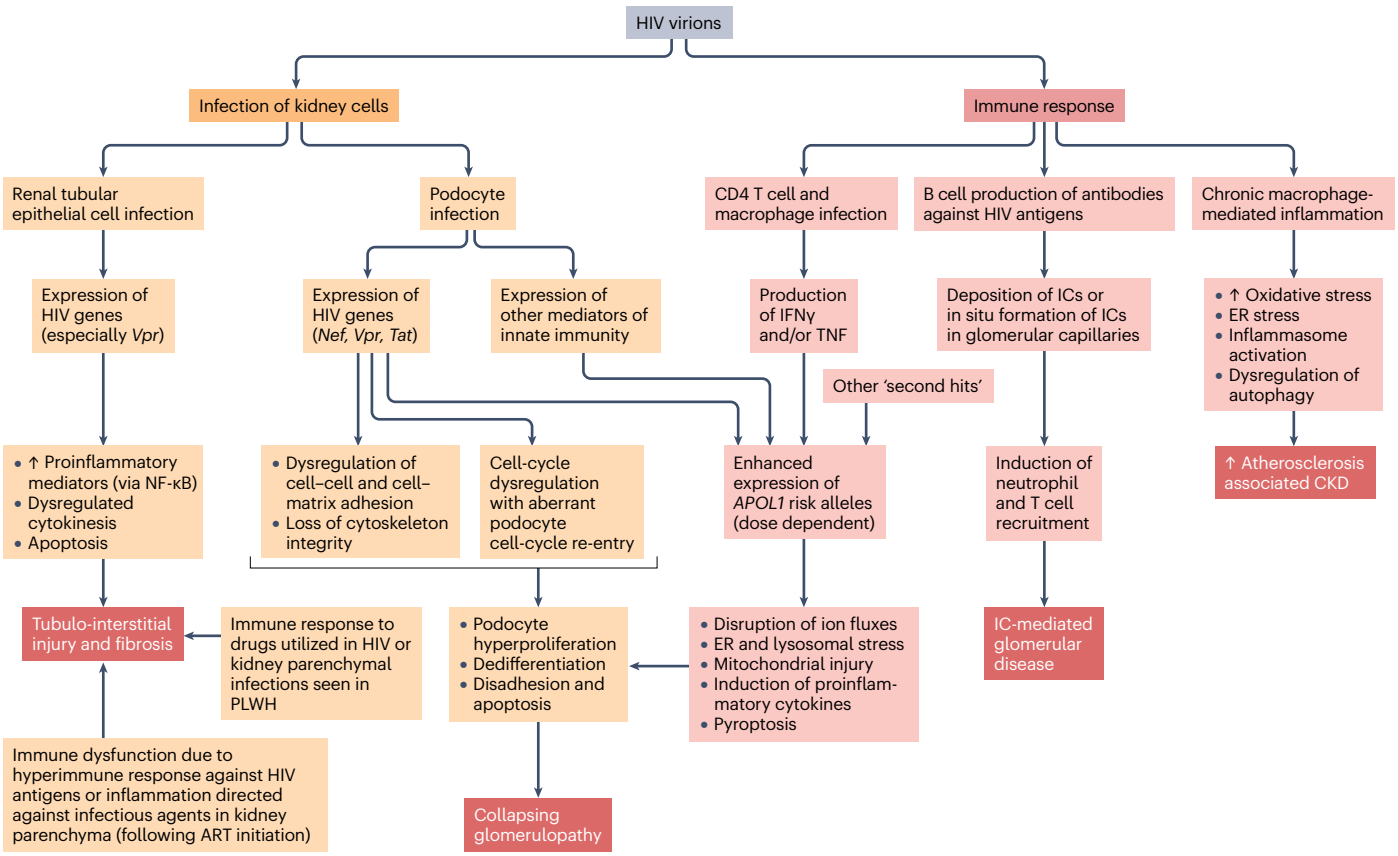

Fig. 3 | Proposed major mechanisms by which HIV infection promotes kidney injury. Circulating HIV virions may affect compartments of the kidney through several mechanisms involving direct infection of the kidney cells and/or activation of the immune system. HIV may infect renal tubular epithelial cells and podocytes, with expression of HIV genes (*Nef, Vpr, Tat*) and induction of innate immune responses. In renal tubular epithelial cells, these processes give rise to an increase in pro-inflammatory mediators (via NF-κB), dysregulated cytokinesis, and apoptosis, ultimately resulting in tubulointerstitial injury and fibrosis. The expression of HIV genes in podocytes elicits podocyte hyperproliferation, dedifferentiation, disadhesion and apoptosis, effectively leading to a collapsing glomerulopathy. HIV activates the immune system through CD4 T cell and macrophage infection, or by stimulating B cell production of antibodies directed against HIV. Immune complex-mediated glomerular disease occurs because of the deposition or in situ formation of immune complexes within the glomerular capillaries and mesangium prompting a detrimental immune cascade involving neutrophil and T cell recruitment. CD4 T cell and macrophage infection increases the production of IFNγ and TNF. This response, along with other 'second hits' and the expression of immune mediators via HIV infection of podocytes, enhances the expression of *APOL1* risk alleles in a dose-dependent manner, ultimately resulting in a collapsing glomerulopathy. Chronic macrophage-mediated inflammation can also lead to atherosclerosis-associated chronic kidney disease. Tubulointerstitial injury and fibrosis may occur through two immune-mediated mechanisms. First, via an immune response, within the tubulointerstitium, to either an infectious pathogen or to drugs utilized to treat opportunistic infections in people living with HIV (PLWH). Second, owing to immune dysfunction and a hyperinflammatory response, either directed against HIV antigens within the tubulointerstitium or as a result of immune reconstitution (following ART initiation) against an infectious agent within the tubulointerstitium. Nephron loss and worsening CKD are a consequence of ongoing glomerular and tubulointerstitial damage. *APOL1*, apolipoprotein L1; ART, antiretroviral therapy; CKD, chronic kidney disease; ER, endoplasmic reticulum; IC(s), immune complex(es); IFN, interferon; *Nef*, negative regulatory factor; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; *Tat*, trans-activator of transcription; TNF, tumour necrosis factor; *Vpr*, viral protein R.

COVID-19 in PLWH and chronic kidney disease

