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## Kidney Disease in the Setting of HIV Infection: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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## Abstract

HIV-positive individuals are at increased risk for kidney disease, including HIV-associated nephropathy, non-collapsing focal segmental glomerulosclerosis, immune-complex kidney disease, and comorbid kidney disease, as well as kidney injury resulting from prolonged exposure to antiretroviral therapy or from opportunistic infections. Clinical guidelines for kidney disease prevention and treatment in HIV-positive individuals are largely extrapolated from studies in the general population, and do not fully incorporate existing knowledge of the unique HIV-related pathways and genetic factors that contribute to the risk of kidney disease in this population. We convened an international panel of experts in nephrology, renal pathology, and infectious diseases to define the pathology of kidney disease in the setting of HIV infection; describe the role of genetics in the natural history, diagnosis, and treatment of kidney disease in HIV-positive individuals; characterize the renal risk-benefit of antiretroviral therapy for HIV treatment and prevention; and define best practices for the prevention and management of kidney disease in HIV-positive individuals.

## Keywords

Antiretroviral therapy; *APOLI1*; CKD progression; HIV; Immune complex kidney disease; Podocytopathy; Renal pathology

## INTRODUCTION

Worldwide, an estimated 37 million people are living with HIV infection, and more than 2 million new infections are diagnosed annually.<sup>1</sup> HIV-positive individuals are at increased risk for both acute and chronic kidney disease (CKD). The classic kidney disease of HIV infection, HIV-associated nephropathy (HIVAN), has become less common with widespread use of antiretroviral therapy (ART); however, there has been a simultaneous increase in the prevalence of other kidney diseases. HIV-positive individuals are also exposed to life-long ART, with the potential to cause or exacerbate kidney injury. Newer guidelines recommending earlier initiation of ART may further reduce the incidence of HIVAN, but the overall risk-benefit for kidney health is unknown.

Clinical guidelines for CKD prevention and treatment in HIV-positive individuals are extrapolated from studies in the general population,<sup>2</sup> and current therapies do not target unique HIV-related pathways and genetic factors that contribute to CKD progression. In March 2017, Kidney Disease: Improving Global Outcomes (KDIGO) convened a multidisciplinary, international panel of clinical and scientific experts to identify and discuss key issues relevant to the optimal diagnosis and management of kidney disease in HIV-positive individuals. The primary goals were to define the pathology of kidney disease in the setting of HIV infection; describe the role of genetics in the natural history, diagnosis, and treatment of kidney disease in HIV-positive individuals; characterize the renal risk-benefit of ART; and define best practices to delay the progression of kidney disease and to treat end-stage kidney disease (ESKD) in HIV-positive individuals.

## RENAL PATHOLOGY IN THE SETTING OF HIV INFECTION

The spectrum of renal pathology in HIV-positive individuals is diverse, including lesions directly related to intrarenal HIV gene expression and lesions related to co-morbidities, drug effects, immune dysregulation, and co-infections.<sup>3</sup> Kidney biopsy is required to distinguish between these lesions. A useful approach to classification is based on the major tissue compartment affected (Table 1). A brief description of each histologic lesion is provided below, and more comprehensive descriptions are available in the Supplementary Appendix.

### Glomerular dominant diseases: Podocytopathy

Glomerular dominant diseases include two main subcategories: podocytopathies and immune complex-mediated.

Four major subtypes of podocytopathy are seen in the setting of HIV: classic HIVAN, focal segmental glomerulosclerosis (FSGS) not otherwise specified (NOS), and rarer cases of minimal change disease and diffuse mesangial hypercellularity.<sup>4</sup> All exhibit extensive podocyte foot process effacement and proteinuria, with absent or minimal immune complex deposition. There is a well-established causal relationship between HIVAN and HIV infection, mediated by direct HIV infection of renal epithelial cells, intrarenal viral gene expression, and dysregulation of host genes governing cell differentiation and cell cycle.<sup>5</sup> The role of genetic susceptibility in the pathogenesis of HIVAN and other podocytopathies is discussed in detail in the next section.

We recommend distinguishing classic HIVAN from FSGS (NOS) in the setting of HIV infection. Direct causality of HIV can only be established with reasonable certainty in classic HIVAN and congenital cases of podocytopathy in infants born to HIV-positive mothers. We recommend that the biopsy report should indicate the degree of certainty that the pathology is causally related to HIV infection as high, moderate, or low.

### Classic HIVAN

Classic HIVAN is defined as collapsing glomerulopathy and attendant tubulointerstitial disease, including tubular microcyst formation, interstitial inflammation, and tubular injury (Figure 1).<sup>6, 7</sup> Glomerular “collapse” is defined as at least one glomerulus with collapse of glomerular basement membranes accompanied by hypertrophy and hyperplasia of the

overlying glomerular epithelial cells. These hyperplastic cells may fill the urinary space, forming “pseudocrescents.”<sup>8, 9</sup>

By electron microscopy, diffuse podocyte foot process effacement and endothelial tubuloreticular inclusions (“interferon footprints”) are classic features.<sup>6, 7</sup> By immunofluorescence, there may be staining for IgM, C3, and C1q in collapsed segments and mesangial areas.<sup>7</sup> Protein resorption droplets may stain for albumin and immunoglobulin. In late stages, the sclerotic tuft is retracted into a tight solid sphere, capped by a monolayer of cobblestone epithelium; this has been described as resembling a “fetal glomerulus.”<sup>10</sup> Phenotypic studies suggest that the glomerular epithelial cell monolayer is composed of parietal epithelial cells.<sup>8</sup> In some cases, sequential biopsy and post-mortem studies have shown an evolution from collapsing glomerulopathy to FSGS (NOS).<sup>7</sup>

Tubulointerstitial disease is an invariable component of HIVAN and often appears out of proportion to the glomerular disease,<sup>6, 7</sup> causing kidney enlargement and hyperechoic appearance by ultrasound. Tubular “microcysts” are dilated tubules (at least 3-fold larger than normal) containing glassy proteinaceous casts and lined by simplified epithelium. Tubular microcysts are easily distinguished from tubular “thyroidization” based on their larger diameter, irregular size, and the absence of tubular atrophy or colloid type casts.<sup>11</sup> The microcysts may involve all tubular segments, and intracellular viral transcript expression has been demonstrated.<sup>12</sup> Prominent interstitial inflammation<sup>7</sup> and tubular degenerative and regenerative changes may also occur.<sup>13</sup> Interstitial edema in the acute phase is followed by fibrosis and tubular atrophy.

### **FSGS (NOS) in the setting of HIV**

In ART-treated patients, non-collapsing FSGS (NOS) is more commonly encountered at biopsy.<sup>9, 14–16</sup> Causality is presumed when no other etiology for FSGS can be identified. Viral load is often undetectable, and biopsy findings may be difficult to distinguish from arterionephrosclerosis of hypertension, aging, and *APOLI*-associated nephropathy. Such cases typically lack prominent tubulointerstitial disease, and the degree of podocyte effacement is generally less severe than in HIVAN (Figure 1). These differences have been hypothesized to reflect attenuation of the renal phenotype by ART.<sup>9</sup>

**Podocytopathy in perinatal HIV infection**—In addition to classic HIVAN, children with perinatal HIV infection can present with minimal change disease or diffuse mesangial hypercellularity with numerous endothelial tubuloreticular inclusions and marked foot process effacement.<sup>17</sup> Tubular microcysts and interstitial inflammation are often lacking. Such cases are rare in the ART era.

### **Glomerular dominant diseases: Immune complex kidney disease in the setting of HIV**

Numerous forms of immune complex-mediated glomerular disease have been reported in HIV-positive individuals.<sup>18</sup> We recommend that the commonly used term “HIV immune complex kidney disease” (HIVICK) be replaced with a specific description of the pattern of immune complex disease “in the setting of HIV.” The rationale for this approach is the heterogeneous spectrum of disease and the lack of certainty of HIV causality in most cases.

