Renal Disease in HIV and Aging

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Educational Objectives
By the end of the session, learners will be able to:

1. Outline risk factors for chronic kidney disease (CKD) in HIV-infected patients.
2. Form the differential diagnosis of CKD in HIV-infected patients.
3. Describe the workup and management of HIV-associated nephropathy (HIVAN).

Suggested reading:

CASE ONE:

Mr. Creatinine is a 55-year-old African American man who just moved to your town and comes to establish care at your clinic. He was diagnosed with HIV many years ago but did not follow up with his HIV provider due to complicated social issues. Now that he moved to live with his daughter and things are more stable, he looks forward to taking care of his HIV. He has never been on ART. Otherwise, he has a history of hypertension, diabetes and hepatitis C. He is not taking any medications since he has not seen a doctor for a while.

He is afebrile, BP127/80, pulse 78, oxygen saturation 98% on room air. Physical exam is unremarkable. Labs show CD4 of 55 cells/mm³, viral load 400,000 copies/mL, creatinine 2.85 mg/dL, eGFR 28.3 mL/min with normal electrolytes, hemoglobin A1C 5.9%. Last year his Cr was 1.75 mg/dL, eGFR 49.6 mL/min.
Questions:

1. What is the definition of chronic kidney disease (CKD)?
   - CKD is defined as the presence of kidney injury (for example, proteinuria detected by routine dipstick urinalysis or microalbuminuria detected by urine albumin:creatinine ratio of ≥30 mg/day) or decreased kidney function (defined as estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73m²) for three or more months, irrespective of the cause.

2. How common is CKD in HIV-infected patients?
   - The prevalence of CKD in HIV-infected patients varies in different population. For example:
     - **Military veterans:** A prospective cohort study of 22,156 HIV-infected military veterans found that 51 patients (0.2%) had CKD at baseline (defined as an eGFR <60 mL/min), while 366 patients (1.7%) later developed end-stage renal disease (ESRD) (1).
     - **Women:** In the Women’s interagency HIV study (WIHS), the incidence of persistent proteinuria is nearly one-third of 2059 subjects (2).
     - **Men:** According to the Multicenter AIDS Cohort Study (MACS), 5-7% of 783 HIV-infected men had CKD (defined as an eGFR <60 mL/min) (3).

3. What are HIV-related risk factors for CKD?
   - Apart from traditional risk factors for CKD, such as diabetes and hypertension, which have become common among HIV-infected patients due to dramatic improvements in survival in the era of ART, HIV-infected patients are at increased risk for CKD due to the following factors:
     - **Hepatitis C virus (HCV) co-infection:** HCV seropositivity has been independently associated with CKD and its progression in multiple studies (4,5). While some studies have demonstrated an association with HCV viremia (4,5), others have found that HCV antibody status is associated with CKD risk regardless of HCV RNA levels (6).
     - **Low CD4 cell count**
     - **High HIV viral load**
     - **African American race**
     - **ART:** Tenofovir disoproxil fumarate (TDF) has been shown to correlate with decreased GFR, while protease inhibitors, such as indinavir or atazanavir, can cause crystalluria and kidney injury. Cobicistat and dolutegravir cause an increase in serum creatinine without a true decline in kidney function, by interfering with the tubular secretion of creatinine. At the same time, ART initiation has also been shown to slow the rate of decline in kidney function.
(GFR loss of 1.4 mL/min/year before vs loss of 2.2 mL/min/year after initiation of ART)(7).

- Other medications commonly used in HIV-infected patients: Antiviral agents, such as acyclovir, foscarnet, and cidofovir, can cause acute kidney injury (AKI). Trimethoprim-sulfamethoxazole can cause interstitial nephritis, while pentamidine can cause reversible acute kidney injury due to nephrotoxic acute tubular necrosis.

4. What is the differential diagnosis of CKD in HIV-infected patients? Which one do you think is the cause of Mr. Creatinine’s CKD?