Data on COVID-19 outcomes among PLWH and CKD are limited. A systematic review and meta-analysis of 44 studies including 38,971,065 patients infected with SARS-CoV-2 reported a pooled prevalence of HIV co-infection of 26.9% (95% CI 22.7–31.3). In a pooled analysis of unadjusted odds ratios from six studies, PLWH were more likely to be hospitalized following SARS-CoV-2 infection than those without HIV (OR 1.49; 95% CI 1.01–2.21). Adjusted analyses suggested that HIV co-infection was independently associated with increased mortality risk in patients with COVID-19. However, the researchers noted that the supporting evidence of this association was weak as it was derived from only two studies[97].

An analysis of data in the WHO Global Clinical Platform from 197,479 individuals from 38 countries hospitalized with COVID-19 found that CKD was more frequent in the cohort of 16,955 PLWH than in the cohort of patients without HIV (5.4% versus 2.3%; $P < 0.0001$). A total of 16,283 (96%) of the individuals with HIV were from Africa, mostly from South Africa (over 94%), and most (91.5%) of the 60% of PLWH for whom data regarding ART use was available were receiving ART[98]. Among PLWH, the most significant risk factor for in-hospital mortality was severe or critical presentation (HR 1.86; 95% CI 1.82–1.9; $P < 0.0001$), followed by CKD (HR 1.41; 95% CI 1.31–1.52; $P < 0.0001$). ART-induced viral suppression was associated with

better outcomes in PLWH than in patients who had not achieved viral suppression[98].

A number of reports have described the presence of glomerular disease in patients with COVID-19. A multi-centre, clinicopathological study of 284 biopsy samples (240 native biopsies and 44 allografts) from patients with COVID-19 identified 28 different histological diagnoses in the native biopsy samples, the most common of which were COVID-associated nephropathy (COVAN, 25.8%), acute tubular injury (13.3%) and diabetic kidney disease (12.2%)[99]. In allograft biopsy samples, the most common pathological conditions were allograft rejection (61.4%), followed by acute tubular injury (27.3%). COVAN is a collapsing FSGS and has many similarities to HIVAN, including a predilection for patients with high-risk *APOL1* genotypes and histology characteristic of interferon-mediated viral infections[100–102]. In patients with biopsy-proven COVAN, the frequency of high-risk *APOL1* genotypes is reportedly 86–94%[99,103,104]. COVAN should be suspected in patients of African descent with COVID-19, AKI and nephrotic-range proteinuria. COVAN outcomes have not been extensively studied; however, in three case series totalling 72 patients kidney prognosis was poor and similar to that of collapsing glomerulopathy from other aetiologies, including HIV[99,103,104].