Early studies that eluted glomerular immune deposits and demonstrated immune complexes containing HIV antigen and specific anti-HIV antibody were performed on a small number of well-characterized cases in the research setting and are not practicable in routine pathology laboratories.<sup>19, 20</sup> Reflex diagnosis as “HIVICK” may preclude workup for other secondary, treatable causes.

A unique lupus-like nephritis with full house immune staining but with negative serologies and no clinical signs of systemic lupus erythematosus has been reported in HIV-positive individuals;<sup>21</sup> true lupus nephritis also occurs.<sup>22</sup> It remains unclear whether IgA nephropathy in the setting of HIV is coincidental and related to undergalactosylated IgA1, or due to deposition of IgA directed to viral antigen, as demonstrated in one well-characterized case.<sup>19</sup> An unusual ultrastructural appearance of subepithelial deposits, or “ball in cup” lesion, has been described in reports from South Africa,<sup>10, 23</sup> but is rarely observed in other settings. Other secondary causes should be sought in cases of membranous nephropathy (i.e., hepatitis B virus co-infection or anti-PLA2R autoantibodies) and membranoproliferative glomerulonephritis (hepatitis C virus co-infection).<sup>24–26</sup>

### **Tubulointerstitial disease in the setting of HIV**

As described above, classic HIVAN is a pan-nephropathy with an important tubulointerstitial component;<sup>6, 7</sup> in biopsies with undersampled glomeruli, the characteristic glomerular lesions may not be demonstrable. Acute tubular necrosis may occur in association with sepsis, volume depletion, and other ischemic or toxic insults.<sup>4</sup> The commonly used antiretroviral agent tenofovir disoproxil fumarate can cause proximal tubulopathy with characteristic dysmorphic mitochondria (Figure 2).<sup>27</sup> Tubulointerstitial nephritis can occur secondary to antibiotics, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, protease inhibitors, and other medications, as well as in response to mycobacterial infection.<sup>28–30</sup> Direct infection of the renal parenchyma by other pathogens can also occur.<sup>7</sup>

Two rare but distinct forms of tubulointerstitial injury relate to immunologic dysfunction in the setting of HIV infection. Diffuse infiltrative lymphocytosis syndrome (DILS) is a hyperimmune reaction against HIV that involves the kidneys in approximately 10% of cases.<sup>31–33</sup> Immune restoration inflammatory syndrome (IRIS) is an inflammatory disorder associated with paradoxical unmasking or worsening of preexisting infectious processes after ART initiation,<sup>34</sup> rarely involving the kidney. Both conditions are characterized by prominent CD8 T-cell infiltrates.

### **Vascular dominant diseases in the setting of HIV**

Thrombotic microangiopathy was reported in the early years of the AIDS epidemic, but is rare in the ART era.<sup>35</sup> A role for direct endothelial dysregulation by HIV has been proposed.<sup>36</sup>

### **Other pathologies in the setting of HIV**

As patients with HIV infection age, comorbid kidney diseases such as diabetic nephropathy and arterionephrosclerosis are increasingly common. When secondary FSGS develops in these contexts, the potential overlap with HIV-related podocytopathy can be diagnostically

challenging. Molecular approaches demonstrating renal epithelial cell infection by HIV have been used in the research setting for decades, but have not been incorporated into routine diagnostic practice.<sup>37</sup> In addition to these established approaches, several novel and emerging techniques could be incorporated into research and diagnostic renal pathology to better characterize the causal relationship between HIV and specific histologic lesions and to further delineate the host pathways involved. The conference attendees identified several particularly relevant techniques (Supplementary Table 1).<sup>38, 39</sup>

## GENETICS/ GENOMICS OF KIDNEY DISEASE IN THE SETTING OF HIV INFECTION

Classic HIVAN occurs predominantly in individuals of African ancestry, with 18–50 fold increased prevalence.<sup>40</sup> Two mapping by admixture linkage disequilibrium studies published in 2008 identified a region on chromosome 22 strongly associated with idiopathic FSGS and HIVAN in African Americans;<sup>41, 42</sup> however, fine-mapping revealed no coding variants to explain the association of intronic single nucleotide polymorphisms in the candidate gene *MYH9* with kidney disease.<sup>43, 44</sup> Subsequently, using data from the ‘1000 Genomes Project,’ Genovese *et al.* identified 2 missense variants (G1 allele) and a 6 bp deletion (G2 allele) in the adjacent *APOL1* gene that were recessively associated with FSGS and non-diabetic ESKD.<sup>45</sup> *APOL1* encodes apolipoprotein L1, which confers innate immunity against most strains of *Trypanosoma brucei*;<sup>46, 47</sup> G2 variants extend immunity to *T.b. rhodesiense* and G1 associates with asymptomatic carriage of *T.b.gambiense*, the causes of acute and chronic African human trypanosomiasis, respectively.<sup>45, 48</sup> Coding variants in *APOL1* are present only on African-ancestry haplotypes.<sup>49, 50</sup>

*APOL1* was strongly associated with FSGS (odds ratio [OR] 17) and HIVAN (OR 29) in African Americans and with HIVAN in South Africans (OR 89).<sup>49, 51</sup> In contrast, HIV-positive Ethiopians, who lack *APOL1* risk variants, do not develop HIVAN.<sup>52</sup> Subsequent studies have confirmed the strong association between the high-risk genotypes and the diagnosis of HIVAN (Table 2). The estimated lifetime risk associated with carrying two *APOL1* risk alleles is 4% for FSGS in the absence of HIV infection, and as high as 50% for HIVAN (Supplementary Table 2).<sup>53</sup> Despite the strong association, ~20–30% of African Americans with HIVAN have zero or one *APOL1* risk allele, suggesting that other genetic, viral, or environmental factors contribute to HIVAN.<sup>54</sup> Characteristics of *APOL1*-mediated kidney disease are summarized in Table 3.

The distribution of the *APOL1* coding variants varies greatly among sub-Saharan African populations, with the highest frequencies reported in Western Africa (> 40% for G1) and much lower frequencies elsewhere in Africa (Supplementary Figure 1).<sup>50, 52, 55</sup> As a consequence of the West African diaspora to the Americas and more recent African emigrations, *APOL1* variants are widely dispersed globally (e.g., 21% and 13% for G1 and G2, respectively, in African Americans).<sup>45, 50</sup>

### Prediction of histology

Given the strong genetic association, investigators in the United States (US) evaluated whether *APOL1* genotype could be used to predict HIVAN or FSGS (NOS) histology in HIV-positive patients of African descent.<sup>56</sup> Inclusion of the high-risk genotype did not significantly add to a predictive model including CD4+ cell count and HIV-RNA, suggesting that *APOL1* genotype cannot replace kidney biopsy for definitive diagnosis of HIVAN.

Carriage of *APOL1* high-risk genotypes in HIV-positive individuals is not associated with immune complex kidney disease (Table 2). In a US series, high-risk genotypes were present in only 3% of patients with biopsy-proven immune complex disease.<sup>57</sup> Similarly, in a South African series, high-risk genotypes were present in 79% of HIVAN cases but in only 25% of those with HIV and immune complex kidney disease.<sup>51</sup>

### Renal survival/ESKD risk

In general population studies, the high-risk *APOL1* genotypes have been associated with increased risk of CKD progression and with lower estimated glomerular filtration rate (eGFR).<sup>58</sup> In children with perinatal HIV infection, those with a high-risk genotype had a 3-fold increased odds of CKD and presented at a younger median age compared with those with zero or one risk allele.<sup>51</sup> In HIV-positive adults with non-HIVAN kidney disease on biopsy, carriage of two *APOL1* risk alleles was associated with more rapid progression and a 2-fold greater risk of ESKD.<sup>57</sup> Carriage of two *APOL1* risk alleles has been associated with proteinuria in HIV-infected women and with accelerated decline in longitudinal kidney function in unsuppressed HIV-infected men.<sup>59, 60</sup>

### Mechanisms of APOL1-mediated disease

Two *APOL1* risk alleles are required to confer increased risk of kidney disease. However, the presence of high-risk genotypes in healthy populations suggests that disease expression requires a “second hit,” such as infections (e.g., HIV, viral hepatitis, and others), interferon, gene-gene interactions, illicit drug use, and other CKD risk factors.

