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HIV at 40: Kidney Disease in HIV Treatment, Prevention, and Cure

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Abstract

Four decades after the first cases of HIV were reported, kidney disease remains an important comorbidity in people with HIV (PWH). Both HIV-associated nephropathy and immune complex kidney disease were recognized as complications of HIV infection in the early years before treatment was available. Although the introduction of effective antiretroviral therapy in the late 1990s resulted in dramatic improvements in survival and health in PWH, several commonly used antiretroviral agents have been associated with kidney injury. HIV infection and treatment may also promote the progression of comorbid chronic kidney disease (CKD) due to traditional risk factors such as diabetes, and HIV is one of the strongest "second hits" for the high risk *APOL1* genotype. Unique considerations in the management of CKD in PWH are largely related to the need for lifelong antiretroviral therapy, with potential for toxicity, drug-drug interactions, and polypharmacy. PWH who develop progressive CKD are candidates for all modalities of kidney replacement therapy, including kidney transplantation, and at some centers PWH may be candidates to serve as donors for recipients with HIV. Transplantation of kidney allografts from donors with HIV also offers a unique opportunity to study viral dynamics in the kidney, with implications for kidney health and for research towards HIV cure. In addition, HIV-transgenic animal models have provided important insights into kidney disease pathogenesis beyond HIV, and experience with HIV and HIV-related kidney disease has provided important lessons for future pandemics.

Keywords

HIV-associated nephropathy; antiretroviral nephrotoxicity; *APOL1*

In the midst of another pandemic, 2021 quietly marked the 40th anniversary of the first reported cases of AIDS (Figure 1).[1] The original case series described 5 cases of

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Pneumocystis carinii pneumonia in previously healthy gay men. Over the next 2 years, additional cases of AIDS were identified in men with male sexual partners, as well as in a small number of hemophiliacs, infants, and women. In 1983, investigators at the Pasteur Institute isolated a novel retrovirus in lymphoid tissue from a man with diffuse lymphadenopathy and suspected AIDS, a discovery that was recognized with the 2008 Nobel Prize for Physiology or Medicine. Subsequent studies confirmed that the virus was the etiologic agent in AIDS, sparking an era of rapid antiretroviral drug development.[1] Patient activists pushed for accelerated approval of new antiretroviral agents, helping to chart a path for the expedited development and approval of novel treatments for other life-threatening conditions, including the “fast track” review of SGLT2 inhibitors for chronic kidney disease (CKD) and the provisional approval of SARS-CoV-2 vaccines in 2020.

In 1984, three separate case series identified glomerular disease as a potential complication of AIDS. Nephrotic range proteinuria was observed in % or more of adult patients with AIDS.[2–4] Among those with kidney tissue available from kidney biopsy or autopsy, focal segmental glomerulosclerosis (FSGS) was the most common histologic diagnosis. The unique picture of collapsing FSGS accompanied by tubular dilatation and interstitial inflammation was quickly accepted as a hallmark of advanced HIV disease and is now commonly known as HIV-associated nephropathy (HIVAN) (Figure 3). In the absence of effective antiretroviral therapy (ART), HIVAN was associated with rapidly progressive kidney failure. [2–4]

Although HIVAN was the most common entity observed in the early case series, immune complex glomerulonephritis (ICGN) was also reported.[2–4] In recent years, there has been a decline in the incidence of classic HIVAN and an accompanying increase in the incidence of non-collapsing FSGS, ICGN, ART nephrotoxicity, and comorbid kidney disease in people with HIV (PWH).[5] This article will review the pathogenesis and changing epidemiology of kidney disease in PWH, as well as unique aspects of management in PWH who develop CKD.

Pathogenesis of Kidney Disease in People with HIV

Multiple factors have been shown to contribute to the pathogenesis of kidney disease in PWH, including HIV infection and treatment, comorbid CKD risk factors, and genetic susceptibility (Figure 2). The emergence of HIVAN in the setting of AIDS suggested the possibility of an infectious etiology, either HIV or an opportunistic infection. Early studies in transgenic animal models confirmed that HIV gene expression is sufficient to cause the HIVAN phenotype,[6] and reciprocal kidney transplant experiments between HIV-transgenic and wild type mice demonstrated a central role for local HIV gene expression in the kidney.[7] Subsequent studies using human biopsy tissue confirmed the presence of viral sequences and replication competent HIV virus in kidney epithelial cells.[8,9] Detailed mechanistic studies have identified specific viral genes and host pathways that contribute to the development of HIVAN, including host signaling pathways that are involved in the pathogenesis of other glomerular diseases.[10] Consistent with the critical role of HIV in HIVAN pathogenesis, the incidence of kidney failure attributed to HIVAN reached a plateau following the introduction of effective combination ART in the late 1990s.[11]