Renal effects of newer ART

WHO guidelines recommend the immediate initiation of ART at HIV diagnosis, with a combination of three drugs to reduce the emergence of drug-resistant viral strains[105]. Dolutegravir in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone or efavirenz in combination with an NTRI backbone are the preferred first-line ART regimens in adults and adolescents. However, early initiation of ART has resulted in a longer cumulative exposure to these medications. Renal toxicity occurs with specific ART agents and contributes to the risk of CKD in PLWH. Additional CKD risk is related to comorbid conditions, increasing age and polypharmacy in these individuals[106,107].

Nucleoside reverse transcriptase inhibitors

TDF is currently recommended as a first-line agent for HIV treatment in settings in which tenofovir alafenamide (TAF) is not available and in patients with normal kidney function. TDF is eliminated through the kidney via glomerular filtration and active proximal tubular secretion[108]. It is commonly associated with subclinical proximal tubular dysfunction, which presents as non-nephrotic range proteinuria and excessive phosphaturia. A therapy-limiting severe tubulopathy is seen in 1–2% of patients on TDF[109], which may manifest as biochemical abnormalities, including Fanconi syndrome, osteomalacia and AKI. Rarely, TDF can also cause toxicity to the distal tubule, which presents as nephrogenic diabetes insipidus and distal renal tubular acidosis[110,111].

Risk factors for TDF-induced kidney injury include underlying CKD and CKD risk factors (such as diabetes mellitus and older age), co-infection with HBV and/or HCV, advanced HIV infection and concomitant use of nephrotoxic agents (particularly didanosine or ritonavir-boosted protease inhibitor regimens)[109]. TDF nephrotoxicity is amplified by the co-administration of drugs that interfere with co-transporters in the proximal tubule[112].

TDF is potentially cumulatively nephrotoxic. In a prospective international cohort study, 1% of PLWH on TDF with normal kidney function at baseline developed CKD over a median follow-up time of 7.2 years[113]. Such nephrotoxicity was not reported with cumulative exposure to another NRTI, abacavir. A meta-analysis that included 10,889 PLWH concluded that TDF-containing ART regimens were associated with loss of kidney function and an increased risk of AKI compared with ART regimens that did not contain TDF[114].

TAF is a prodrug of tenofovir and is also recommended as a first-line treatment in PLWH[105]. TAF has minimal mitochondrial toxicity in vivo and a more favourable kidney and bone safety profile than TDF-containing regimens[115]. Potential nephrotoxicity associated with TAF has been reported, including Fanconi syndrome, but causation has not been confirmed[116,117]. Switch studies from TDF to TAF show that renal toxicity is potentially reversible[118].

A robust systematic review and meta-analysis of 14,894 patients across 14 trials reported no difference in renal outcomes between TAF- and TDF-treated groups in terms of actual tubular events or overall number of ART discontinuations due to kidney adverse events[119]. A small but significantly higher number ($P = 0.03$) of discontinuations due to kidney adverse effects occurred in the boosted TDF versus boosted TAF subgroups. The authors concluded that TDF is safe and well tolerated in young, otherwise healthy individuals.

Protease inhibitors

Protease inhibitors do not require dose adjustment in patients with kidney dysfunction but are used less commonly with the advent of newer ART regimens[120]. Cohort studies have suggested that certain protease inhibitors are associated with an increased risk of CKD, but these

Table 2 | Prevalence of *APOL1* high-risk genotypes in different populations of African ancestry

Histology in PLWH	Population (*n*)	*APOL 1* high-risk genotype frequency (%)			Odds ratios (95% CI) for 2 versus 1 or 0 risk alleles	Ref.
		HIV negative no CKD	HIV positive no CKD	HIV positive with specific histology		
HIVAN	African American (*n*=54)	NR	NR	72	29.2 (13.1–68.5)	77
	African American (*n*=60)	NR	NR	NR	3.01 (1.2–7.59)	79
	South African (*n*=38)	1.9	3.7	79	89 (17.7–912)	78
	Northern Nigerian (*n*=17)	5.8	0	12.5[a]	5.5 (0.83–36.29)	80
FSGS	South African (*n*=22)	1.9	3.7	8	2.1 (0.03–44)	78
	Northern Nigerian (*n*=20)	5.8	0	12.5[a]	9.0 (1.62–50.12)	80
ICD	South African (*n*=12)	1.9	3.7	25	5.6 (0.4–86)	78

CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; ICD, immune complex-mediated disease; NR, not reported; PLWH, people living with HIV. [a]*APOL1* high-risk genotype frequency of 12.5% among those with HIV-associated kidney disease in the Northern Nigerian cohort.

changes in kidney function may reflect a pharmaco-enhancer ('booster') effect on tubular creatinine transport[121]. Cobicistat and ritonavir are used as 'boosters' with protease inhibitor regimens. Atazanavir and indinavir have been most commonly linked to interstitial nephritis and nephrolithiasis[122–124]. Data from 1,430 patients from the UK CHIC study, who had a median eGFR of 93 ml/min/1.73 m^2, and switched their protease inhibitor from atazanavir or lopinavir to darunavir showed stable or improved kidney function over a 6-month period, suggesting that darunavir may have the more favourable kidney safety profile[125].