The mechanism of *APOL1*-mediated kidney disease is currently unknown. Evidence from *in vitro* experiments in human cells and *APOL1* transgenic mouse models suggests that interferon upregulates *APOL1* expression, causing podocyte injury.<sup>61, 62</sup> Intracellular apolipoprotein L1 in renal epithelium may cause apoptosis or autophagy by increasing cellular and mitochondrial membrane permeability.<sup>63–65</sup> In cell culture, G1 and G2 *APOL1* variants induce intracellular loss of potassium, cell swelling, and cell lysis.<sup>66</sup> Studies in yeast, *Drosophila*, and human cells indicate that variant apolipoprotein L1 depolarizes cell membranes, which disrupts intracellular processes including endosomal trafficking, vesicle acidification, and mitochondrial function.<sup>63–65</sup>

*In vivo*, the expression of high-risk *APOL1* variants in transgenic mouse models has produced variable effects. In a model with inducible *APOL1* expression, high-risk variants disrupted endosomal trafficking and vesicle acidification, similar to the effects observed *in vitro*. Affected animals developed podocyte death, proteinuria, and glomerulosclerosis.<sup>61</sup>



However, another transgenic mouse model with constitutive expression of *APOL1-G2* did not develop kidney disease.<sup>67</sup>

*APOL1* is encoded in the genome of only a few primate species, complicating the extrapolation of data from murine models. Mechanistic studies have also been limited by the use of overexpression assays. *In vitro*, the overexpression of wildtype *APOL1-G0* in cultured human renal epithelial cells also induces cell death, suggesting that the overexpression model may not be biologically relevant.<sup>62, 68, 69</sup>

## ANTIRETROVIRAL THERAPY (ART) NEPHROTOXICITY

HIV treatment guidelines recommend immediate initiation of ART in all HIV-positive individuals. Immunovirological control is an important strategy to reduce the incidence of acute kidney injury (AKI) and HIV-related kidney diseases.<sup>70-73</sup>

The presence of CKD affects the choice and dosing of renally-cleared antiretrovirals. Kidney function and CKD risk factors should be assessed prior to ART initiation (Figure 3). CKD risk scores have been developed to guide clinicians, although future studies are needed to determine their utility in diverse populations (Supplementary Table 3).<sup>74, 75</sup>

The widely used antiretroviral agent tenofovir disoproxil fumarate (TDF) is generally safe and well tolerated, but has important potential for cumulative nephrotoxicity. Subclinical proximal tubular dysfunction (low level proteinuria and excessive phosphaturia) is common, and approximately 1–2% of recipients develop treatment-limiting tubulopathy.<sup>76</sup> Risk factors for tubulopathy include aging, immunodeficiency, diabetes, prolonged exposure, and concomitant use of didanosine or ritonavir-boosted protease inhibitors.<sup>77</sup> Severe tubulopathy may progress to eGFR decline, osteomalacia, and pathological fractures. In large observational studies, TDF has also been associated with decreased eGFR or creatinine clearance,<sup>78, 79</sup> as well as with rapid eGFR decline and proteinuria.<sup>78, 79</sup> Co-administration of TDF with ritonavir-boosted protease inhibitors increases the risk.<sup>78, 79</sup> Although not well studied, the newer pharmacoenhancer cobicistat also increases tenofovir exposure and may increase the risk of toxicity. TDF discontinuation and switches from TDF to the newer prodrug tenofovir alafenamide (TAF) have been associated with improved kidney function, although the long-term safety of TAF is not known.<sup>80-83</sup>

Any drug (antiretroviral or other) may cause interstitial nephritis. New onset eGFR decline or proteinuria should prompt careful review of CKD risk factors and medications.<sup>29, 84</sup> Among antiretrovirals, atazanavir and indinavir have been most commonly linked to interstitial nephritis and nephrolithiasis; other protease inhibitors have been implicated in case reports.<sup>85-89</sup>

Observational cohort studies have also linked atazanavir and lopinavir/ritonavir to rapid eGFR decline and incident CKD,<sup>78, 79</sup> and switching from ritonavir-boosted atazanavir or lopinavir to boosted darunavir has been associated with improved kidney function.<sup>90</sup> In settings where TAF, abacavir, and darunavir are available, the use of TDF, atazanavir, and lopinavir/ritonavir should ideally be avoided in those with CKD, rapid eGFR decline (> 3–5 ml/min/1.73 m<sup>2</sup> per year), or at high CKD risk. The threshold for avoiding or discontinuing

these agents may be influenced by local circumstances. In resource-limited settings, TDF dose adaptation may be an option. Dual therapy (i.e., boosted protease inhibitor plus lamivudine or raltegravir) has been proposed as a way to avoid concomitant use of boosted protease inhibitors with TDF, thereby minimizing the nephrotoxic potential.<sup>91–93</sup>

### Pharmacological considerations

Several antiretrovirals require dose adjustment in individuals with decreased eGFR (Supplementary Table 4). If continued use of TDF is required when eGFR is  $< 60$  ml/min/1.73 m<sup>2</sup> (or  $< 70$  ml/min/1.73 m<sup>2</sup> with eGFR decline), dose adjustment should be considered.

Drug-drug interactions are common with ART. Several antiretrovirals induce or inhibit absorption (through P-glycoprotein), hepatic metabolism (through the cytochrome P450 system or glucuronidation), and/or tubular excretion (through organic anion/cation transporters, multidrug resistant/multidrug and toxin extrusion proteins) of co-administered medications. We recommend that clinicians consult available resources such as [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

## CKD PROGRESSION AND ESKD IN THE SETTING OF HIV INFECTION

### Risk factors for CKD

Both HIV-related and traditional CKD risk factors influence CKD development and progression (Figure 4). With improved longevity among HIV-positive individuals, traditional CKD risk factors, particularly hypertension and diabetes, are of increasing concern worldwide.<sup>94–96</sup> Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infections are associated with a 2- to 3-fold increased risk of progressive CKD.<sup>97, 98</sup> Other co-infections such as tuberculosis and syphilis may also contribute to CKD risk.<sup>99–101</sup> In addition, severe AKI has been associated with a 3.8- to 20-fold increased risk of progression to ESKD.<sup>102</sup>

### CKD screening and monitoring

Studies to inform the optimal CKD screening and monitoring strategies among HIV-positive individuals are lacking. Until such studies exist, current CKD guidelines should be followed.<sup>2, 103</sup> CKD screening is recommended at the time of HIV diagnosis and ART initiation or modification (Figure 5).

Serum creatinine is the preferred biomarker for estimating GFR.<sup>2, 103</sup> Serum cystatin C may be considered in patients receiving medications that alter tubular creatinine handling. Cystatin C may also better predict long-term mortality,<sup>104, 105</sup> but is susceptible to bias in the setting of inflammation. The serum creatinine-based CKD-EPI equation is generally preferred;<sup>2, 103</sup> however, none of the available estimates have been validated in diverse populations or in the setting of drugs that alter creatinine secretion.<sup>106–108</sup> Use of the antiretrovirals dolutegravir or rilpivirine or the pharmacoenhancers ritonavir or cobicistat may result in average reductions in calculated creatinine clearance of around 5–20 ml/min, which should be taken into account when interpreting eGFR or creatinine clearance.<sup>109</sup> Clinicians should also be aware that serum creatinine measurements may not be

standardized in resource-limited regions and that extrarenal factors may alter both serum creatinine and cystatin C concentrations (Supplementary Table 5).<sup>110–112</sup> Rather than a single eGFR value, eGFR trajectories are useful for identifying individuals with progressive decline in kidney function.

