The Kidney in HIV and Aging

- Identify the cause and when possible treat all changes in kidney function.
- Kidney function should be monitored at least annually using serum creatinine and other clinically available estimates of GFR.
- Urinary albumin excretion should be measured at least annually.
- Individuals with eGFR < 60ml/min (defined as CKD, NKF Stage 3a) should have a nephrologist involved in the patient care team.
- Individuals with known CKD should be referred for planning for kidney replacement therapy when eGFR <15 ml/min.
- In order to minimize the risk of acute kidney injury, careful monitoring and adjustment of drug dosing, particularly tenofovir, should be performed.

The use of antiretroviral therapy (ART) in HIV-infected individuals has substantially reduced morbidity and mortality from HIV-related causes; as life expectancy has improved, however, complex interactions between aging-associated and other comorbidities complica medical management and limit survival in these individuals [1]. Treatment of HIV-infected individuals prior to a reduction in CD4 count has significantly reduced the rate of HIV-associated nephropathy (HIVAN) [2]; nevertheless, age-related factors, co-infections such as HCV, drug toxicity, and acute kidney injury contribute to acute and chronic kidney diseases that account for significant morbidity and mortality in HIV-infected individuals [3].

Aging Nephropathy (AN) and HIV Infection

Recent data from biopsies of older individuals without clinical evidence of kidney disease or other known potential causes of kidney disease (e.g., hypertension, diabetes, HIVAN, etc.) have shown significant structural abnormalities, including glomerulosclerosis and tubulointerstitial fibrosis, that correlate with advancing age [4, 5]. Longitudinal studies in older individuals show progressive loss of kidney function and development of complications with time, implying that these structural changes eventually have clinical consequences [6-8]. AN increases the risk for development of acute kidney injury, often followed by rapid progression to ESKD, even in individuals who initially recover from the acute injury [9].

Although the cause of AN is unknown, loss of Klotho with age may be an important contributor [10], and prediction of AN with clinical measures of Klotho is under study [11]. As existing kidney disease is associated with faster progression to AIDS and death, older individuals with AN who become infected with HIV should be considered at increased risk for AIDS progression. Recent publication of data quantifying the degree of glomerulosclerosis seen in otherwise healthy older individuals allows determination in
biopsies of the likely presence of an additional form of kidney disease [12].

**ART and Kidney Complications**

Several types of ART have been associated with changes in kidney function, nephrolithiasis (associated with atazanavir), rhabdomyolysis, and acute kidney injury. Individuals with underlying AN are at increased risk for development of drug-related toxicities, therefore requiring careful adjustment of drug doses in all older individuals.

Proximal tubulopathy (Fanconi syndrome), characterized by tubular proteinuria, glycosuria, hypophosphatemia, hypouricemia, hypokalemia, and renal tubular acidosis, is a recognized form of tenofovir toxicity, which mimics abnormal tubular function seen with AN [13], possibly making identification of etiology difficult.

Although acute kidney injury (AKI) is increased in tenofovir-treated individuals, no specific characteristics have been identified that predict which individuals are at particular risk [14, 15]. Although careful adjustment of drug dosing with tenofovir has reduced the risk for acute effects on kidney function, long-term studies have established increased risk for development of CKD in tenofovir-treated patients [16]. Furthermore, discontinuation of tenofovir was associated with improved kidney function without loss of viral suppression, arguing for the benefit and safety of discontinuation of tenofovir in the presence of a change in kidney function [17].

**Chronic Kidney Disease (CKD) in Persons with HIV**

Reports of CKD in HIV-positive individuals vary significantly, from approximately 3% to 50% depending on the study population. Key factors include duration of HIV infection, access to ART, African heritage, age, co-infections (e.g., HCV), and other co-morbidities. Half of individuals with HIV infection and African heritage will develop HIVAN, often associated with two alleles with APOL1 G1 and G2 mutations. These mutations are known to influence risk for the development of collapsing nephropathies with injury to podocytes, the sites of HIV reservoirs within the kidney [18, 19].

Early use of ART has substantially reduced viral load in HIV-infected individuals, and with it kidney infection with HIV and the consequent development of HIV-associated nephropathy (HIVAN). Nevertheless, among HIV-infected individuals with CKD, up to 60% have evidence of collapsing glomerulopathy (HIVAN) on biopsy, representing a significant cause of CKD in this population [20, 21]. Also, despite advances in HIV treatment, African heritage, co-infection with hepatitis C, hypertension, diabetes, nephrotoxicity from medications, age, male gender, and the use of tenofovir or ritonavir-boosted protease inhibitors contribute to the high prevalence of advanced CKD in HIV-infected individuals.

