Global Action. Local Change.

KDIGO Controversies Conference on HIV-Related Kidney Diseases

March 17-20, 2017
Yaoundé, Cameroon

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

Background

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), is less common with the widespread use of early antiretroviral therapy; however, there has been a simultaneous increase in the prevalence of non-collapsing FSGS. There is also growing evidence that HIV-positive individuals are at risk for immune-complex kidney diseases and for more rapid progression of comorbid CKD. In addition, patients with HIV infection are exposed to life-long antiretroviral therapy, with the potential to cause or exacerbate kidney injury. Newer guidelines recommending early initiation of

antiretroviral therapy are likely to reduce the incidence of HIVAN, but the overall risk-benefit for kidney health is not known.

Decades of laboratory studies have established that both direct HIV infection of the kidney and host genetic susceptibility are central to the pathogenesis of HIVAN.[1, 2] Nonetheless, available evidence suggests that African ancestry or even the presence of the *APOL1* risk alleles is insufficient to make a definitive diagnosis of HIVAN, which still requires kidney biopsy.[3] The role and utility of genetic testing in the diagnosis and prognosis of HIV-related kidney disease has not been defined. There is also a lack of consensus on the specific histologic features required to distinguish HIVAN from idiopathic FSGS on kidney biopsy, and there is no consensus on which immune-mediated kidney diseases should be classified under the term HIV-immune complex kidney disease (HIVICK).[4] This lack of consensus is partially driven by the limited understanding of disease pathogenesis and by the heterogeneity of diseases that have been categorized as HIVICK. The diagnosis of kidney disease in HIV-positive individuals is also confounded by the potential nephrotoxicity of some ART agents, in particular tenofovir and the protease inhibitors, and kidney biopsy may be helpful to distinguish between intrinsic and medication-related kidney injury.[5]

In addition to HIV-related diseases, HIV-positive individuals are also at risk for comorbid kidney disease unrelated to HIV infection or its treatment.[6] Basic and epidemiologic studies have suggested an additive effect of HIV infection and traditional CKD risk factors in promoting CKD progression.[7, 8] Nonetheless, clinical guidelines for CKD prevention and treatment are largely extrapolated from studies in the general population, and current therapies do not target unique HIV-related pathways that may

contribute to CKD progression in this population.[9] Recently developed prediction models for CKD progression incorporate markers of HIV disease severity, but these risk scores must be validated in more diverse patient populations before they are adopted for clinical use.[10] Finally, although observational studies support the safety of dialysis and kidney transplantation in patients with well-controlled HIV infection, there is also a lack of consensus on the optimal management of end-stage kidney disease in this population.[11]

CONFERENCE OVERVIEW

To this end, this KDIGO conference will gather a multidisciplinary, international panel of clinical and scientific experts (e.g., nephrology, infectious diseases, renal pathology, pharmacology, etc.) to identify and discuss key issues relevant to the optimal diagnosis and management of HIV-related kidney diseases. The specific goals of this KDIGO conference are to define the pathology of HIV-related kidney disease; describe the role of genetics in the natural history, diagnosis, and treatment of HIV-associated nephropathy; characterize the renal risk-benefit of antiretroviral therapy in HIV treatment and prevention; and define best practices to delay the progression of kidney disease and to treat end-stage kidney disease in HIV-positive individuals. The conference will also identify knowledge gaps and areas for future research.

Drs. Charles Swanepoel, MBChB (UCT), MRCP (UK), FRCP (Edin) (Groote Schuur Hospital and University of Cape Town, South Africa) and Christina M. Wyatt, MD, MS (Icahn School of Medicine at Mount Sinai, NY, USA) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused

discussion groups that will report back to the full group for consensus building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research in this area.