Integrase strand transfer inhibitors

Integrase strand transfer inhibitors are the preferred third agent, in combination with two NRTIs, for the treatment of ART-naïve patients[105]. Drugs in this class include raltegravir, dolutegravir, elvitegravir, bictegravir and cabotegravir (a long-acting injectable integrase strand transfer inhibitors used in combination with rilpivirine).

Raltegravir has been reported to cause small reductions in kidney function by an unknown mechanism[126]. It may also be associated with rhabdomyolysis[127]. Elvitegravir is usually co-administered with cobicistat to boost its levels and allow once-daily dosing. Cobicistat inhibits the excretion of creatinine into the proximal tubule, giving the appearance of an elevated serum creatinine[128]. Bictegravir and dolutegravir also reduce the tubular secretion of creatinine, with a resultant rise in serum creatinine without any alteration in actual GFR[129,130]. The increase in serum creatinine is non-progressive, occurs within the first 4 weeks of treatment and is reversible[131]. This non-pathological effect is not observed when eGFR is calculated using inulin or cystatin C; cystatin C is the preferred method for calculating eGFR in these patients[132].

Single-tablet regimens

In 2006 the first single-tablet regimen (STR) containing emtricitabine, TDF and efavirenz was launched[133]. Many other STRs are now available that reduce the ART pill burden and reduce selective non-adherence to components of the ART regimen, potentially lowering the risk of viral resistance[134,135]. An inability to adjust doses in patients with CKD limits their use.

No STRs are approved for PLWH with kidney failure on dialysis. A case series of nine HIV-positive patients on haemodialysis receiving a STR containing abacavir, lamivudine and dolutegravir demonstrated that the STR was well tolerated. After switching to the STR, 5 (85%) patients achieved undetectable viral loads compared with 4 prior to the switch[136]. The findings of a phase IIIb trial using an STR containing elvitegravir, cobicistat, emtricitabine and TAF in PLWH on chronic haemodialysis suggests that this STR might be tolerable and a convenient option for HIV treatment in this patient group[137].

Two-drug HIV treatment regimens with renal 'safety'

The past few years has seen a shift towards two-drug ART regimens, which are aimed at eliminating the toxicity of the third drug. For example, renal and bone adverse events could be reduced by avoiding TDF. Dolutegravir–lamivudine is an STR and the only two-drug regimen approved in 2020 for use in ART-naïve patients, with viral loads <500,000 copies per ml and CD4 count >200 cells/ml[138]. This regimen may be beneficial in patients with kidney impairment in whom even TAF should be avoided.

In two large, randomized trials, dolutegravir–lamivudine demonstrated similar efficacy to that of dolutegravir–emtricitabine–TDF at 96 weeks, with similar rates of viral suppression[139]. Only 1 patient in the dolutegravir–lamivudine arm developed resistance to both dolutegravir and lamivudine at 144 weeks. The two-drug arm was associated with better kidney, urine and bone turnover biomarker profiles than the triple regimen.

Despite evidence of equivalent efficacy, concern remains that dual ART may be inferior to triple ART with respect to suppression of HIV-related immune activation and inflammation. Persistent inflammation and immune activation have key roles in the development of serious non-AIDS events, including cancer and cardiovascular and kidney disease[140–142]. Further studies are needed to investigate these potential affects.

Polypharmacy in HIV-positive patients

In PLWH, polypharmacy is not only related to ART exposure and medications used for the treatment of concomitant opportunistic infections, but also because of the use of medications for chronic non-communicable diseases[143]. Drug–drug interactions between ART and other drugs are well recognized and must be considered in the management of PLWH and comorbidities, including CKD (Table 3).

Treatment of CKD in HIV-positive patients

Expert guidelines recommend screening and early identification of CKD in PLWH[11]. Current therapies for CKD do not specifically target the pathways and/or genetic factors that contribute to HIV-related CKD progression. PLWH should be started on ART (if not already initiated) and assessed for reversible factors — such as hyperglycaemia, hyperuricaemia, hyperlipidaemia, hypertension, lifestyle factors and co-infections — that may increase their risk of kidney disease progression. Patients with HIV-related proteinuric CKD should be treated with an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB)[144]. Patients with persistent proteinuria despite treatment with an ACE inhibitor or ARB may benefit from the addition of a sodium–glucose cotransporter 2 (SGLT2) inhibitor. Potential benefit has been extrapolated from large, randomized trials demonstrating that SGLT2 inhibitors delay the progression of non-diabetic proteinuric CKD, including FSGS[145]. Dose adjustment of renally excreted medications should be performed and nephrotoxic agents avoided. (Table 3).