The epidemiology of HIVAN also suggested an important role for host genetic susceptibility, with nearly all cases diagnosed in PWH of African descent.[11] HIVAN is now recognized as the kidney disease most strongly linked to the high risk *APOL1* genotype, which has been associated with as much as 89-fold increase in the odds of HIVAN.[12–16] Despite this strong association, not all people with HIVAN carry the high-risk *APOL1* genotype, suggesting that other genes or environmental factors increase susceptibility to HIVAN. Several other genetic loci have been associated with HIVAN in HIV-transgenic murine models, which demonstrate significant phenotypic variability on different genetic backgrounds.[17–20]

The pathogenesis of other kidney diseases in PWH has not been as well defined, in large part because of a lack of relevant animal models. In small but carefully conducted human studies, immune complexes eluted from PWH with ICGN were found to be directed against HIV antigens.[21,22] These findings suggest a pathogenic role for HIV in some cases of ICGN; however, the complexity of this approach has limited its widespread application to the investigation of HIV-related ICGN. Epidemiologic studies have been complicated by the inclusion of a heterogeneous group of ICGN pathologies under the single umbrella term “HIV immune complex kidney disease” (HIVICK), prompting an expert panel of renal pathologists convened by KDIGO to recommend a more detailed histologic classification (Table 1).[23] A large biopsy series utilizing the new KDIGO classification system identified a small number of ICGN cases without another likely etiology, such as viral hepatitis co-infection or anti-PLA2R antibodies, suggesting that these cases may represent true HIVICK rather than coincidental ICGN.[5] This approach may help to identify high-yield cases for more detailed laboratory investigation in order to provide a clearer picture of ICGN pathogenesis in PWH. Adoption of this more detailed classification system for future clinical studies may also improve our understanding of prognosis and optimal management of ICGN in PWH.

The role of HIV in promoting comorbid kidney disease due to traditional risk factors is also an area of active investigation. Epidemiologic studies suggest an additive effect of HIV and diabetes on kidney disease progression.[24] Similarly, in a mouse model of streptozotocin-induced diabetes, kidney pathology is more pronounced in HIV-transgenic animals compared to wild type animals.[25,26] Differential regulation of inflammatory pathways and downregulation of Sirtuin-1 deacetylase in this model suggested potential mechanisms, although factors such as exposure to nephrotoxic ART may also play a role in PWH.

The antiretroviral agents most commonly implicated in kidney toxicity include the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) and some of the older protease inhibitors (PI).[23,27] TDF is a prodrug of tenofovir, which is structurally similar to the older antiviral agents cidofovir and adefovir.[28] Proximal tubular injury is a dose-limiting side effect of cidofovir at therapeutic doses and of adefovir at the higher doses initially studied for HIV treatment. Although rare, overt proximal tubulopathy can also occur with TDF, and milder abnormalities in proximal tubular function and glomerular filtration rate are more common. Because tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion, the higher concentration of tenofovir in proximal tubular cells is thought to predispose these cells to mitochondrial

damage, a common mechanism of toxicity with other NRTI. Indeed, mitochondrial injury is a prominent feature of the kidney histology in PWH with suspected TDF toxicity (Figure 4).[29] The newer prodrug tenofovir alafenamide (TAF) achieves similar antiretroviral efficacy with much lower plasma tenofovir concentrations, resulting in lower exposure of proximal tubular cells. This appears to translate into a lower risk of kidney injury, although studies with longer follow-up are needed to exclude the potential for cumulative toxicity with TAF.[30,31]

Concomitant use of TDF with a boosted PI has been associated with increased risk of kidney injury, in part because the pharmacoenhancers ritonavir and cobicistat also increase tenofovir exposure. In addition, some older PI are independently associated with kidney injury as a result of low urine solubility, which can result in nephrolithiasis, parenchymal crystal deposition, and interstitial nephritis.[32] This risk is lower with contemporary PI, in particular darunavir, which has improved solubility in urine and has not been associated with increased risk of CKD in observational studies.[33] Although current clinical practice is moving away from the use of both TDF and PIs, the widespread use of these potentially nephrotoxic ART agents, and in particular the frequent combination of TDF with a boosted PI, likely had an important if not fully measurable impact on the epidemiology of kidney disease in PWH over the past 20 years.

Changing epidemiology of CKD in People with HIV

In the early years of the HIV epidemic there was a rapid increase in the incidence of kidney failure attributed to HIVAN, predominantly affecting PWH of African descent.[11] Although the incidence of kidney failure attributed to HIVAN plateaued following the introduction of effective ART in the second half of the 1990s, studies from the early ART era continued to find a high prevalence of kidney failure in PWH, particularly among those of African descent or with traditional CKD risk factors.[34,35] A recent biopsy series including 437 PWH who underwent clinically indicated kidney biopsy between 2010–2018 found that HIVAN remained the most common diagnosis in PWH who were not on active ART at the time of biopsy, while ICGN and diabetic nephropathy were the most common diagnoses overall.[5]

Less is known about the epidemiology of CKD in PWH following the adoption of contemporary treatment guidelines, which recommend the immediate initiation of ART at the time of HIV diagnosis regardless of CD4 cell count or symptoms. In a landmark randomized trial that helped to establish the superiority of immediate ART initiation in reducing mortality and AIDS-related outcomes, this strategy was also associated with a small but significant improvement in estimated glomerular filtration (eGFR) slope as compared to deferred ART initiation.[36] The benefits of immediate ART may become even more evident with the shift away from potentially nephrotoxic ART regimens, although these changes in prescribing patterns are likely to be delayed in low- and middle-income countries.