Urinalysis should be performed in all HIV-positive individuals to detect worsening or new onset of proteinuria or hematuria. Where feasible, quantification of proteinuria (urine albumin:creatinine or protein:creatinine ratio) should also be performed. In individuals on TDF, urinalysis may also detect glycosuria, and plasma phosphate should be monitored if possible. Evaluation of cystatin C, low molecular weight (“tubular”) proteinuria, or phosphate reabsorption is not indicated in individuals with stable kidney function and no indication of TDF toxicity.<sup>113</sup>

In most HIV-positive individuals who are stable on ART, annual monitoring of kidney function appears appropriate. In those with or at increased risk of CKD and those who receive TDF with ritonavir- or cobicistat-boosted protease inhibitors, more frequent monitoring is recommended, typically 2–4 times per year depending on risk factors.<sup>113</sup> Kidney function should also be carefully monitored during hospitalization, particularly in individuals receiving TDF and concomitant nephrotoxic medications.

If CKD is identified, patients should undergo work-up based on available resources and risk-stratification, including consideration of potential medication toxicity, screening for hypertension, diabetes, and co-infections, and assessment of region-specific risk factors such as traditional medicines. HIV-specific CKD risk scores may facilitate risk-stratification,<sup>74, 75</sup> although these scores have not been validated in diverse populations or in resource-limited settings (Supplementary Table 3). Referral to nephrology should be considered in certain settings (Figure 5).<sup>103</sup> When the cause of CKD is unclear, CKD progression is rapid, or prognostication is needed, a kidney biopsy should be considered.

### **CKD management**

Evidence from observational studies strongly supports the beneficial effect of early ART initiation on the risk of classic HIVAN.<sup>114</sup> The impact of ART on CKD progression in patients with immune complex kidney diseases is more variable.<sup>71, 72</sup> Given the overwhelming benefit on survival, ART is recommended for all HIV-positive individuals.<sup>115</sup> Evaluation of other treatment strategies for kidney disease in the setting of HIV has been limited to small, single-center studies with short duration, and has focused largely on HIVAN (Supplementary Table 6). No rigorous study has evaluated the efficacy of blood pressure control, diabetes treatment, or ACE-inhibitors and angiotensin receptor blockers in slowing CKD progression in HIV-positive individuals. However, extrapolating from the strong evidence supporting the efficacy of these interventions in the general population is reasonable (Table 4).<sup>103, 116, 117</sup> Treatment of HBV, HCV, and tuberculosis co-infections should be considered based on existing treatment guidelines.<sup>118–121</sup>

### **Kidney replacement therapy (KRT) in HIV-positive individuals**

With ART, survival of HIV-positive individuals receiving KRT is comparable to their HIV-negative counterparts.<sup>122</sup> Therefore, HIV serostatus should not influence candidacy for KRT.

Observational studies demonstrate similar outcomes between hemodialysis (HD) and peritoneal dialysis (PD) among ART-treated individuals, and modality selection depends upon patient preference and regional resources.<sup>123, 124</sup> Arteriovenous fistulas are the preferred vascular access, as arteriovenous grafts and catheters are associated with higher risk of infection and thrombosis.<sup>125</sup> There is no evidence supporting isolation of HIV-positive patients in HD units, except those with HBV co-infection.<sup>126</sup> Dialyzer reuse by the same patient is practiced in resource-limited settings as a cost-saving alternative. Evidence supporting the safety of dialyzer reuse by HIV-positive individuals is limited,<sup>127, 128</sup> and precautions to avoid HIV transmission to other patients and dialysis staff must be adhered to. HIV-positive PD patients may have higher risk of PD-catheter infections; however, PD catheter failure rates are similar to that of HIV-negative patients.<sup>129</sup> PD consumables must be discarded properly, as HIV persists in PD materials and fluid.<sup>130, 131</sup>

### **Kidney transplantation in HIV-positive individuals**

Kidney transplantation in HIV-positive recipients is associated with excellent 1-year and 3-year recipient and allograft survival rates, intermediate to those observed in the overall US kidney transplant population and in a higher risk subgroup of recipients < 65 years.<sup>132</sup> Registry data also suggest good 5- and 10-year outcomes, with an improvement in survival compared to patients who remain on the waitlist.<sup>133</sup> Studies in other settings have confirmed the safety of kidney transplantation in individuals with well-controlled HIV.<sup>132, 134–138</sup> Eligible patients with advanced CKD and well-controlled HIV infection should be referred for kidney transplant evaluation (Table 5).

Immunosuppressant protocols for the general population can be applied to HIV-positive individuals. In view of the increased immunological risk, some centers prefer induction therapy with an interleukin-2 receptor antagonist, polyclonal antithymocyte globulin, or alemtuzumab.<sup>132, 134, 139</sup> Tacrolimus is the calcineurin inhibitor of choice for maintenance immunosuppression.<sup>132, 140</sup>

Existing guidelines for prophylaxis against opportunistic infections<sup>141, 142</sup> and management of hepatitis co-infection should be followed.<sup>143, 144</sup> HCV-co-infected recipients have poorer outcomes compared to recipients with HIV or HCV mono-infection, but still superior to those who remain on the waitlist. Clinicians should be aware of significant drug-drug interactions among immunosuppressive agents, ART, and antiviral medications for HCV co-infection. To minimize drug-drug interactions and achieve steady-state drug levels, integrase inhibitors and nucleoside reverse transcriptase inhibitors are the preferred antiretroviral agents, while protease inhibitors and the pharmacoenhancers ritonavir and cobicistat are best avoided.<sup>145</sup> Given the complexity of issues, a multidisciplinary team comprising experts in transplant nephrology, infectious disease, and clinical pharmacology is imperative.

Given the strong association between the *APOL1* risk variants and HIVAN, HIV-positive recipients of African descent and those who receive an allograft from a donor of African descent should be monitored for recurrent HIVAN.<sup>146</sup> The relative contribution of donor and recipient *APOL1* risk status to the risk of HIVAN recurrence is the subject of ongoing research. The *APOL1* Long-term Kidney Transplantation Outcomes (APOLLO) Research

Network<sup>147</sup> will investigate the influence of donor *APOLI* risk variants on long-term outcomes among recipients and African American donors, including those with HIV.

Based on experience in South Africa, there is growing evidence to support the safety of kidney transplantation from HIV-positive donors.<sup>148, 149</sup> The US HIV Organ Policy Equity (HOPE) Act allows the use of organs from HIV-positive donors in approved research programs.<sup>150, 151</sup> Questions remain about the implications of super-infection in settings where ART resistance is common.

## CHILDREN AND ADOLESCENTS WITH HIV

As in adults, CKD screening and monitoring are recommended, and ART should be provided as per international and regional guidelines (Supplementary Table 7).<sup>2, 115</sup>