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APPENDIX: SCOPE OF COVERAGE

GROUP 1: GENETICS & HIVAN

- ***Genetics of kidney disease with HIV infection in the African genetic milieu***
  - Can effect sizes and population attributable risk from studies in South Africa and among African Americans be extrapolated to other African populations?
  - Are there additional susceptibility and resistance genetic factors remaining to be discovered in African populations?
  - What are the genetic and environmental factors which affect penetrance of *APOL1* and does this differ by ethnicity or race?
  - Do we need more granular data for epidemiology of HIV and prevalence of kidney disease in Africa for public health policy decisions?
  - What is the role of *APOL1* in children with HIV-1 infection? Should cohorts be assembled to assess the role of *APOL1* risk variants on CKD in children and adolescents with HIV infection?
  - What studies are warranted to assess utility of genetic screening for *APOL1* risk factors versus testing for microalbuminuria, proteinuria, and estimated eGFR?
  - Will knowledge of *APOL1* genotype change clinical management?
  - Is there a role for aggressive blockade of the renin-angiotensin aldosterone (RAAS) pathway (i.e., with ACE plus aldosterone receptor inhibitors) in patients carrying *APOL1* risk alleles?

- ***APOL1 interactions with HIV in causing kidney disease; APOL1 structure and functional role in HIV kidney disease***
  - Does *APOL1* interact with tenofovir to promote tubular and glomerular injury?
  - Since about 10-20% of people with HIVAN carry only 1 or no *APOL1* risk allele, are there other genetic variants in African ancestry chromosomes that increase susceptibility to HIVAN or increase penetrance for carriers of one-risk allele?

  - Is *APOL1* an initiator of HIV-associated kidney disease or a progression factor?

- ***Correlations of HIV kidney disease with genetics: Rapid decline in eGFR, premature aging, collapsing GN, immune complex disease/IgAN***
  - Should cross-sectional or longitudinal cohort studies be assembled to determine the genetic correlates of premature aging, decline of kidney function, and specific etiologies in the HIV population?
  - Will durable viral suppression mitigate or prevent renal injury differentially in persons carrying renal risk variants, including *APOL1*?
  - How much of HIV-associated kidney disease is attributable to known genetic factors?

- ***Genetic modifiers for kidney function decline or pathology (e.g., MYH9, APOL1)***
  - What is the best method to identify additional genetic factors that modify penetrance of *APOL1*—admixture linkage studies, whole genome/exome studies, gene expression?

- ***Biomarkers for kidney dysfunction or systemic inflammation in HIV***
  - What are the best biomarkers for predicting decline in kidney function?
    - Pro-inflammatory cytokines, d-dimer, cystatin C, INF-gamma
    - Genetic markers
    - Gene expression profiles
    - ACR, PCR , and albumin-to-total protein ratio (uAPR)
    - Do circulating levels of IFN predict ACR, PCR or eGFR? Is there a positive correlation between IFN levels and HIV burden?

GROUP 2: RENAL PATHOLOGY: HIVAN & HIVICK

Classification of HIV-related kidney diseases

- How can we classify HIV-related kidney diseases in general?
- How can we diagnose HIV-related kidney diseases directly caused by intrarenal HIV transcript expression versus others?
- How can we classify HIV-related podocyte diseases?
    - How do we define classic HIVAN and should it be differentiated from other forms of podocytopathy?
- How can we classify HIV-related immune complex diseases?
    - Lupus-like
    - Related to co-infections
    - Others
- How can we classify HIV-related tubulointerstitial lesions?
    - Viral-mediated
    - Cytokine-mediated/DILS/Immune reconstitution syndrome
    - Drug effects (tenofovir and protease inhibitors)
    - Other causes of ATN/AKI
- Potential for overlap?

Knowledge gaps for above

Utility of ancillary studies (e.g., special stains, etc.) for research and clinical practice

GROUP 3: HIV AND CKD PROGRESSION & END-STAGE KIDNEY DISEASE

What factors influence the natural history of CKD progression in HIV-infected individuals?

