



HIV and Kidney

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ABSTRACT

HIV infection is associated with a broad spectrum of renal disorders. Some of them are directly related to the HIV infection like the HIV-associated nephropathy (HIVAN) while others are a consequence of the various metabolic disturbances leading to ARF. HIVAN is characterized by a nephrotic syndrome like presentation consisting of proteinuria (>3.5 g/d), azotemia, and hypoalbuminemia. On microscopy there is focal segmental glomerulosclerosis. The current treatment is to initiate aggressive antiretroviral therapy (i.e. HAART) for all patients with HIVAN with CD4 count less than 500/ μ L. ACE inhibitors should be offered to all patients. Renal replacement therapy in HIV positive patients is an upcoming trend. The most common renal replacement modality for HIV-infected patients is haemodialysis. An arteriovenous fistula should be placed when creatinine clearance is less than 25ml/min. Considering the fewer invasive procedures, lesser exposure to potential nosocomial infections and lesser stimulation of the immune system, CAPD seems to be a more promising modality for renal replacement in such patients. The standard Dialysis Outcome Quality Initiative (DOQI) recommendations should be followed for HIV-infected patients with ESRD. The goals for dialysis dose (Kt/V), renal osteodystrophy and anemia management, and vascular access monitoring should be followed as outlined in the DOQI recommendations. The role of renal transplant is still not well established.

INTRODUCTION

Human immunodeficiency virus (HIV) infection can cause a broad spectrum of clinical manifestations, ranging from an asymptomatic carrier state to severe immunodeficiency.

Renal disorders are encountered at all stages of HIV infection, and range from fluid and electrolyte imbalances commonly seen in hospitalized HIV-infected patients, to HIV-associated nephropathy (HIVAN), which can progress rapidly to end-stage renal disease (ESRD). This article reviews the various renal manifestations of HIV, their pathogenesis, clinical aspects and management.

Renal disorders in patients with HIV infection are either a direct consequence of viral-mediated glomerular/tubular/interstitial injury, or an indirect result of systemic derangement induced in the host by the virus and from various drugs used in the treatment (Table 1).

From a clinical point of view and for devising management strategies these patients can be considered under three broad categories,

1. Chronic irreversible renal failure from glomerulonephritis.
2. Renal failure from microangiopathies, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura.
3. Potentially reversible ARF

HIV-ASSOCIATED GLOMERULOPATHIES

Biopsy studies have revealed a wide spectrum of glomerular pathologies including various immune-complex disorders like MPGN, proliferative glomerulonephritis, and IgA nephropathy, but the most common, widely studied and well-investigated lesion is FSGS.¹ To characterize this syndrome that has a distinct clinicopathological presentation, the term HIVAN (HIV-associated nephropathy) was coined.

HIVAN

HIVAN is characterized by a nephrotic syndrome like presentation consisting of nephrotic-range proteinuria (>3.5 g/d), azotemia, and hypoalbuminemia, occasionally with edema and hyperlipidemia. Normal renal function upon presentation is uncommon. On microscopy, there is focal segmental glomerulosclerosis (FSGS) with collapse of the capillary walls and diffuse mesangial expansion, interstitial fibrosis with cystic tubular degeneration, and occasionally deposition of immunoglobulins (predominantly IgM), and complements. Glomerular sclerosis with tubuloreticular inclusions may be seen on electron microscopy. The remarkable racial predilection of HIVAN for blacks and its near absence in Whites strongly suggests that genetic cofactors are required for development of HIVAN in Blacks. The role of cytokines and related factors in

Table 1. Spectrum of Renal Involvement In HIV**Acute Renal Failure**

- Hemolytic uremic syndrome (53%)
- ATN either of ischemic, toxic, or drug origin or due to rhabdomyolysis (40%)
- Obstructive renal failure- extrinsic, drug-induced, paraprotein precipitation (26%)
- HIV-associated nephropathy (23%)
- Acute interstitial nephritis (3%)
- Glomerulonephritides (6%)

Chronic Renal Failure

- Glomerular
- HIV-associated nephropathy (FSGS)
- Membranous GN (chronic HBV)
- Minimal change disease
- MPGN
- Mesangioproliferative GN
- Other
- Renal amyloidosis
- Haemolytic uremic syndrome
- Renal parenchymal invasion by malignancies (lymphoma, Kaposi sarcoma)
- Interstitial nephritis

Fluid And Electrolyte Disorders

- **Hyponatremia**
 - Fluid loss
 - SIADH
 - Infections - toxoplasmosis, tuberculosis, pneumocystis
 - Adrenal insufficiency
- **Hyperkalemia**
 - Adrenal insufficiency
 - Hyporeninemic hypoaldosteronism
 - IDDM (Pentamidine-induced pancreatic cell dysfunction)
 - Severe ARF
- **Hypokalemia**
 - GI losses
 - Renal potassium wasting (Gentamicin, Ampho B)
- **Metabolic Alkalosis**
 - Upper GI loss
 - Hypokalemia
- **Metabolic Acidosis**
 - Renal failure
 - Septic shock
 - Diarrhea
 - Drug-induced interstitial nephritis

HIVAN is currently under active review. Overproduction of three tumour growth factor- β (TGF- β) isoforms 1, 2 and 3 has been seen in HIVAN.