## CONCLUSION

Despite improved survival with ART, HIV-positive individuals remain at increased risk for kidney disease. This report summarizes recommendations for diagnosis, management, and prevention of kidney disease in this population, including a proposed histologic classification. In the absence of data from randomized controlled trials, these recommendations reflect the expert opinion of conference attendees, incorporating combined clinical experience and evidence from observational studies and laboratory research. A second major outcome of this conference was the identification of knowledge gaps and areas for future research (Table 6), with the long-term goal of improving the diagnosis and management of kidney disease in HIV-positive individuals.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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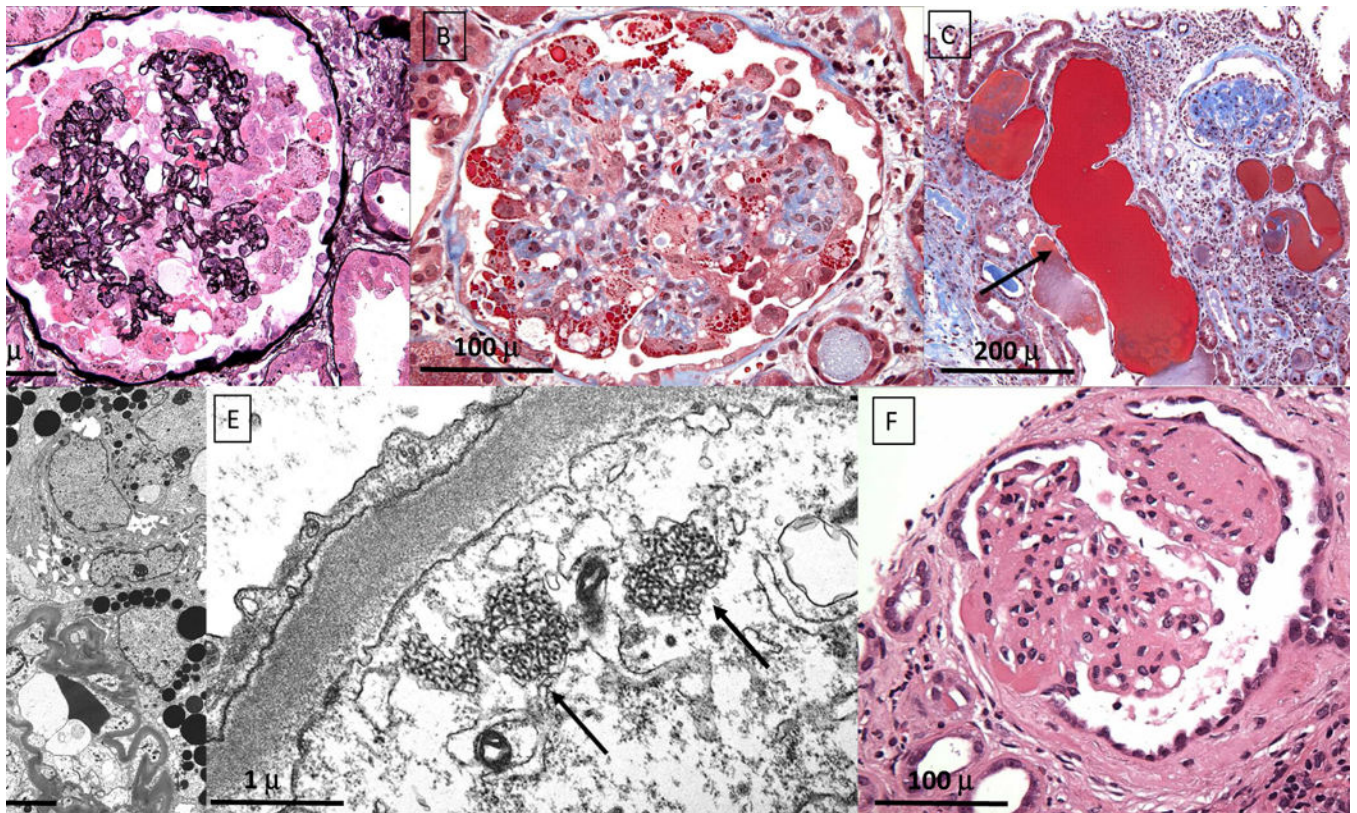
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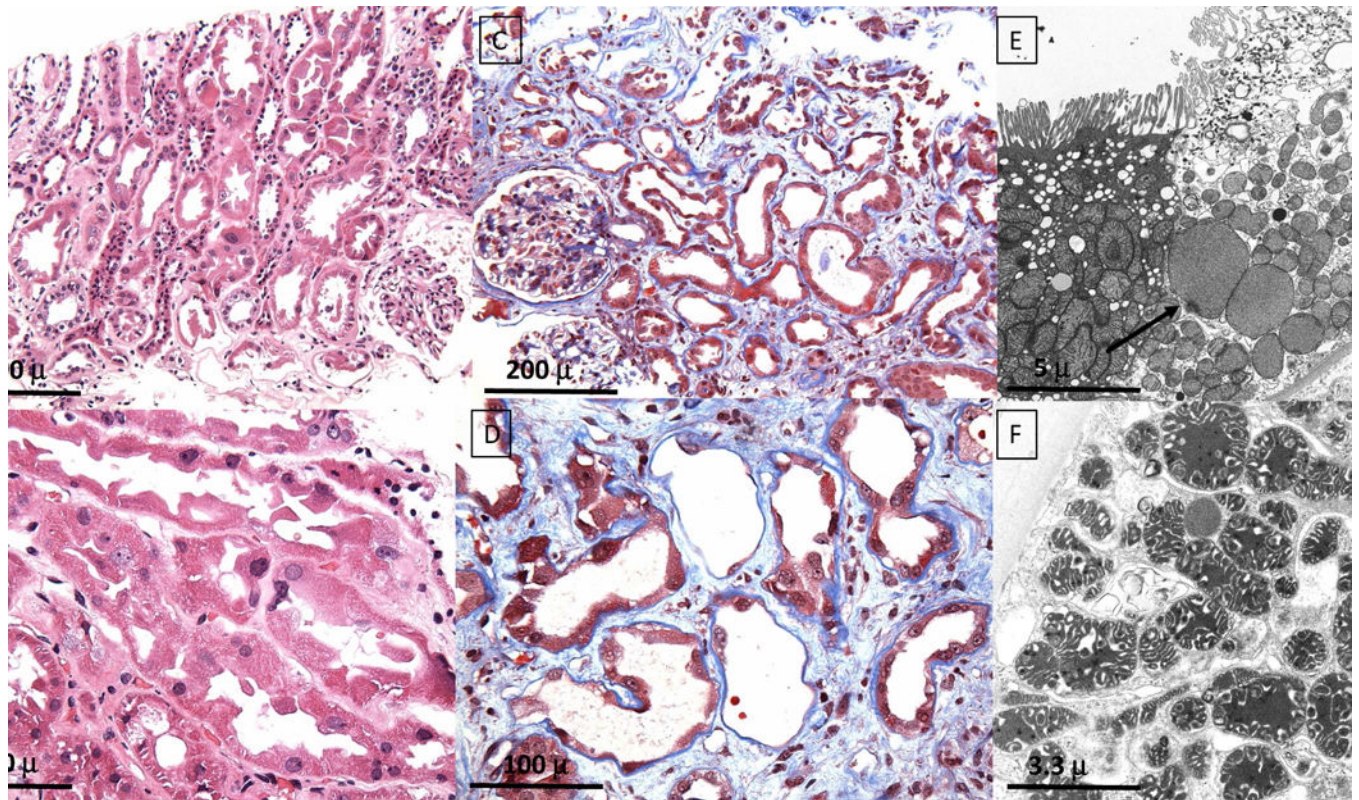
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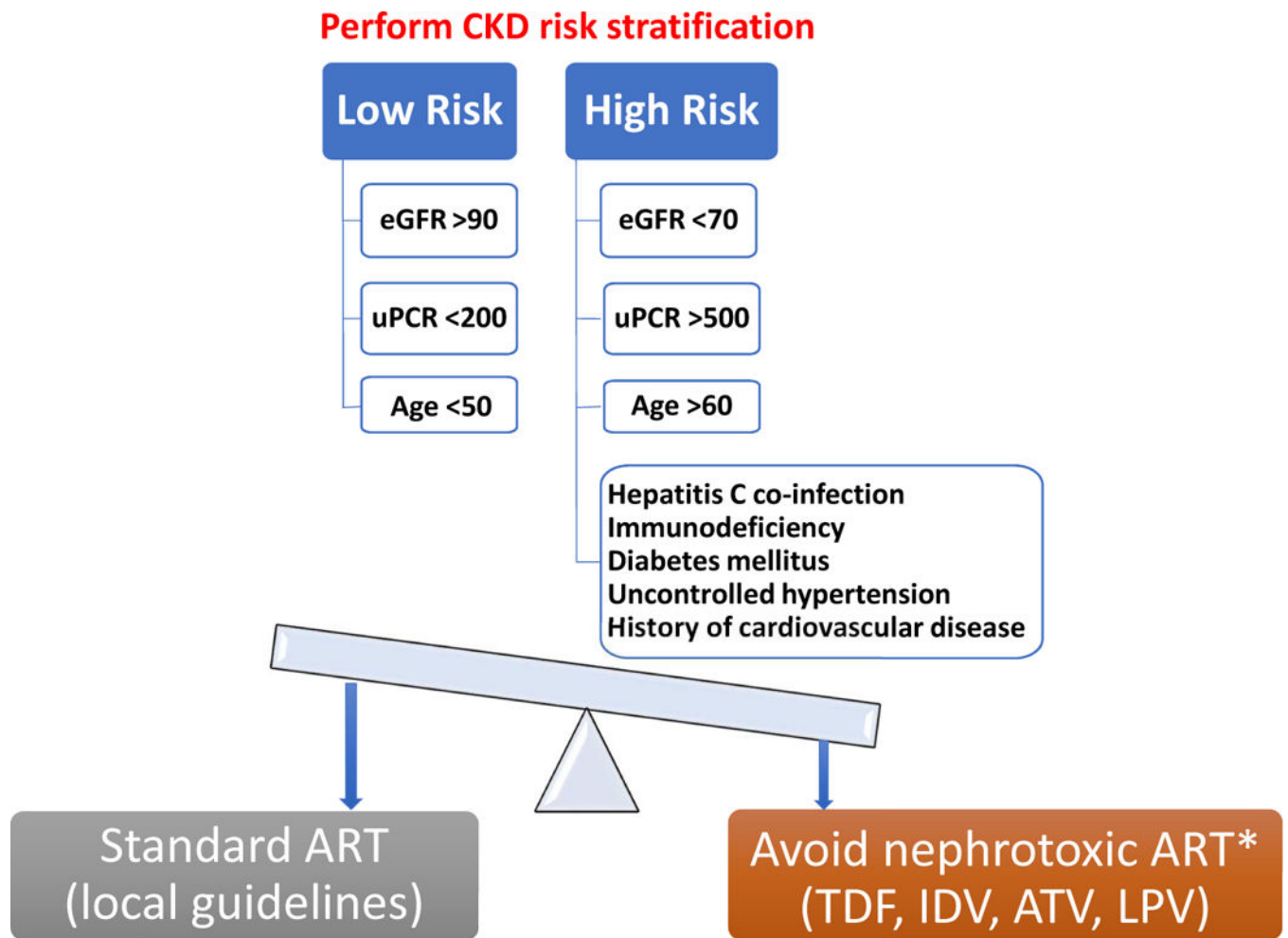
**Figure 1. Classic HIVAN and FSGS (NOS) in the setting of HIV**