All PLWH are at an increased risk of developing CKD and should receive frequent monitoring of GFR and early referral to nephrology services. Such an approach is important in order to co-ordinate CKD treatment, prepare for dialysis and list the patient for kidney transplantation.

Novel therapies for APOL1-associated nephropathy

Available therapy options for patients with *APOL1*-associated kidney diseases do not target the underlying pathogenesis and thus fail to prevent progression of kidney disease[146,147]. As described above, available evidence suggests that *APOL1* risk alleles are toxic, gain-of-function variants; available evidence also suggests that *APOL1* is not necessary for normal kidney function[88,89], suggesting that therapeutic options that reduce APOL1 protein and or its activity might ameliorate its potential harm.

A number of targeted therapies are under investigation for *APOL1*-associated kidney diseases, including APOL1 small molecule inhibitors, APOL1 antisense oligonucleotides and inhibitors of APOL1-associated inflammatory pathways[148]. A series of APOL1 small molecule inhibitors have been shown to block APOL1 function in vitro and reduce proteinuria in transgenic mice[149]. In a proof-of-concept phase IIa study, administration of the oral APOL1 small molecule inhibitor, inaxaplin,

Table 3 | Antiretroviral dosing in adults with CKD and potential drug–drug interactions

ART drug class	Drug	CrCl (ml/min) at which dose adjustment is recommended	Haemodialysis dose adjustment required	Peritoneal dialysis dose adjustment required	Potential drug–drug interactions for ART class[a]
Nucleos(t)ide reverse transcriptase inhibitors	Emtricibine	CrCl <50	Yes	No data	Adefovir Carbemazepine Ledipasvir/sofosbuvir Orlistat Rifabutin/rifampin/rifapentine Boosted PIs
	Lamivudine	CrCl <30*	Yes	Yes	
	TDF	CrCl <50	Yes	No data	
	TAF	CrCl <15	NDA	No data	
	Abacavir	NDA	NDA	NDA	
	Zidovudine	CrCl <15	Yes	No data	
Non-nucleoside reverse transcriptase inhibitors	Efavirenz	NDA	NDA	NDA	Azoles Bedaquiline Calcineurin inhibitors Carbamazepine/phenytoin Hepatitis C DAA agents Omeprazole Rifabutin/rifampin/rifapentine Statins
	Nevirapine	NDA	Additional dose after each dialysis session	NDA	
	Doravirine	NDA	NDA	NDA	
	Delavirdine	NDA	NDA	NDA	
	Rilpivirine	NDA	NDA	NDA	
	Etravirine	NDA	NDA	NDA	
Protease inhibitors	Atazanavir/cobicistat	NDA	Not recommended	NDA	Antacids Anti-arrhythmics Antiplatelet agents Alpha adrenergic antagonists Bedaquiline Buprenorphine Calcineurin inhibitors Calcium channel blockers Carbamazepine/phenytoin Dapagliflozin/saxagliptin Eplerenone Everolimus Hepatitis C DAA agents Midazolam/triazolam Rifabutin/rifampin/rifapentine Statins
	Atazanavir/ritonavir	NDA	Not recommended	NDA	
	Lopinavir/ritonavir	NDA	Yes	NDA	
	Darunavir/ritonavir	NDA	NDA	NDA	
	Darunavir/cobicistat	NDA	No data	NDA	
Integrase strand inhibitors	Dolutegravir	NDA	NDA	NDA	Alfuzosin/silodosin Antiplatelet agents Anti-arrhythmics Apixaban/rivaroxaban Calcineurin inhibitors Carbamazepine/phenytoin Dapagliflozin/saxagliptin Eplerenone Hepatitis C DAA agents Metformin Rifabutin/rifampin/rifapentine Statins
	Raltegravir	NDA	NDA	NDA	
	Bictegravir	NDA	NDA	NDA	
	Cabotegravir/rilpivirine	NDA	NDA	NDA	
	Elvitegravir/cobicistat	NDA	NDA	NDA	
Binding/entry inhibitors	Maraviroc	CrCl <30	Yes	No data	Carbamazepine/phenytoin Rifabutin/rifampin/rifapentine
	Mavaviroc with CYP3A inhibitor	CrCl <30 not recommended	Not recommended	No data	
	Enfuvirtide	NDA	NDA	NDA	
	Ibalizumab	No data	No data	No data	
	Fostemsavir	NDA	NDA	NDA	
	Lenacapavir	NDA	NDA	NDA	

