Global Action. Local Change.

KDIGO Controversies Conference on HIV-Related Kidney Diseases
- Breakout Group Discussion Questions -

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?