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).



**Figure 2. Tenofovir nephrotoxicity**

Acute tenofovir nephrotoxicity is characterized by irregular proximal tubular profiles with atypical, irregular lining epithelial cells and mild interstitial edema (A, H&E, x200). The atypical proximal tubular cells display loss of brush border, marked irregularity of tubular epithelial height and shape, focal shedding of cytoplasmic fragments, and enlarged atypical nuclei with prominent nucleoli (B, H&E, x400). Chronic nephrotoxicity displays increased separation of the irregular proximal tubules by interstitial fibrosis and mild inflammation with focal tubular atrophy (C, Masson trichrome, x200). The tubules show focal loss and flattening of lining epithelium leaving some desquamated tubular basement membranes, as well as prominent epithelial simplification and irregularity with atypical nuclei. There is intervening interstitial fibrosis and mild inflammation, without tubulitis (D, Masson trichrome, x400). The characteristic features are focal giant mitochondria with few residual peripheral cristae (arrow) within the proximal tubular epithelial cells, as well as cytoplasmic swelling with disruption of brush border, (E, electron micrograph x8000). In some cases, the dysmorphic mitochondria exhibit irregular size and shape with bizarre patterning of their cristae (F, electron micrograph x12,000).

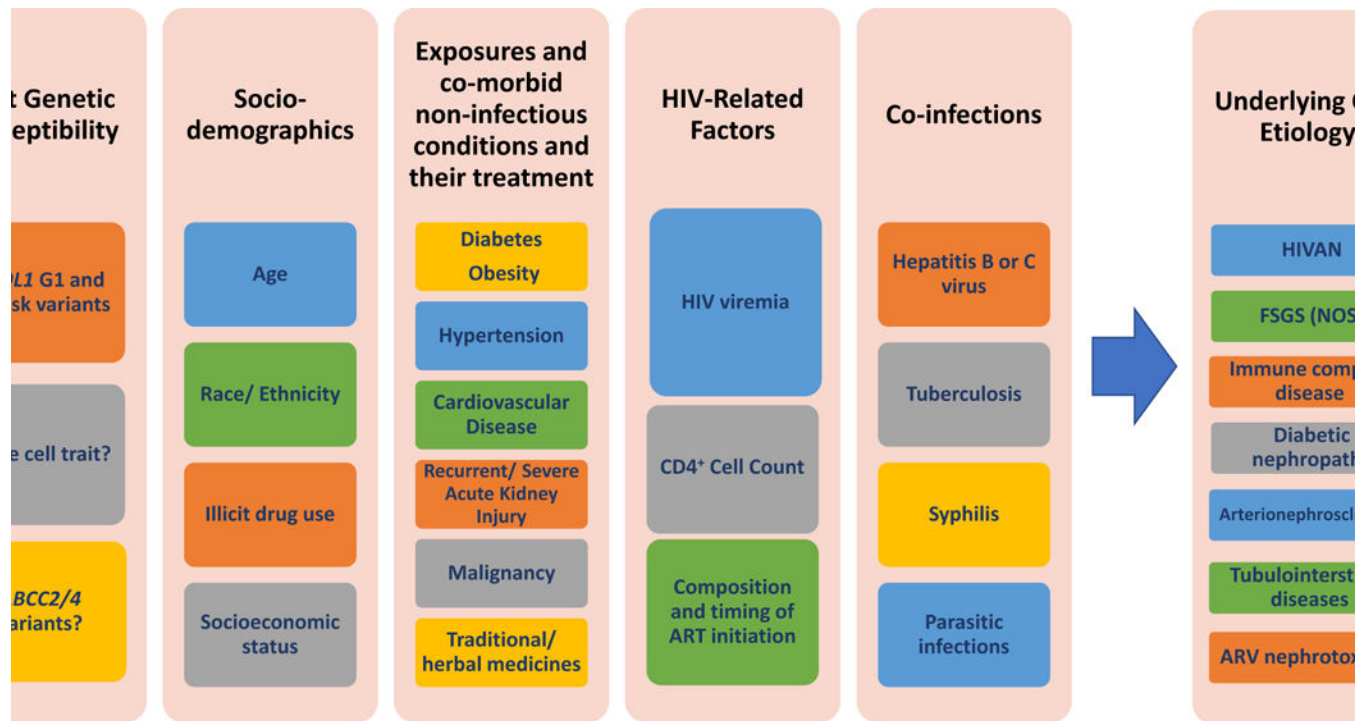


**Figure 3. Recommendations at starting ART**

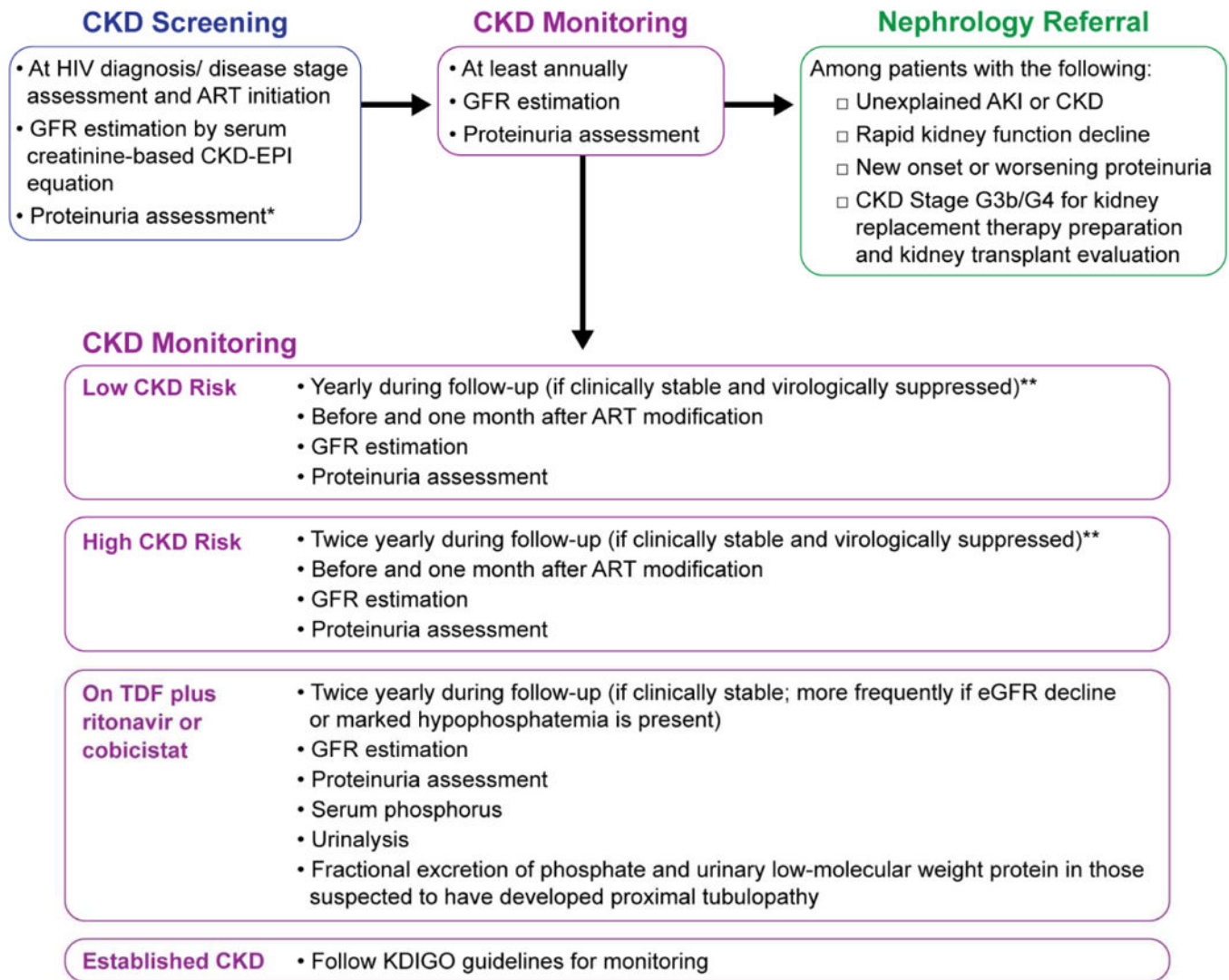
\*if suitable alternatives available

ART, antiretroviral therapy; ATV, atazanavir; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (CKD-EPI, expressed in ml/min/1.73 m<sup>2</sup>); IDV, indinavir; LPV, lopinavir; TDF, tenofovir disoproxil fumarate; uPCR, urine protein:creatinine ratio (values above are in mg/g; multiply by 0.10 to obtain values in mg/mmol).





**Figure 4. Risk factors and underlying etiologies of CKD in HIV-positive individuals**  
*APOL1*, apolipoprotein L1; *ABCC*, ATP-binding cassette transporter proteins; ARV, antiretroviral; CKD, chronic kidney disease; FSGS (NOS), focal segmental glomerulosclerosis, not otherwise specified; GN, glomerulonephritis; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy.



**Figure 5. Recommendations for kidney disease screening and monitoring in HIV-positive adults**

\*Urinalysis should be performed in all HIV-positive individuals to detect worsening or new onset of proteinuria or hematuria. Where feasible, quantification of proteinuria (spot urine albumin:creatinine or protein:creatinine ratio) should also be performed.

\*\*More frequent monitoring is recommended in persons who are clinically unstable, severely immunocompromised, or viremic.

AKI, acute kidney injury; ART, antiretroviral therapy; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; KDIGO, Kidney Disease: Improving Global Outcomes; TDF, tenofovir disoproxil fumarate.

**Table 1**

## Pathologic classification of HIV-related kidney diseases

**I. Glomerular Dominant\***

- 
- a. Podocytopathies (all characterized by extensive foot process effacement)\*\*
- 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\*
- 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. Tubulointerstitial injury in the setting of classic HIVAN