Biomarkers of kidney function, injury, and inflammation in people with HIV

The detection and staging of CKD in PWH relies on established biomarkers including serum creatinine and urine albumin. Several antiretroviral agents have been shown to interfere

with tubular secretion of creatinine *in vitro*, with the potential to influence creatinine-based eGFR ($eGFR_{Cr}$) in PWH.[37] In clinical trials, some of these agents have been shown to cause a small but discernible rise in serum creatinine and a corresponding decrease in $eGFR_{Cr}$. When observed, these changes occur quickly and remain stable over time. Although the effect on creatinine secretion does not appear to significantly impact the performance of $eGFR_{Cr}$ on a population level, larger increases in creatinine can be observed in individual patients. Estimates based on Cystatin C ($eGFR_{Cys}$) are an alternative when accurate estimation of GFR is required in clinical practice, and evidence-based GFR adjustments can be applied as a sensitivity analysis in epidemiologic studies when only $eGFR_{Cr}$ is available.[38] Although there are potential concerns with the use of cystatin C in the setting of ongoing systemic inflammation, $eGFR_{Cys}$ and $eGFR_{Cr}$ appear to have similar performance in PWH on stable ART, and $eGFR_{Cys}$ has been shown to be a stronger predictor of adverse outcomes in PWH.[39]

Much of the work investigating urine biomarkers of kidney disease in PWH has been conducted in the Women's Interagency HIV Study (WIHS), a prospective multicenter cohort study of women with HIV and HIV-negative women at 6 sites in the United States. Older studies in WIHS identified even transient albuminuria as an independent predictor of all-cause and AIDS mortality and established an association between the *APOL1* high-risk genotype and proteinuria in women with asymptomatic HIV.[40,41] Women with HIV were found to have significantly higher levels of urine albumin and several novel biomarkers of kidney injury, including IL-18 and alpha1-microglobulin, compared to HIV-negative women.[42] Longitudinal studies in WIHS have identifed urine alpha-1 microglobulin, a biomarker of proximal tubule dysfunction, as a strong independent predictor of $eGFR_{Cys}$ decline, incident CKD, and mortality in women with HIV.[42] Combinations of urine biomarkers of tubular resorption (alpha1-microglobulin, beta2-microglobulin, and trefoil factor 3) and tubular injury (IL-18 and KIM-1) appear to be even stronger predictors of incident CKD in women with HIV.[43] Although it is unlikely that biomarker panels will be cost-effective for use in clinical practice, combinations of urine biomarkers may provide insight into potential mechanisms of injury and could be useful to identify high-risk individuals for prospective research studies.

Unique populations: Pregnant women and children

In 2020, nearly 50% of new HIV infections worldwide occurred in women or girls, who accounted for almost two-thirds of new HIV infections in Africa.[44] Approximately 1.3 million women with HIV gave birth in 2013. Data on the prevalence and impact of CKD and related disorders among pregnant women with HIV are limited. In a cross-sectional study of pregnant women in Cameroon, women with HIV had more than two-fold higher odds of proteinuria than women without HIV (adjusted OR 2.45).[45] Among women with HIV, ART use was associated with significantly lower odds of proteinuria in pregnancy (adjusted OR 0.39).

Retrospective studies have suggested a complex relationship between HIV, ART use, and hypertensive disorders of pregnancy. In a retrospective study from South Africa, women with HIV had a significantly lower risk of death from hypertensive disorders

of pregnancy compared to women without HIV (RR 0.47, 95%CI 0.51–0.64).[46] Results were similar in the subgroup of women with HIV who were not on ART. In contrast, a retrospective study of Italian women demonstrated higher odds of preeclampsia among women with HIV on ART compared to women without HIV (OR 3.52, 95%CI 2.51–4.94).[47] Interestingly, pre-eclampsia was also more common in women on ART compared to women with HIV not taking ART (OR 3.08, 95%CI 1.34–5.07)[47]. A systematic review examining the association of ART with hypertensive diseases of pregnancy found that PI were independently associated with the risk of pregnancy-related hypertension.[48] Because integrase inhibitors and non-nucleoside reverse transcriptase inhibitors have also been implicated in hypertensive disorders of pregnancy[49], there are no clear recommendations for ART regimens that may reduce this risk during pregnancy. The established benefits of ART for maternal health and maternal-fetal HIV transmission far outweigh the risk of hypertensive disorders in pregnancy, but these data suggest that women with HIV should be considered at higher risk for these conditions.