This table was compiled using data from refs. 138,192. ART, antiretroviral therapy; CrCl, creatinine clearance; DAA, direct acting antiviral; NDA, no dose adjustment; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. [a]This is not a comprehensive list of all potential drug–drug interactions.

in addition to standard-of-care medication, reduced proteinuria by 47.6% (95% CI −60.6 to −31.3%) in 13 participants with two *APOL1* mutations, biopsy-proven FSGS and nephrotic- or subnephrotic-range proteinuria at baseline[150]. A rapid and linear reduction in proteinuria from baseline was observed by day 15, and continued until the study end at 13 weeks, prompting the researchers to suggest that longer periods of inaxaplin treatment might slow kidney function decline. A phase II/III adaptive placebo-controlled trial, AMPLITUDE, is currently in progress to evaluate inaxaplin in *APOL1*-associated kidney disease[151]. Although APOL1 inhibitors such as inaxaplin offer the potential of a 'precision medicine' approach for *APOL1*-associated kidney diseases, in West Africa — the area with the highest prevalence of *APOL1* risk genotypes — these genotypes confer a survival advantage against African Sleeping Sickness and the use of APOL1 inhibitors may increase morbidity related to *Trypanosoma brucei gambiense* infection in these populations. Should such therapeutics become available in the future, caution is therefore potentially needed with their use in people living in areas in which African sleeping sickness occurs.

Interferons, Toll-like receptor agonists and other cytokines can increase *APOL1* expression, as can activation of the JAK–STAT pathway[91,152,153]. Inhibition of these APOL1-associated inflammatory pathways may therefore represent a therapeutic option for *APOL1*-associated kidney diseases. Indeed, JAK kinase inhibitors are currently under investigation as a potential therapy to reduce inflammation-induced upregulation of *APOL1* (ref. 154). However, the risk versus benefit of such an approach remains to be assessed. Antisense oligonucleotides to APOL1 are another potential therapeutic approach and have been shown to be effective in transgenic mice[155].

Renal transplantation in PLWH

For decades, PLWH were excluded from kidney transplantation programmes owing to high rates of AIDS-related morbidity and mortality. In the late 1990s, the widespread availability of ART transformed HIV into a controllable chronic disorder. In acknowledgement of the increasing number of PLWH awaiting kidney transplantation, in 2007 the Swiss Federal Act for the transplantation of organs, tissues and cells permitted HIV-positive organs to be transplanted into recipients living with HIV. In 2013, the USA followed with the HIV Organ Policy Equity (HOPE) Act[156]. Following these regulatory changes, several studies have confirmed that short-term graft survival, intermediate-term graft survival and patient outcomes are comparable in HIV-positive recipients with well-controlled HIV disease and no comorbidities and HIV-negative recipients[7,157,158].

Long-term outcomes of kidney and liver transplants have been evaluated in a retrospective single-centre cohort of transplantations performed between 2000 and 2019, including kidney transplants in 119 PLWH and 655 matched recipients without HIV[159]. HIV status was not associated with adverse graft survival and overall graft and patient survival remained comparable up to 10 years post-transplantation. Poorer outcomes were initially reported in PLWH who were co-infected with HBV and/or HCV[160,161]; however, outcomes for these patients improved markedly with the advent of direct-acting antiviral therapies[162]. Kidney transplant is associated with significant survival benefit compared with chronic dialysis in PLWH with kidney failure. A national study of 1,431 PLWH on the kidney transplant waiting list in the USA found that kidney transplantation was associated with a 79% (adjusted relative risk (aRR) 0.21, 95% CI 0.10–0.42) lower risk of mortality compared with dialysis and a significant survival benefit by 194 days post-transplantation[163].

In 2010, four successful kidney transplants involving donors with HIV and recipients living with HIV were reported in Cape Town, South Africa[164]. By 2019, a total of 51 PLWH had received kidneys from deceased HIV-positive donors[165]. No donor-derived drug-resistant mutations have been found in transplant recipients since 2011, and no recipients have had to change their ART regimen owing to virological failure[165,166]. The outcomes of these transplantations are comparable with those of HIV-negative to HIV-positive kidney transplants performed in the USA[7].