Patients with HIVAN are not typically hypertensive, even in the face of renal insufficiency, and their kidneys are usually normal-to-large sized and highly echogenic on ultrasonography images. Routine urinalysis may occasionally reveal findings of nonnephrotic proteinuria in patients being evaluated for other medical conditions. The urinalysis reveals microhematuria, leukocytes, hyaline casts, and oval fat bodies, but no cellular casts. Serum complement levels are normal.

Table 2: Nucleoside reverse transcriptase inhibitors

Drug	CCR >50 ml/min	CCR 10-50 ml/min	CCR <10ml/min
Zidovudine	200 mg tid	100 mg tid	100 mg tid
Zalcitabine	0.75 mg bid	0.75 mg qd	Avoid
Stavudine	40 mg bid	15-20 mg bid	No data
Lamivudine	150 mg bid	50-100 mg bid	50 mg qd
Didanosine	200 mg bid	150 mg qd	100 mg qd
Abacavir	300 mg bid	No dose reduction	No dose reduction
Tenofovir	300 mg qd	300 mg twice wkly	300 mg weekly

(NRRRTIs and NNRTIs must be administered after the dialysis session; however PI's can be administered regardless of dialysis schedule)

Table 3: Non-nucleoside reverse transcriptase inhibitors

Drug	Dose
Nevirapine	200 mg qd
Delavirdine	400 mg tid
Efavirenz	600 mg qd

No dose reduction reqd in renal insufficiency

Prognosis

The CD4 count in these patients is usually depressed below 200 cells/ μ L, but HIVAN has been reported in patients with higher CD4 counts. The prognosis for renal survival is worse in patients with clinical AIDS, especially if their CD4 count is less than 50 cells/ μ L. The rate of progression from the initial presentation to ESRD was 2.5 months in the pre-HAART (highly active antiretroviral therapy) era. With the introduction of HAART in 1996-1997, the traditional natural history of rapid progression of HIVAN has been slowed significantly. HAART therapy has been shown to retard the progression of renal disease in persons with HIVAN.²

What are the indications of biopsy?

The decision to obtain a biopsy sample is somewhat controversial in the general medical community. Even if a patient presents with the classic clinical features of HIVAN, clinical consideration is predictive of the biopsy diagnosis in only 55-60% of patients. Therefore, to distinguish HIVAN from other forms of renal disease (e.g. immune-complex glomerulonephritis, immunoglobulin A nephropathy); patients who are seropositive for HIV require a renal biopsy. The typical practice is to obtain a renal biopsy specimen if the patient's daily protein excretion is greater than 1 gram.

Management**HAART—the gold standard treatment**

The current standard is to initiate aggressive antiretroviral therapy (i.e. HAART) for all patients with advanced or symptomatic HIV disease, defined as a CD4 count of fewer than 500 cells/ μ L or a high viral load. Renal dosing of antiretroviral drugs and adjustments for creatinine clearance must be made as discussed in Tables 2 - 5. Most reported experience is with zidovudine. It

Table 4: Protease inhibitors

Drug	Dose
Saquinavir	600 mg tid
Indinavir	800 mg tid
Ritonavir	600 mg tid
Nelfinavir	1250 mg bid
Amprenavir	1200 mg bid
Fosamprenavir	1400 mg qd
Atazanavir	400 mg qd

No dose reduction reqd in renal insufficiency

does appear that AZT may slow progression of HIVAN but may not be able to recover any lost renal function if initiated after the appearance of significant kidney disease. To date there are no definite randomized prospective studies with other antiviral agents, except for a few case reports.

ACE inhibitors?

Like in many other renal diseases, the role of ACE inhibitors cannot be overemphasized as shown by Kimmel et al in their study on captopril and by Burns et al by using fosinopril in biopsy proven HIVAN patients where a significant reduction in proteinuria was observed in both nephrotic and non-nephrotic patients.

Is there a role of steroids or immunosuppressants?

A number of reports suggest that corticosteroids offer some short-term benefit. Some reports on pediatric populations suggest that cyclosporine can be effective in reducing the proteinuria observed in persons with HIVAN. However a lot more data needs to be generated to justify the role of these drugs in such immunocompromised patients.

RENAL REPLACEMENT THERAPY IN HIV POSITIVE PATIENTS-AN UPCOMING TREND

Haemodialysis - How and when?