- i. Hyaline droplet tubulopathy
  - ii. Tubular microcysts
  - iii. Tubulointerstitial inflammation
- b. Acute tubular injury/ 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 restoration inflammatory syndrome (IRIS)
- f. Other tubulointerstitial inflammation in the setting of HIV
- 

**III. Vascular Dominant\***

- 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
- 

\* Indicate the likelihood of HIV causality

\*\* Indicate association with APOL1 risk allele genotype

ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy; NSAID, nonsteroidal anti-inflammatory drug.

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**Table 2**

Prevalence of *APOL1* high-risk genotypes and association with kidney disease in HIV-positive African Americans and Black South Africans

Histology	Population	Population Controls	Cases	Odds Ratio (95% CI)	Reference
HIVAN	African-American (n=54)	13%	72%	29 (14, 68)	49
HIVAN	African-American (n=60)	13%	62%	–	54
HIVAN	South Africa (n=38)	3%	79%	89 (18, 912)	51
HIV + FSGS	African-American (n=35)	13%	63%	–	57
HIV + FSGS	South Africa (n=22)	3%	8%	2.1 (0.03, 44)	51
HIV + ICD	African-American (n=31)	13%	3%	–	57
HIV + ICD	South Africa (n=12)	3%	25%	5.6 (0.4, 86)	51

*APOL1*, apolipoprotein L1; CI, confidence interval; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy; ICD, immune complex kidney disease.

**Table 3**Features of *APOLI*-mediated kidney disease in the setting of HIV

	References
• <i>MYH9</i> variants are not independently associated with HIVAN or FSGS (NOS)	45, 52, 152
• <i>APOLI</i> kidney disease manifests as HIVAN or FSGS (NOS) with or without microcystic tubular dilatation	49, 56, 57
• S342G and N388Y389/- confer risk of kidney disease; therefore genotyping only the G1 rs73385319 missense and G2 rs71785313 indel (i.e., insertion–deletion mutations) variants are sufficient to determine risk of CKD	49
• HIVAN is associated with low CD4+ cell counts, and often improves with effective ART	56
• HIV-associated FSGS is associated with higher CD4+ cell counts and occurs in patients undergoing ART	56
• <i>APOLI</i> high-risk genotypes are associated with progression to ESKD in HIV-positive patients with non-HIVAN kidney diseases	57
• Histological features of HIVAN in patients carrying two copies of <i>APOLI</i> risk variants are similar to those carrying 0 or 1 copies	54
• High-risk genotypes predict FSGS (NOS) or HIVAN, but kidney biopsy is required to distinguish between these two diagnoses	56
• HIV-infected children with CKD and high-risk genotypes have lower eGFR and experience more rapid progression	58, 153
• Multiple mechanisms have been proposed for <i>APOLI</i> -mediated podocyte injury, but they converge in perturbations of endosomal trafficking, increased membrane permeability, and cytotoxicity	61, 63 – 65
• APOL1, a component of the innate immune system, is up-regulated by interferons	61, 62
• High levels of APOL1 may be a “second hit” and sufficient to cause kidney disease	61, 62

*APOLI*, apolipoprotein L1; ART, antiretroviral therapy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS (NOS), focal segmental glomerulosclerosis, not otherwise specified; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy.