A prospective pilot study that compared kidney transplant outcomes between HIV-positive donors to HIV-positive recipients with those of HIV-negative donors to HIV-positive recipients across 14 transplantation centres in the USA from 2016 to 2019, found no significant difference in rates of acute rejection at 1 year post-transplantation[167]. Transplant and HIV outcomes in recipients who received HIV-positive donor kidneys were excellent. With the use of stable ART regimens and prophylaxis against opportunistic infections during the early post-transplantation period, progression to AIDS has not been an issue in these studies. The use of HIV-positive donor organs has decreased waiting times for recipients living with HIV from more than 8 years to less than 1 year, in certain parts of the USA.

Post-transplantation complications

Rejection. A number of studies indicate that HIV-positive kidney transplant recipients have higher rejection rates than HIV-negative recipients. In a large, multicentre trial from the USA, the cumulative incidence of graft rejection among HIV-positive recipients was 31% (95% CI 24 to 40) at 1 year and 41% (95% CI 32 to 52) at 3 years post-transplantation, compared with an estimated 1-year rejection rate for all kidney transplant recipients, of 12.3% (95% CI 11.9 to 12.7), according to the National Scientific Registry of Transplant Recipients. A multivariate proportional-hazards analysis showed that the risk of graft loss was increased among patients treated for rejection (HR 2.8; 95% CI 1.2–6.6; $P = 0.02$)[7]. However, among HIV-positive recipients, rejection rates are similar regardless of whether the allograft originated from an HIV-positive or an HIV-negative donor[7,165]. Possible reasons underlying the high rejection rates in recipients living with HIV include subtherapeutic plasma levels of immunosuppressive drugs due to drug–drug interactions that affect cytochrome P450 enzymes or the frequency of protease inhibitor dosing (resulting in potential adherence difficulties); chronic immune activation and dysregulated immune responses in PLWH; or the use of IL-2 induction rather than lymphocyte-depleting induction agents owing to concerns over immunosuppression[168–172]. Drug–drug interactions can in principle be mitigated by swapping protease inhibitors for integrase inhibitor regimens prior to transplantation.

Recurrence of HIVAN. The recurrence of HIVAN was not considered to be a clinical problem in a multicentre trial of 150 kidney transplant recipients living with HIV in the USA[7]. However, of the 51 patients in a South African cohort of transplant recipients living with HIV who received an allograft from an HIV-positive donor, histological changes of HIVAN were observed in 12 patients, and 2 patients lost their allografts as a consequence[165]. Patients' viral loads were undetectable for the duration of the study, and no correlation was found between HIVAN recurrence and donor viral load[165].

In another study, in situ hybrid hybridization was used to demonstrate the presence of HIV RNA in the podocytes and tubules of 13 of 19 kidney allografts from HIV-negative donors following transplantation

into HIV-positive donors[70]. None of the 19 recipients had detectable plasma HIV RNA levels at transplantation. Podocyte infection with HIV was associated with nephrotic-range proteinuria, progressive development of FSGS and decline in kidney function. Kidney allografts in which only tubule cells were infected with HIV had fewer clinical manifestations.

As described earlier, donor and recipient HIV-1 strains have been identified in biopsy samples from transplanted allografts, suggesting transmission of donor virus to the recipient kidney[71]. However, the detection of donor HIV was transient and did not affect the outcome of the recipient[71].

Opportunistic malignancies. Kidney transplant recipients have a higher risk of cancer than the general population. Human papillomavirus-mediated cancers can be problematic because the activation of latent infection in the context of immunosuppression increases the risk of progression to malignancy. Thus, transplant recipients living with HIV should undergo screening cervical and anal pap smears regularly, to ensure early diagnosis and prevent the need for major surgical resection[173]. In addition, regular surveillance for malignancies should be carried out in HIV-positive transplant recipients, as in all transplant recipients.

HIV-positive living donation

PLWH are at an increased risk of kidney failure compared with individuals without HIV. This risk is exacerbated by the presence of comorbid conditions, such as diabetes mellitus and hypertension, which may exclude affected individuals from kidney donation programmes[174,175].

The additional risk of kidney failure among PLWH who met the eligibility criteria for kidney donation was assessed in a study of 41,968 HIV-positive participants of NA-ACCORD (median follow-up 5 years) and comparable HIV-negative participants from NHANES III (median follow-up 14 years)[176]. The study found that the risk of kidney failure depended on the age and race of the potential donor, and was 6.9-fold higher in Black than in white PLWH. A limitation of the study was the unavailability of *APOL1* genotypes and thus the inability to calculate how much of the excess risk in Black PLWH was influenced by *APOL1* risk alleles. Nevertheless, the researchers concluded that PLWH who have no comorbidities and well controlled disease have an acceptable risk of kidney failure and can be considered low-risk kidney-donor candidates.