Despite the widespread use of ART to reduce transmission of HIV during pregnancy, birth, and breastfeeding, children and adolescents under the age of 15 still account for nearly five percent of the worldwide HIV population. HIV-associated glomerular diseases observed in adolescents and children include HIVAN and ICGN. As in adults, HIVAN largely occurs in children and adolescents of African descent, consistent with the distribution of *APOL1* variants. The Pediatric HIV/AIDS Cohort Study, a prospective study in youth with perinatal HIV infection, evaluated the association of high-risk *APOL1* genotype with CKD in children and adolescents.[50] Eighteen percent of those with high-risk *APOL1* genotypes developed CKD, and the odds of CKD were 3–4-fold higher compared to those with low-risk genotypes.[50] Although classic HIVAN is less common with ART use, a recent US study found that CKD is still common in children and adolescents with HIV, particularly in those of African descent. Overall, one-third of children and adolescents with HIV had intermittent proteinuria and 6% had persistent proteinuria or a biopsy diagnosis of HIVAN or ICGN. Viral load was higher and hypertension was more common in children and adolescents with persistent proteinuria or biopsy-proven kidney disease.[51]

Management of Chronic Kidney Disease in People with HIV

The diagnosis of CKD should prompt immediate initiation of ART in PWH who are not currently treated, consistent with clinical practice guidelines recommending ART for all PWH regardless of CD4 cell count. In PWH with suppressed HIV viral load, a diagnosis of CKD should prompt evaluation and optimized management of traditional CKD risk factors, including the use of evidence-based therapies such as renin angiotensin aldosterone system blockers and sodium glucose co-transporter-2 inhibitors as appropriate. Kidney biopsy is strongly recommended for definitive diagnosis in PWH with albuminuria, given the broad spectrum of glomerular disease observed in this setting.[23] In patients with asymptomatic HIV, a diagnosis of ICGN should prompt consideration of immunosuppressive therapy as determined by the specific histologic diagnosis and the severity of the clinical presentation. Unique considerations in the management of CKD in PWH are largely related to the need for lifetime suppressive ART, with the potential for nephrotoxicity, drug-drug interactions, and polypharmacy (Table 2). Conventional ART regimens include the use of

two NRTI and either an integrase inhibitor, protease inhibitor, or non-nucleoside reverse transcriptase inhibitor. Recent studies support the use of simplified 2-drug regimens in carefully selected patients. Single-tablet regimens may also improve adherence, although dose adjustments limit the options available to PWH with decreased GFR. Collaboration between nephrologists and HIV providers can help to ensure optimal ART regimen selection and dosing in PWH with or at high risk of CKD.

Dialysis in PWH

Available data suggest that PWH are at increased risk of CKD progression and that ESKD may occur at a younger age in PWH compared to people without HIV.[24,52] In PWH with progressive CKD, education and preparation for ESKD should not be influenced by asymptomatic HIV infection. PWH who are approaching ESKD are candidates for in-center and home hemodialysis and peritoneal dialysis, and may also be candidates for kidney transplantation, as discussed below. Despite improvements in overall survival and life expectancy in PWH, survival on dialysis still appears to be lower among PWH, particularly those of non-white race.[53] There are no unique considerations for the care of PWH in the dialysis unit; universal precautions are adequate to protect other patients, healthcare providers, and care partners.

Kidney transplantation in PWH

In 2010, the results of a prospective cohort study in the US confirmed the safety and success of kidney transplantation in PWH who are virologically suppressed on ART, paving the way for transplants to occur outside the context of a research protocol.[54] The observational study in 150 PWH demonstrated 1- and 3-year patient and allograft survival rates that fell between those observed in transplant recipients over age 65 years and those observed in the overall recipient population. Acute rejection rates were higher than expected, with 31% of participants experiencing an episode of acute rejection in the first year post-transplant. Subsequent studies have demonstrated reductions in acute rejection and graft loss following induction with antithymocyte globulin, as well as improved outcomes with triple immunosuppression including tacrolimus, an anti-metabolite, and a corticosteroid.[55–58]

Clinically significant drug-drug interactions with the HIV PI and the pharmacoenhancers ritonavir and cobicistat can lead to marked increases in calcineurin inhibitor trough levels, resulting in decreased dosing frequency and highly variable drug exposure, which was likely the primary contributor to the high rates of acute rejection observed in earlier studies.[59,60] With the availability of alternative ART regimens, many transplant centers prefer to avoid PI and pharmacoenhancers in favor of unboosted integrase inhibitor-based regimens. Where feasible, many centers have also replaced TDF with TAF and other NRTIs with more favorable kidney safety profiles. Because of the potential for significant drug-drug interactions, as well as the need for dose adjustment with changes in allograft function (Table 2), close communication between the transplant team and HIV providers is essential to the success of kidney transplantation in PWH.