As individuals with HIV age and older individuals become infected with HIV, appropriate diagnosis and management of these risk factors are important in preserving kidney function.

**Diagnosis and Management of CKD in Older HIV-Infected Persons**

In order to identify individuals with kidney disease accurately and to make appropriate adjustments in drug dosing, ongoing efforts seek to identify the best clinically available means of accurately estimating GFR.

Initial studies using cystatin C measurements appeared promising, but recognition of limitations prompted evaluation of combinations of creatinine- and cystatin C-based equations [22-24]. Despite these efforts, considerable variability in results persists. These have been attributed to small numbers of subjects, the possibility that different methods perform differently in different subpopulations, and the lack of
correlation with clinical outcomes [24]. Recent studies in HIV-infected individuals indicate persistence of the limitations of these formulae [25].

Although the use of very accurate estimates of GFR within and across study populations is essential for establishing outcomes in clinical trials, when using the same method over time existing methods are reliable in assessing stability or change of kidney function in individual persons. Furthermore, they provide general guidance in staging CKD.

With regard to adjustment of drug dosing, two studies in older individuals or HIV-infected persons concluded that the most commonly used creatinine-based methods (Cockcroft-Gault equation or Modified Diet in Renal Disease [MDRD] formulae) performed best [26, 27].

In older persons with HIV infection, multiple etiologies may contribute to loss of kidney function, e.g., AN, hypertension, diabetes, HIVAN, infections, obstructive uropathy, and acute kidney injury [28]. Thus a change in kidney function and its likely cause must be identified to guide diagnosis-driven therapy that protects kidney function. For some etiologies, cure is not possible and CKD ensues.

In 2013, the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [29] report proposed clinical practice Guidelines for the risk of CKD progression. These Guidelines incorporate the cause of CKD, GFR category, and albuminuria category, where CKD is defined as abnormal kidney structure or function that is present for more than three months. For any given level of GFR, the greater the degree of albuminuria, the higher the risk for progression, including in HIV-infected individuals [30]. Based on these criteria, in addition to eGFR, it is essential to measure urinary albumin excretion (mg albumin/mg creatinine) to assess risk. Since the publication of these Guidelines, commentary has suggested only minor modifications [30, 31].

The KDIGO Guidelines suggest involvement of a nephrologist in the care of all individuals with identified CKD (Stage3a), and certainly in all individuals with eGFR less than 30 ml/min. Prevention of progression of disease is an important goal prior to the time when referral for evaluation for dialysis and transplantation are required (eGFR less than 15 ml/min). In complex individuals with multiple comorbidities, such as older individuals with HIV infection, a nephrologist should be a part of the health care team when eGFR is less than 60ml/min [28].

Similar approaches that did not include measures of albumin excretion have been applied in individuals with HIV with reasonable predictive accuracy if those who would develop CKD [32]. In that study, the development of CKD was quite low, which likely reflects the access to care and ART in the study population; additional studies in HIV-infected subjects are therefore needed.

**Kidney Transplantation in HIV-Infected individuals**

In this era of improved survival with antiretroviral treatment of HIV-positive individuals with ESKD, kidney transplantation has become feasible. Similarly, increasing numbers of older individuals have also achieved satisfactory outcomes with organ transplantation. Yet, in both groups, recent studies have shown reduced graft function as compared to HIV-negative and younger individuals.

Canaud et al. [33] showed that, despite a lack of detectable HIV in the blood of individuals previously diagnosed with the virus, the kidney allograft becomes infected with HIV in 68% of biopsies, and a significant number develop clinical evidence of HIVAN in the transplanted kidney. Kidney infection correlated with, and could potentially be diagnosed by, detection of HIV DNA in the urine. This study suggests that nearly half of
transplant recipients will have had episodes of acute rejection at the end of one year, a rate double that of HIV-negative individuals [34].

Frassetto et al. [35] and Harbell et al. [36] have examined drug-drug interactions among allograft immunosuppressive agents and ART, finding a variety of complex interactions that require frequent monitoring of drug levels to avoid drug toxicities or inadequate immunosuppression.

Evidence that individuals with clinically diagnosed acute rejection also have kidney infection with HIV complicates selection of appropriate therapy in the face of a change in kidney function still further [33].

Despite these difficulties, adequate graft function at one and three years post-transplantation was present even in those who experienced an acute rejection episode, supporting the argument for a continued role for transplantation in the management of older and HIV-infected individuals with ESKD [37].

Although transplantation of kidneys from HIV-positive donors into HIV-positive recipients was authorized in 2013, additional experience is needed before firm recommendations emerge [38, 39]. Nonetheless, this possibility increases the potential for donor availability.

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References