- HIV-independent disorders: Similar to the general population, HIV-infected patients are vulnerable to traditional causes of CKD such as hypertension, diabetes, amyloidosis, or incomplete recovery from an episode of acute kidney injury.
- HIV-related disorders:
  - HIV-associated nephropathy (HIVAN): HIVAN is a collapsing form of focal segmental glomerulosclerosis (FSGS), which can be distinguished from idiopathic FSGS by tubular microcysts and interstitial inflammation. Patient usually presents with significant proteinuria and rapidly progressive kidney disease in the setting of normal blood pressure and normal to enlarged kidneys. Of note, HIVAN usually presents in patients with advanced HIV disease, with low CD4 count and detectable viral load (average CD4 count 127 cells/mm³ and mean viral load greater than 30,000 copies/mL according to Bigen et al) (8), although presentation in less advanced HIV disease or acute HIV infection is possible. HIVAN occurs almost exclusively in patients who are of African descent.
  - Immune complex mediated glomerulonephritis:
    - A variety of immune complex kidney diseases occur in HIV-infected patients, such as membranous nephropathy, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, “lupus-like” proliferative glomerulonephritis, or IgA nephropathy. A study by Szczech et al (9) found that ART does not significantly improve the course of non-HIVAN kidney diseases, which are typically associated with slower progression to end-stage renal disease (ESRD) regardless of therapy. Lupus-like proliferative glomerulonephritis may follow a more aggressive course, with a small retrospective study showing 10 of 14 patients progressing to ESRD within one year (10).
    - A unique form of HIV immune complex kidney disease (HIVICK) was first described in black South African patients with advanced HIV disease (11), although the pathogenic relationship between HIV infection and the
development of HIVICK has been debated. In a case series from Johns Hopkins (12), ART was not associated with improved renal outcomes in patients with HIVICK.

- **HCV glomerulonephritis**: HCV co-infection correlates with the development of acute and chronic kidney disease in HIV-infected patients. Although the histologic patterns have not been extensively studied, membranoproliferative glomerulonephritis (MPGN) is usually suspected, since this form is commonly associated with HCV infection in HIV-uninfected patients. The usual findings of cryoglobulinemia and low complement levels may be less common in HCV/HIV coinfected patients (13).

  - Mr. Creatinine’s rapidly progressive kidney disease in the setting of advanced HIV is concerning for HIVAN, especially since he is an African American patient with normal blood pressure and well-controlled diabetes as shown by hemoglobin A1C of well below 7%. HCV glomerulonephritis, although less likely, cannot be ruled out without a kidney biopsy.

5. **What is the pathogenesis of HIVAN?**

- **Infection of kidney epithelial cells by HIV**: The infection and expression of HIV genes within infected kidney cells is currently considered a requirement for the development of HIVAN. Infection of glomerular epithelial cells in vitro results in loss of maturity markers, de-differentiation and proliferation of these terminally differentiated cells.

- **Genetic susceptibility**: Studies have shown that single-nucleotide polymorphisms in the APOL 1 gene (on chromosome 22), present almost exclusively in African American individuals, are strongly linked to the risk of HIVAN (14).

6. **What workup would you perform for Mr. Creatinine? How would you establish diagnosis?**

- All HIV-infected patients should be screened for proteinuria (by urine dipstick or by measuring urinary albumin excretion) and reduced kidney function at diagnosis. GFR should be estimated using a creatinine-based GFR equation. The CKD-EPI GFR estimate is the most accurate for use in HIV-infected adults on stable ART (15), while the Crockcroft-Gault calculated creatinine clearance currently remains the standard of care for medication dosing.

- For newly discovered kidney disease, workup should include serum chemistry panel, complete urinalysis, albumin-to-creatinine ratio from spot sample or total albumin from 24-hour collection, renal sonogram, blood glucose control, and blood pressure check (30).

- Due to suspicion of HIVAN in Mr. Creatinine, the diagnosis must be established by a kidney biopsy. Histologically, HIVAN can be differentiated from idiopathic collapsing FSGS by tubular microcysts and interstitial inflammation. Kidney biopsy will also exclude other potentially...
treatable diagnoses and provide valuable information about disease prognosis.

CASE ONE CONTINUED:

After a 24-hour urine collection, Mr. Creatinine is found to have a protein excretion of 2.5g/day and albumin excretion of 300mg/day. Kidney biopsy shows a collapsing form of focal segmental glomerulosclerosis with tubular microcysts and interstitial inflammation. He is diagnosed with HIVAN.