Also in 2010, a small case series from South Africa provided the first evidence in support of using HIV-positive donor organs for kidney transplantation in PWH.[61] Transplant surgeons

in Capetown offered HIV-positive donor kidneys to PWH who would otherwise be denied a kidney transplant or dialysis, at the same time preventing the discard of these organs in a setting with high HIV prevalence and a limited donor pool. Patient and allograft survival were good, and HIV control was not adversely affected. The initial report and subsequent long-term follow-up prompted a change in regulations prohibiting the use of HIV-positive donor organs,[62] and in early 2019 HIV-to-HIV kidney transplants became a reality at some centers in the US. These transplants are largely being performed under an ongoing research protocol to evaluate the potential for HIV transmission and superinfection and the impact of drug resistant viral strains on the long-term safety of this approach.[63] Although the use of HIV-positive donor organs has not had a dramatic effect on the donor pool in the US and other countries with relatively low HIV prevalence compared to South Africa, an unanticipated benefit has been the use of high-quality kidney allografts that initially screened false-positive for HIV, saving these valuable organs from discard.[64]

HIV Prevention: Potential for Kidney Injury with Pre-exposure Prophylaxis

The earlier initiation and widespread use of ART has improved kidney and overall outcomes in PWH, and virologic suppression with ART has also been shown to reduce the risk of HIV transmission to sexual partners of PWH. In 2010, a large randomized clinical trial demonstrated efficacy of antiretroviral pre-exposure prophylaxis (PrEP) with daily oral emtricitabine/TDF (FTC/ TDF) to reduce the risk of HIV acquisition in HIV-negative men at high risk of exposure.[65] Although FTC/TDF PrEP was well tolerated in healthy clinical trial participants, secondary analyses have demonstrated a potential risk of subclinical tubular dysfunction and GFR decline, as well as rare cases of overt kidney injury with longer-term use.[66–68] Although the relative safety of TAF has not been well studied in healthy individuals, FTC/TAF is now approved for use as PrEP in some populations and may be a safer alternative in individuals with or at risk of CKD. For now, FTC/TDF PrEP remains a mainstay of HIV prevention in resource-limited settings and in heterosexual women and other populations where FTC/TAF has not yet demonstrated efficacy. In the interim, PrEP prescribers and nephrologists should be aware of the potential for kidney injury with FTC/TDF PrEP.

HIV Cure Research: The Kidney as a Potential Viral Reservoir

Although HIV is now a treatable disease, current therapy requires lifelong suppressive ART. In 2007, investigators from Germany reported the first case of HIV cure in the “Berlin patient,” who later identified himself as Timothy Ray Brown.[1] At the time, Brown had no evidence of HIV after receiving a stem cell transplant for leukemia from a donor with a CCR5Δ5 mutation, which essentially prohibits HIV entry into cells. Brown remained free of HIV until his death from recurrent leukemia in 2020, living just long enough to hear news of a second HIV cure. A third case of HIV cure was reported at the Conference on Retroviruses and Opportunistic Infections in February 2022, confirming the potential for HIV cure in women.

Demonstration that HIV cure is reproducible has generated new enthusiasm for research into potential viral reservoirs, including the kidney. Viral infection of kidney epithelial cells

is a key step in HIVAN pathogenesis, with *in vitro* studies suggesting that this occurs most efficiently via cell-cell transfer from infected lymphocytes and macrophages.[69–71] Co-culture experiments have demonstrated the transfer of virus from infected renal tubular epithelial cells to T cells, suggesting that HIV harbored in the kidney could be a source of viral rebound after ART interruption.[69] Ongoing studies are using urine as a non-invasive source of kidney epithelial cells and HIV-to-HIV kidney transplants as a model system to study the kidney as a potential reservoir for HIV.[72]

HIV and Kidney Disease: Lessons for the New Pandemic

In the past 2 years, glomerular disease has also emerged as an important complication of COVID-19.[73–80] The collapsing glomerulopathy of COVID-19 shares many similarities with HIVAN, including strikingly similar histology and a strong association with the high-risk *APOL1* genotype. Although many questions remain, including whether direct viral infection of the kidney occurs and is required for the pathogenesis of collapsing glomerulopathy in the setting of SARS-CoV-2 infection, it is likely that overlapping cellular pathways are involved. Data generated in established HIVAN animal models may identify high yield targets for investigation in COVID-related glomerular disease.

Antiviral drug development for the treatment of SARS-CoV-2 infection has benefitted from accelerated approval pathways forged during the early AIDS epidemic and from decades of research into different approaches to target viral replication and achieve therapeutic drug levels. Experience with antiretroviral drug dosing and drug-drug interactions in PWH and CKD may also help to guide the management of patients who require antiviral treatment for SARS-CoV-2 infection. As an example, the most promising antiviral agent to date, nirmatrelvir, is a ritonavir-boosted PI, which should prompt close monitoring for drug-drug interactions that were previously identified in PWH.

Finally, both pandemics have exposed significant health disparities, with a disproportionate burden of viral infection and adverse outcomes affecting minority populations as well as LMIC.[81] Overlapping disparities in the risk and outcomes of CKD mean that nephrologists will play an important role in efforts to control these and future pandemics.

