Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Charles R. Swanepoel[1], Mohamed G. Atta[2], Vivette D. D'Agati[3], Michelle M. Estrella[4], Agnes B. Fogo[5], Saraladevi Naicker[6], Frank A. Post[7], Nicola Wearne[1], Cheryl A. Winkler[8], Michael Cheung[9], David C. Wheeler[10], Wolfgang C. Winkelmayer[11] and Christina M. Wyatt[12]; for Conference Participants[13]

[1]Division of Nephrology and Hypertension, University of Cape Town, Cape Town, South Africa; [2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [3]Department of Pathology & Cell Biology, Columbia University Medical Center, New York, New York, USA; [4]Department of Medicine, San Francisco VA Medical Center and University of California, San Francisco, California, USA; [5]Department of Pathology, Microbiology and Immunology, Vanderbilt University, Nashville, Tennessee, USA; [6]Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [7]King's College Hospital NHS Foundation Trust, London, UK; [8]Basic Research Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health and Leidos Biomedical Research, Frederick National Laboratory, Frederick, Maryland, USA; [9]KDIGO, Brussels, Belgium; [10]University College London, London, UK; [11]Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; and [12]Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA

HIV-positive individuals are at increased risk for kidney disease, including HIV-associated nephropathy, noncollapsing 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.

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Correspondence: *Charles R. Swanepoel, Division of Nephrology and Hypertension, University of Cape Town, Cape Town, South Africa. E-mail: charles.swanepoel@uct.ac.za; or Christina M. Wyatt, Mount Sinai School of Medicine, Nephrology, Box 1243, One Gustave L. Levy Place, New York, New York 10029, USA. E-mail: christina.wyatt@mssm.edu*

[13]See Appendix for list of other conference participants.

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Worldwide, an estimated 37 million people are living with HIV infection, and more than 2 million new infections are diagnosed annually.[1] 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 lifelong 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,[2] 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 comorbidities, drug effects, immune dysregulation, and co-infections.[3] 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 2 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.[4] 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.[5] 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).[6,7] Glomerular "collapse" is defined as at least 1 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.[8,9]

By electron microscopy, diffuse podocyte foot process effacement and endothelial tubuloreticular inclusions (interferon footprints) are classic features.[6,7] By immunofluorescence, there may be staining for IgM, C3, and C1q in collapsed segments and mesangial areas.[7] Protein resorption droplets may stain for albumin and Ig. 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."[10] Phenotypic studies suggest that the glomerular epithelial cell monolayer is composed of parietal epithelial cells.[8] In some cases, sequential biopsy and postmortem studies have shown

Table 1 | Pathologic classification of HIV-related kidney diseases

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]Indicates likelihood of HIV causality.
[b]Indicates association with *APOL1* risk allele genotype.