**Table 4**

Recommendations for management of CKD risk factors in HIV-positive individuals

Risk Factor	Recommendations
<b>Hypertension</b>	
<b>Non - proteinuric</b>	• Target systolic blood pressure 140 mmHg <sup>116</sup>
<b>Proteinuric</b>	• Target systolic blood pressure 130 mmHg <sup>116</sup> • Preferred antihypertensive: ACE inhibitors or angiotensin receptor blockers <sup>116</sup>
<b>Diabetes mellitus</b>	• Target hemoglobin A1c ~7% <sup>*103</sup>
<b>Hepatitis B virus co - infection</b>	• Treat per existing guidelines <sup>118, 121</sup> • TAF may be used in patients with eGFR $\geq 30$ ml/min/1.73 m <sup>2</sup> . <sup>154</sup> • Where TAF is unavailable or in patients with eGFR $< 30$ ml/min/1.73 m <sup>2</sup> , dose-adjusted TDF or entecavir may be considered.
<b>Hepatitis C virus co - infection</b>	• Treatment per existing guidelines <sup>120, 155</sup> • In patients with HCV genotypes 1 or 4 and CKD G4/5, ribavirin-free grazoprevir and elbasvir regimens may be effective. <sup>156-158</sup> • In patients with genotypes 2, 3, 5 or 6, sofosbuvir-based regimens are required; however, sofosbuvir-based regimens should be avoided or alternate-day sofosbuvir dosing should be considered in patients with eGFR $< 30$ ml/min/1.73 m <sup>2</sup> . <sup>159-161</sup> In addition, the combination of ledipasvir/sofosbuvir with TDF should be avoided.

\* Note: Hemoglobin A1c may underestimate glycemia in HIV-positive individuals.<sup>162, 163</sup>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HCV, hepatitis C; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

**Table 5**

## Selection criteria for potential HIV-positive kidney transplant recipients

- 
- Meets standard criteria for kidney transplant recipients, PLUS the following:
  - Effective HIV suppression for 6 months prior to transplantation
    - Undetectable plasma HIV-1 RNA
    - CD4+ cell count >200 cells/mm<sup>3</sup>
  - No active opportunistic infections
  - No prior history of:
    - Progressive multifocal leukoencephalopathy
    - Primary central nervous system lymphoma
    - Pulmonary aspergillosis
    - Visceral Kaposi's sarcoma
    - Coccidiomycosis
    - Chronic intestinal cryptosporidiosis >1 month
  - Hepatology evaluation for patients co-infected with hepatitis B or hepatitis C virus *et al.* and Muller E *et al.*<sup>132, 137</sup>
- 

Criteria adapted from Stock HIV, human immunodeficiency virus.



**Table 6****Controversies, knowledge gaps, and areas for future research****Renal pathology**

- What is the spectrum of renal pathology in the setting of HIV infection in the current era and in diverse patient populations?
- How do pathologic features correlate with the duration of ART, HIV viral load, racial and geographic origin, and *APOL1* risk allele genotype?
- What is the relative contribution of de-differentiated podocytes versus parietal epithelial cells to the glomerular epithelial cell hyperplasia seen in HIVAN?
- What are the roles of specific HIV transcript expression in promoting proliferation and possible transdifferentiation of podocytes and parietal epithelial cells, and in mediating the tubular phenotype of cell cycle arrest and microcyst formation?
- What is the pattern of HIV viral transcript expression in specific renal cell types and tissue compartments in FSGS (NOS) and other non-HIVAN lesions in the setting of HIV?
- Is FSGS (NOS) in the setting of HIV representative of attenuated or partially treated HIVAN?
- How can immune complex disease that is causally related to HIV infection be distinguished from coincident disease?
- Can HIV infection of renal dendritic cells, infiltrating monocyte/macrophages, or intrinsic renal epithelial cells produce a viral reservoir that is capable of reactivation?
- What is the composition of the inflammatory infiltrates in HIV-related tubulointerstitial disease?

**Genetics/ Genomics**

- What is the prevalence of *APOL1* risk alleles among ethnic and tribal populations in Sub-Saharan Africa, particularly in central and southeastern Africa?
- What is the prevalence of *APOL1* risk alleles in African admixed populations as a consequence of the African diaspora in Central and South America and in the Caribbean?
- What other genes or viral or environmental factors cause HIVAN in 30% of individuals with 0 or 1 *APOL1* risk alleles? Why isn't HIVAN observed more frequently in other populations lacking *APOL1* risk alleles?
- Why do *APOL1* gain-of-function variants show recessive inheritance?
- Is a single copy of *APOL1* G1 or G2 sufficient to cause HIVAN in a setting of HIV infection?
- What are the genetic and environmental factors which affect penetrance of APOL1 and does this differ by ethnicity or ancestry?
- What is the role of APOL1 in children with HIV infection?
- What are the mechanisms by which APOL1 precipitates kidney disease? Do these mechanisms differ in the setting of HIV infection?
- Is APOL1 an initiator of HIVAN or a progression factor?
- What are the public health implications of APOL1 in resource-limited settings?

**Antiretroviral therapy and nephrotoxicity**

- What is the clinical significance of TDF-induced sub-clinical renal tubular dysfunction, and what is the value of monitoring for low-molecular weight proteinuria and reduced phosphate reabsorption in patients on TDF?
- What is the rate of TDF nephrotoxicity in individuals without access to regular kidney function monitoring, including HIV-negative individuals taking TDF to prevent HIV infection?
- What is the long-term renal safety of TAF in individuals with a history of TDF-associated nephrotoxicity, CKD, or relevant comorbidities?
- What is the long-term safety of TAF in children, particularly with respect to bone health?
- Would epidemiologic studies linking ritonavir-boosted protease inhibitors to decreased eGFR yield similar results with cystatin C-based eGFR estimates?

**Management of CKD and ESKD**

- What are the optimal strategies for assessing and monitoring kidney health among ART-treated adults and children in resource-rich and resource-limited settings?
- Are existing CKD risk scores developed in HIV-positive US and European populations valid in other populations?
- How well do creatinine-based eGFR estimates predict true GFR in ART-treated individuals, especially those on ART that interferes with creatinine secretion and in sub-Saharan African populations?
- What is the role of serum cystatin C, alone or in combination with creatinine, in evaluating kidney function in specific clinical contexts, such as the use of ART that interferes with creatinine secretion?
- What is the clinical utility of novel urine biomarkers of kidney injury in assessing and monitoring kidney health?

- Are clinical guidelines for diabetes, hypertension, and cardiovascular disease developed in the general populations effective in preventing CKD onset and progression in HIV-positive individuals?
- Do ACE inhibitors and ARBs confer similar renoprotective effects among HIV-positive individuals with CKD as in the general population?
- What is the impact of tuberculosis co-infection and its treatment on the risks of CKD development and progression among HIV-positive individuals?
- What is the role of adjunctive therapy with corticosteroids or immunosuppressive therapy in patients with HIVAN or other kidney disease that may be causally related to HIV infection?
- What is the role of HIV infection in immune complex kidney disease, and what is the optimal therapy for specific immune complex diseases in this setting?
- Has the epidemiology of acute kidney injury changed in the era of modern ART, and what is the impact on CKD risk in the setting of HIV?
- What is the optimal antiviral therapy for HBV or HCV co-infection with regards to efficacy and safety in HIV-positive individuals?
- Does treatment of HBV or HCV co-infection impact CKD prognosis?
- How does the peritonitis risk among ART-treated HIV-positive patients undergoing peritoneal dialysis compare to that of their HIV-negative counterparts?
- Are existing treatment guidelines for catheter-related infections developed in HIV-negative populations effective among HIV-positive patients with ESKD?
- What are the optimal strategies for anemia and mineral-bone disease management in the HIV-positive population with CKD or ESKD?

#### **Kidney Transplantation**

- Among HIV-positive patients being considered for kidney transplantation, what is the optimal timing of HBV or HCV treatment relative to kidney transplantation? This is particularly important based on the worse post-transplant outcomes among recipients with HIV-HCV co-infection.
- What is the optimal induction therapy for highly sensitized HIV-positive transplant recipients?
- What are the optimal ART and immunosuppressive regimens for HIV positive kidney transplant recipients?
- What is the optimal strategy for selecting and matching potential HIV-positive organ donors and recipients?
- What are the long-term implications of HIV-to-HIV kidney transplantation on patient and allograft outcomes and HIV disease course?

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ACE, angiotensin-converting enzyme; APOL1, apolipoprotein L1; ARB, angiotensin receptor blocker; ART, antiretroviral treatment; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C C; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy; NOS, not otherwise specified; TDF, tenofovir disoproxil fumarate; US, United States.