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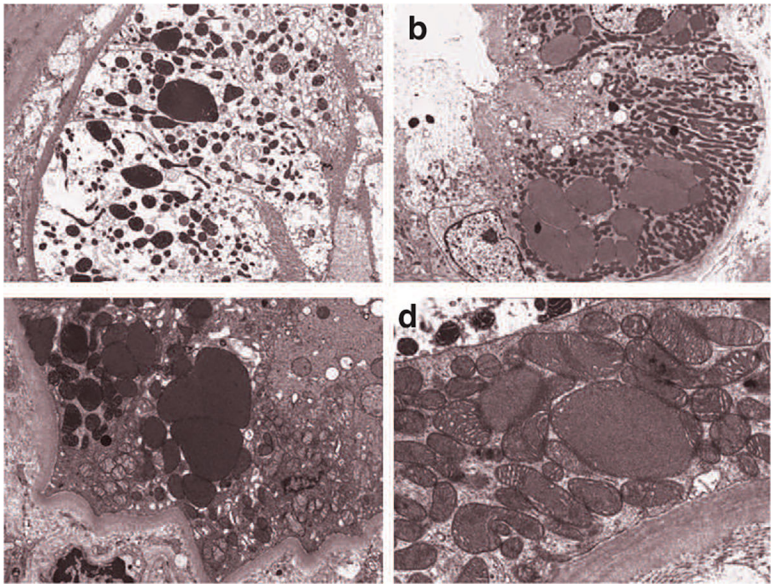

Figure 1. Brief History of HIV and HIV-related Kidney Disease

The timeline summarizes key events in the history of the HIV epidemic, with a focus on those of particular relevance to kidney disease (red dots) and HIV treatment (green dots). HIVAN, HIV-associated nephropathy; ART, antiretroviral therapy; FTC/TDF/EFV, emtricitabine/tenofovir disoproxil fumarate/ efavirenz (Atripla®); PWH, people living with HIV; WHO, World Health Organization

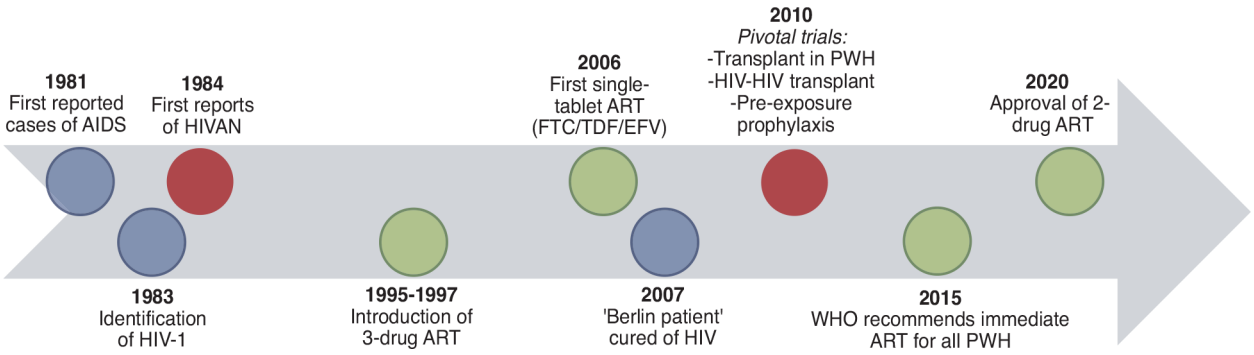

Figure 2. Potential contributors to kidney disease in people with HIV

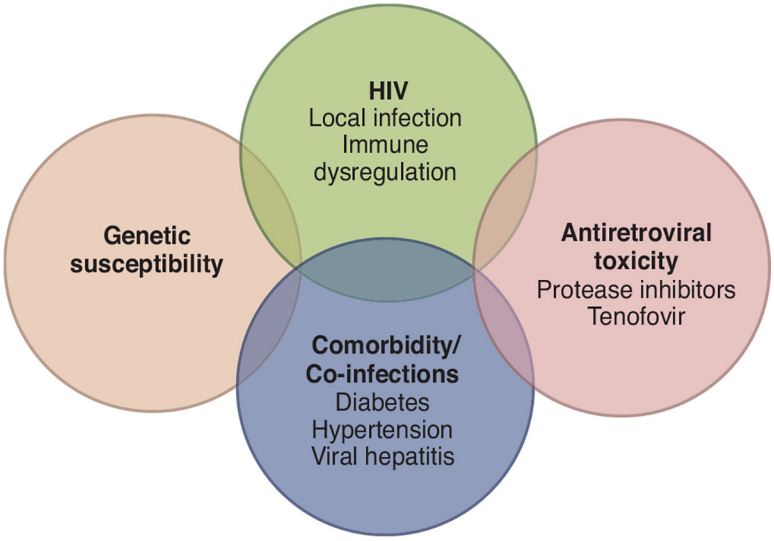

Figure 3. Classic HIVAN and FSGS (NOS) in the setting of HIV

Classic HIVAN (A–E) shows typical global collapse of the glomerular tuft with loss of luminal patency and hypertrophy and hyperplasia of the overlying glomerular epithelial cells, some of which contain intracytoplasmic protein resorption droplets. (A, Jones methenamine silver x400; B, Masson trichrome, x400). The tubulointerstitium shows focal tubular microcysts containing glassy casts, associated with tubular atrophy, interstitial fibrosis and inflammation (C, Masson trichrome, x200). There is marked foot process effacement overlying the collapsed capillaries associated with glomerular epithelial cell hyperplasia forming a pseudocrescent. Some glomerular epithelial cells contain numerous intracytoplasmic protein resorption droplets. No immune type electron dense deposits are seen. (D, electron micrograph x4000). The glomerular endothelial cells contain multiple intracytoplasmic tubuloreticular inclusions (arrows). Foot processes are effaced. (E, electron micrograph, x40,000). FSGS (NOS) in the setting of HIV shows discrete segmental scars with segmental adhesions to Bowman's capsule. No collapsing features or glomerular epithelial cell hyperplasia are identified. (F, H&E, x400). Adapted from Swanepoel et al. *Kidney International* 2018, Figure 1.[23]