- Timing and components of combination antiretroviral therapy (cART)
- Effectiveness of treatments other than cART (e.g., steroids, RAAS antagonists) in the management of CKD in HIV-infected patients
- Co-infections and their treatment: HBV, HCV, TB
- Non-infectious comorbid conditions: Diabetes, hypertension, obesity
- Co-existent histopathological diseases: Primary and secondary glomerulonephritides

Among HIV-infected patients who have advanced CKD and are co-infected with the hepatitis B or C virus, what are the optimal antiviral treatment strategies?

- Subset of patients who should receive antiviral treatment
- Early versus late initiation and pre- vs. post-transplant antiviral treatment
- Risks and benefits among antiviral treatment regimens in the context of advanced CKD/ ESKD and potential drug-drug interactions

What are cost-effective, feasible strategies for screening, monitoring and managing CKD in HIV-positive individuals?

- Strategies in developed countries vs. resource-limited settings
- Strategies in urban vs. rural areas

Can existing CKD risk scores for incident CKD and CKD progression be generalized to HIV-infected populations to inform CKD screening and monitoring and HIV care strategies?

- Current status of use in clinical practice in HIV care in developed and developing countries
- Clinical context in which serum cystatin C should be used instead of or in addition to serum creatinine to assess kidney function
- Utility of urine biomarkers of kidney injury in prognostication of CKD progression

For kidney transplantation among HIV-infected persons with advanced CKD or ESKD,

- Who are the optimal candidates for HIV+ to HIV+ transplantation?
- How does co-infection with the HBV or HCV influence kidney transplant listing?
- What are the long-term outcomes among HIV-infected patients following kidney transplantation? (e.g., recurrence of HIVAN, risk for acute and chronic cellular or antibody-mediated rejection, allograft failure)
- What are the optimal cART, immunosuppressive and antimicrobial prophylaxis regimens among HIV+ patients who undergo transplantation?

To what extent does the excess risk of acute kidney injury among HIV-infected persons contribute to incident CKD and CKD progression in this patient population? What factors contribute to this excess risk of AKI among HIV-infected persons?

How are the outcomes among HIV-infected patients with CKD or ESKD compared to their HIV-uninfected counterparts? Consider:

- Risk of cardiovascular disease events, including heart failure, and generalizability of existing guidelines on cardiovascular disease prevention and management
- Rates of vascular access failure and catheter-related infection in HIV-infected vs. uninfected individuals receiving chronic hemodialysis
- Rates of catheter-related infection and peritonitis in HIV-infected vs. uninfected individuals receiving peritoneal dialysis
- Does the nature of bone mineral disease differ between HIV-infected vs. uninfected individuals? Can current guidelines be generalized to the HIV-infected population?

GROUP 4: ANTIRETROVIRAL THERAPY (ART) NEPHROTOXICITY

What antiretroviral drugs have nephrotoxicity? How can kidney toxicity be assessed?

- Drugs and known/ hypothesized mechanisms, pharmacokinetic studies
- Trials, cohort data, case series for the following outcomes of interest:
  - AKI
  - CKD
  - Interstitial nephritis
  - Proximal tubular toxicity
  - Nephrolithiasis/ urolithiasis
  - Kidney injury following kidney transplantation
  - Kidney injury associated with HIV pre-exposure prophylaxis
- Implications

What is the optimal strategy for determining and monitoring kidney function in HIV-positive patients on ART?

- GFR estimating equations
- Urinalysis
- What about newer ART agents that interfere with creatinine or cystatin C?
- What about in CKD?

How can we minimize ART toxicity? Consider:

- Strategies for avoiding nephrotoxic ART in populations at high risk of CKD
- Drug adjustments during specific clinical practice settings and conditions in outpatient clinic setting vs hospitalization setting
- Drug-drug interactions

What considerations are important in selecting ART in HIV-infected patients with CKD?

- TDF vs. TAF vs. ABC vs. NRTI-sparing regimens for patients with decreased GFR
- Special considerations for HIV-positive children

What is the optimal ART in kidney transplant recipients?

- What are the ART agents to avoid?
- What drug interactions are important in managing kidney transplant recipients in HIV- positive individuals?