A small number of case reports have described kidney transplantations from living, HIV-positive donors into recipients with HIV, all with favourable outcomes[177–180]. A case of a successful kidney transplantation from a living donor with HIV to a recipient living with HIV, with 7 years' follow up, reported that the donor developed worsening hypertension but was well controlled on two agents, and that her kidney function and immune status remained stable post-donation[177].

These reports suggest that the donor pool for PLWH and kidney failure can be expanded by using organs from living donors with HIV. However, no reports exist of living donors with HIV of Black African descent — a population that is at a particularly high risk of kidney failure. High-risk *APOL1* haplotypes found in PLWH greatly increase the risk of the development of FSGS, HIVAN and rapid deterioration to kidney failure[78]. The presence of high-risk *APOL1* genotypes in the donor kidney are also associated with adverse graft outcomes[181,182]. All potential living donors with HIV of Black African descent should therefore be screened for *APOL1* high-risk genotypes as part of the risk assessment process.

ABO-incompatible live donation

ABO-incompatible transplantation requires an intensified immunosuppressive regimen and is associated with a greater risk of graft rejection[183], which can be a concern given the already increased risk of rejection in transplant recipients living with HIV. However, case reports have described the successful transplantation of ABO-incompatible kidneys from living, HIV-negative donors into recipients with HIV. In one report that described the transplantation of a single ABO-incompatible kidney from a living donor into a recipient with HIV, both the recipient and donor had stable renal function at 17 months' follow-up; one infectious episode occurred and one suspected rejection episode was successfully treated with steroids[184]. Another report documented the successful transplantation of an ABO-incompatible kidney from a living donor into a 47-year-old African American recipient living with HIV; at 170 days post-transplantation, his serum creatinine was maintained, despite two acute cellular rejection episodes[185].

Future options to expand organ donation in PLWH

Mismatch between the demand and supply of organs continues to be a clinical challenge and novel approaches are required to expand the donor pool.

In 2021, a report claimed that the UK was considering the transplantation of organs from deceased HIV-positive donors into recipients without HIV[186]. The report emphasized that such a scenario would occur in very limited circumstances, such as in patients with fulminant liver failure for whom no other organ was available or in highly sensitized patients on the waiting list for a kidney transplant. There are some important considerations to such an approach, including the almost inevitable risk of HIV transmission despite viral suppression in the donor, the potential for drug–drug interactions due to a need for the recipient to initiate ART, the potential risks of acquiring a drug-resistant strain of HIV, the ongoing stigma of HIV positivity, the psychological impact on the recipient and the complex aspects of fully informed consent.

In South Africa in 2017, the first living HIV-positive donor to HIV-negative recipient liver transplant was performed when a mother donated part of her liver to her child[187]. The donor was virally suppressed and both donor and recipient were reported to be stable a year post-transplant on ART.

The long-term follow-up of a kidney transplant recipient unknowingly infected with HIV via a live donor kidney allograft in 2009 has also been reported[188]. ART was initiated at time of HIV diagnosis a year post-transplantation. At 11 years post-transplantation the recipient's eGFR was 19 ml/min. Four other cases of unintentional HIV transmission via kidney organ donation have been reported in the post-ART literature[189–191]. Under the appropriate circumstances, the use of HIV-positive organs could be lifesaving if no alternative viable transplant options are available.

Conclusions

HIV-associated kidney disease remains an important cause of morbidity and mortality. The increasing use of ART has seen a change in the kidney pathology associated with HIV, with a shift away from HIVAN towards comorbid diseases of ageing and ART-related nephrotoxicity. HIVAN has not been eliminated, potentially because of the genetic diversity of PLWH and treatment-related issues. Clinicians need to be mindful of the potential nephrotoxicity of ARTs and their potential adverse interactions with other drugs. Traditional treatments for CKD do not target specific HIV-related CKD pathways; however, the identification of genetic factors, such as the *APOL1* risk variants, as a risk factor for

kidney disease, particularly in PLWH, highlights the need to perform *APOL1* genotyping in individuals with pathology compatible with kidney diseases in the *APOL1* spectrum, and opens up opportunities for *APOL1*-targeted therapies. Kidney transplantation in PLWH has comparable outcomes with those of patients without HIV and is associated with a significant survival benefit over remaining on chronic dialysis. Nevertheless, the number of organs available for transplantation remains insufficient to meet the demand; hence, new boundaries are being redefined to reduce the mismatch between organ demand and supply and improve outcomes for patients living with HIV and CKD.

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