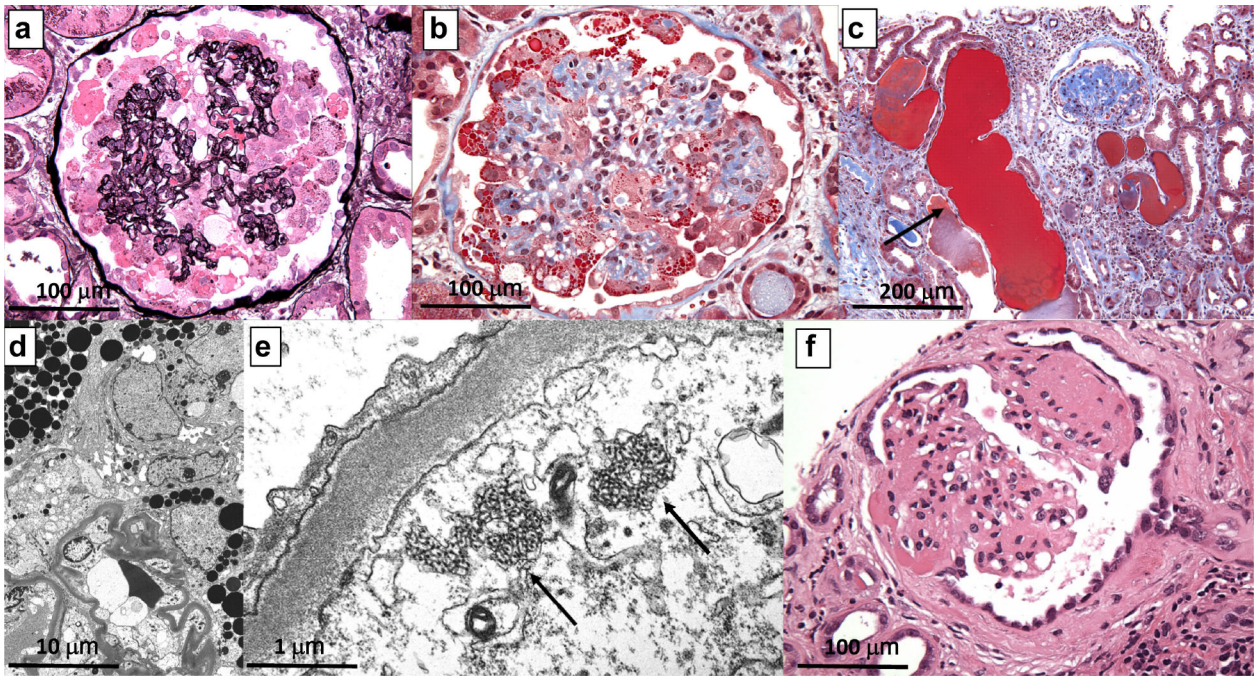

Figure 4. Ultrastructural findings in tenofovir nephrotoxicity

(a) A low-magnification field demonstrates the wide range in size and shape of mitochrondria within proximal tubular epithelial cells (× 5000). (b) Markedly enlarged mitochondria are interspersed with normal-sized mitochrondria in proximal tubular cells. One cell is undergoing degeneration with shedding of cytoplasmic fragments into the tubular lumen (× 5000). (c) At higher magnification, the enlarged mitochrondria are largely devoid of cristae. In contrast, cristae are easily identified in adjacent, normal-sized mitochondria (× 8000). (d) Abnormalities in the number and distribution of mitochondrial cristae are best appreciated at high magnification. In this field, there is focal loss of cristae, as well as clustering of residual cristae at the peripheral mitochrondrial membrane (× 20,000). Adapted from Herlitz LC et al. *Kidney International* 2010, Figure 2.[29]

Table 1 |

KDIGO Classification of Kidney Pathology in People with HIV

I. Glomerular-dominant [a]

a. Podocytopathies (all characterized by extensive foot process effacement)[b]

i. Classic HIVAN

ii. FSGS (NOS) in the setting of HIV

iii. Minimal change disease in the setting of HIV

iv. Diffuse mesangial hypercellularity in the setting of HIV

v. Other podocytopathy in the setting of HIV

b. Immune complex-mediated glomerular disease[a]

i. IgA nephropathy in the setting of HIV

ii. Lupus-like glomerulonephritis in the setting of HIV

iii. Lupus nephritis in the setting of HIV

iv. Membranous nephropathy in the setting of HIV

■ Indicate whether HBV positive, HCV positive, PLA2R positive (should not preclude workup for other secondary causes)

v. Membranoproliferative pattern glomerulonephritis in the setting of HIV

■ Indicate whether HCV positive (should not preclude workup for other secondary causes)

vi. Endocapillary proliferative and exudative glomerulonephritis in the setting of HIV