7. What pharmacologic treatment would you recommend?

- **ART**: The initiation of ART is likely to improve Mr. Creatinine’s kidney function as well as his overall health. The use of ART for HIVAN is the standard of care, although this recommendation is based on the disease pathogenesis and the results of observational studies since randomized trials are not available. For example, a study by Atta et al followed patients with biopsy-proven HIVAN, 26 with ART and 10 without. Renal survival was significantly better in HIVAN patients with ART (adjusted hazard ratio 0.30, 95% CI 0.09-0.98) (16).

- **ACEI/ARB**: Since Mr. Creatinine has proteinuria and hypertension, he should also be initiated on either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) if ACEI is not tolerated. No randomized controlled trials exist, so guidelines are largely based on rigorous studies in other glomerular diseases. A small observational study by Wei et al (17) followed patients with biopsy-proven HIVAN for 1890 days/5.1 years, 28 received fosinopril 10mg/day vs 16 others who served as controls. Results showed that treated patients had a median renal survival of 479.5 days with only 1 patient developing ESRD, compared to untreated patients who all progressed to ESRD with medial renal survival of 146.5 days. In terms of overall survival, 87.5% of treated patients survived vs 21.4% of the control group.

- **Statin**: patients with pre-ESRD CKD should receive statin to prevent cardiovascular similar to persons in the highest cardiovascular risk group.

- **Aspirin**: 75-100mg daily to prevent cardiovascular disease if benefits outweigh bleeding risk.

- **Steroids**: Corticosteroids may reduce the progression of kidney disease in HIVAN, but evidence of this benefit was studied before combination ART became available. As a result, it is unclear if adding corticosteroids to ART produces any benefit. Moreover, corticosteroids are not recommended in other HIV-related kidney diseases as there is no published evidence in these conditions. Providers may consider prednisone 60mg/day or 1mg/kg/day. Improvement is usually seen after 1-4 weeks, and responders should continue the same dose for 2-11 weeks then taper off over 2-26 weeks. Patients who do
not respond after 1-4 weeks should be rapidly tapered (3) as there are risks of avascular necrosis.

- All medication doses, especially nucleoside and nucleotide reverse transcriptase inhibitors, should be adjusted based on creatinine clearance calculated using the Crockcroft-Gault equation.

8. How would you monitor treatment?
- Based on data from studies in other proteinuric CKD, goal proteinuria should be less than 1000mg/day, and goal blood pressure should be less than 130/80 mmHg as Mr. Creatinine had severely increased albuminuria (>30-300mg/day). For patients with normal to mildly increased albuminuria (<30mg/day), goal blood pressure is <140/90 mmHg.

9. When would you refer him to a nephrologist?
- Nephrologists can help with the discussion of future dialysis need and ensure timely discussion of renal replacement therapy (dialysis or kidney transplant). HIV-infected patients with CKD should be referred to a nephrologist when the following occurs:
  o Significant GFR decline (>25% from baseline and to a level <60 mL/minutes/1.73m²) that fails to resolve after potential nephrotoxic agents are removed.
  o Albuminuria >300mg/day
  o Hematuria combined with either albuminuria/proteinuria or increased blood pressure.
  o Advanced CKD (GFR<30 mL/minutes/1.73m²)

CASE ONE CONTINUED:

You decide to start Mr. Creatinine on dolutegravir, abacavir and lamivudine. You also start him on lisinopril 5mg daily, along with statin and aspirin. He will also continue to see the nephrologist who performed his kidney biopsy. You plan to have a discussion regarding goals of care to see whether dialysis would be consistent with his wishes. You wonder about the prognosis for this kidney disease, since this information will help guide your discussion with Mr. Creatinine.

10. What is the prognosis for Mr. Creatinine with HIVAN?
- The prognosis in patients with HIVAN and advanced kidney injury is poor, even in those on ART or with complete virologic suppression. A study by BigeN et all (8) followed 51 patients with biopsy-proven HIVAN for 2 years. Results showed that ESRD occurred in 30 patients (58.8%), while 6 others died (11.7%). Median renal survival was 40 months. Clinical features significantly associated with ESRD included severity of kidney dysfunction, higher percentage of sclerotic glomeruli on kidney biopsy, longer time from HIV infection to HIVAN diagnosis (>1 year), and prior exposure to ART.
Despite the reasonable likelihood of ESRD, Mr. Creatinine should be reassured that he would be a candidate for both hemodialysis and peritoneal dialysis if he does progress to ESRD despite the initiation of ART. In addition, he may be a candidate for kidney transplantation if his HIV infection and comorbid conditions are well-controlled.