■ Post-streptococcal, staphylococcal-associated, other

vii. Fibrillary or immunotactoid glomerulonephritis in the setting of HIV

viii. Other immune complex disease in the setting of HIV

II. Tubulointerstitial-dominant [a]

a. Tubulointerstitial injury in the setting of classic HIVAN

i. Hyaline droplet tubulopathy

ii. Tubular microcysts

iii. Tubulointerstitial inflammation

b. Acute tubular injury or acute tubular necrosis

i. Ischemic

ii. Toxic (associated with ART vs. other)

c. Drug-induced tubulointerstitial nephritis (other than ART)

i. Antibiotics

ii. Proton pump inhibitors

iii. NSAIDs

iv. Other

d. Direct renal parenchymal infection by pathogens (bacterial, viral, fungal, protozoal, etc.)

e. Immunologic dysfunction-related tubulointerstitial inflammation

i. Diffuse infiltrative lymphocytosis syndrome (DILS)

ii. Immune reconstitution inflammatory syndrome (IRIS)

f. Other tubulointerstitial inflammation in the setting of HIV

III. Vascular-dominant [a]

a. Thrombotic microangiopathy in the setting of HIV

b. Arteriosclerosis

IV. Other, in the setting of HIV infection

a. Diabetic nephropathy

b. Age-related nephrosclerosis

ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; NOS, not otherwise specified; NSAID, nonsteroidal anti-inflammatory drug; PLA2R, M-type phospholipase A2 receptor.

[a] Indicate likelihood of HIV causality.

[b] Indicate association with *APOL1* risk allele genotype.

Table adapted from Swanepoel et al. *Kidney International* 2018, Table 1.[23]

Table 2.

Antiretroviral agents: Special Considerations for the Diagnosis and Management of People with HIV and Chronic Kidney Disease

	Inhibition of tubular creatinine secretion	Recommended dose adjustment in CKD*	Relevant drug-drug interactions**
Nucleos(t)ide reverse transcriptase inhibitors	**None reported**	**CrCL < 50 mL/min** TDF Emtricitabine Lamivudine **CrCL < 15 mL/min** TAF (approved in HD) Zidovudine (rare use) **No dose adjustment** Abacavir	**No relevant DDI**
Non-nucleoside reverse transcriptase inhibitors	**Modest effect***** Rilpivirine	**Not required** Doravirine Efavirenz Etravirine Rilpivirine **Extra dose after HD** Nevirapine	**Moderate DDI with calcineurin inhibitors** Efavirenz Etravirine Nevirapine **Mild DDI with calcium channel blockers, statins** Same as above
Protease inhibitors	**None reported**	**Not required**	**Significant DDI with eplerenone** Boosted PIs only **Significant DDI with lovastatin, simvastatin, atorvastatin** **Moderate DDI with calcineurin inhibitors** **Mild DDI with beta-blockers, calcium channel blockers, other statins**
Integrase inhibitors	**Prominent effect** Dolutegravir Elvitegravir/ cobicistat **Modest effect** Bictegravir Raltegravir Cabotegravir/ rilpivirine	**Not required**	**Severe DDI with eplerenone, lovastatin, simvastatin, atorvastatin** Elvitegravir/cobicistat only **Moderate DDI with calcineurin inhibitors** Elvitegravir/cobicistat only
Other antiretroviral classes	**None reported**	**CrCL < 30 mL/min** Maraviroc **No dose adjustment** Enfurvitide Ibalizumab	**No relevant DDI**
Pharmacoenhancers	**Prominent effect** Cobicistat ***In vitro* effect** Ritonavir	**Not required**	**Severe DDI with eplerenone, lovastatin, simvastatin, atorvastatin** **Moderate DDI with calcineurin inhibitors**

* Dose adjustment or discontinuation is recommended below the calculated creatinine clearance (CrCl) listed in the table. Readers are encouraged to review the package insert for detailed dosing recommendations.

** Drug-drug interactions (DDI) of particular relevance to patients with chronic kidney disease, including antihypertensive therapy, lipid-lowing therapy, and immunosuppressive therapy. This is not a comprehensive listing of all potential interactions.

*** Agents with a modest effect on tubular secretion of creatinine result in an average increase in serum creatinine of 0.1 mg/dL, while agents with a prominent effect on tubular secretion of creatinine result in larger increases of 0.2 mg/dL or greater. An effect of ritonavir on tubular secretion has been observed *in vitro* but has not been reported to impact serum creatinine or the performance of creatinine-based GFR estimates. Updated information is available online at clinicalinfo.hiv.gov/en/guidelines.