The most common renal replacement modality for HIV-infected patients is haemodialysis. Potential disadvantages include risk of infection from temporary catheters and grafts, and risk to dialysis providers of blood and needle stick exposure.³ Thrombus-free survival for native arteriovenous fistulas in HIV-positive patients is comparable to that reported for HIV-negative patients. The fulminant progression of renal failure in patients with HIVAN described in earlier reports has changed with the use of HAART, steroids and ACE inhibitors. This poses a challenge to a nephrologist in selecting the appropriate time to place a permanent vascular access. An arteriovenous fistula should be placed when creatinine clearance is less than 25ml/min. Alternatively an arteriovenous graft can be placed three to six weeks before the anticipated need for dialysis.

Infection Control in Hemodialysis

Careful adherence to universal body substance precautions must be followed. Routine infection-control precautions and cleaning with sodium hypochlorite solution of dialysis equipment and of surfaces that are frequently touched are sufficient in HIV-infected patients on haemodialysis. Precautions such as isolation of HIV-

Table 5 : Fusion inhibitors

Drug	Dose
Enfuvirtide	90 mg s/c bid

No dose reduction reqd in renal insufficiency

infected patients from other dialysis patients are unnecessary and could violate medical confidentiality.

Peritoneal Dialysis

Considering the fewer invasive procedures, lesser exposure to potential nosocomial infections and lesser stimulation of the immune system, CAPD is a rapidly upcoming modality for renal replacement in such patients, however peritoneal protein losses in malnourished HIV patients and severe peritonitis are potential concerns. HIV has been identified in peritoneal dialysate fluid, which should be handled as a contaminated body fluid.⁴ Peritoneal dialysis patients should be instructed to pour dialysate into the home toilet and to dispose of dialysate bags and lines by tying them in plastic bags and disposing of the plastic bags with conventional home garbage. Survival is better in patients on CAPD than those on haemodialysis.

GOALS FOR MEDICAL MANAGEMENT

The standard Dialysis Outcome Quality Initiative (DOQI) recommendations should be followed for HIV-infected patients with ESRD.⁴ The goals for dialysis dose (Kt/V), renal osteodystrophy and anemia management, and vascular access monitoring should be followed as outlined in the DOQI recommendations.

Managing anemia

The problem of anemia in ESRD is compounded in HIV-infected dialysis patients because it is the most common hematological abnormality in HIV patients despite the use of antiretroviral therapy. Its origin is multifactorial and is a consequence of HIV infection of stromal cells, opportunistic infections, cancer and medications (AZT, sulfa drugs).

HIV-infected patients with ESRD respond well to erythropoietin therapy. Another rare cause of anemia in patients with AIDS is parvovirus B19 infection. It should be suspected if anemia does not respond to erythropoietin therapy. Studies have shown that oxidative stress and iron may be important in activation of HIV. High serum ferritin levels and iron administration have been associated with an increase in mortality in HIV infection.

Coinfection with HCV is very common in HIV-infected ESRD patients. Optimal therapy for HCV infection in the ESRD patient is not known, especially as ribavirin is not recommended in patients with renal failure. At a minimum, HIV/HCV-coinfected patients should be discouraged from alcohol use and should be vaccinated for hepatitis A and B virus. In the absence of ESRD, HIV-infected patients have an 88% antibody response rate to hepatitis A virus vaccine, but only a 42% response to hepatitis B virus vaccine.^{5,6}

THE PROSPECTS OF A RENAL TRANSPLANT

The general consensus is that immunosuppression after kidney transplantation would pose a substantive risk of opportunistic infections in this population. As such, kidney transplantation

in these patients is still considered experimental, with only few transplant centers considering cadaver kidney transplantation in compliant, stable patients with no prior opportunistic infections who have an undetectable viral load and a CD4 count of fewer than 300 cells/ μ L. Anecdotal reports of small samples of this selected group of patients with HIVAN suggest no extra risk of opportunistic infections; however, until larger studies are performed, transplantation in persons with HIVAN remains largely contraindicated.

ACUTE RENAL FAILURE IN AIDS-CRITICAL ISSUES

We have already listed the various causes of ARF in an HIV patient. Here we address certain critical issues pertaining to ARF due to HIV or its treatment.

Mild ARF, defined as a peak serum creatinine \geq 2.0 mg/dL, has been reported to occur in up to 20% of hospitalized HIV-infected patients.⁶ This percentage compares to an incidence rate of 4-5% in hospitalized non-HIV-infected patients.⁷ The two most common causes of ARF in this population are dehydration and acute tubular necrosis.

DRUG-INDUCED ARF

Aminoglycosides, pentamidine, acyclovir, foscarnet, amphotericin, tenofovir, adefovir, and cidofovir are a common cause of ATN.⁸ In addition, foscarnet may produce a dose-related hypocalcemia and a transient hyperphosphatemia during the second week of induction therapy.⁸ Drugs like adefovir and cidofovir and tenofovir are associated with ARF, proximal tubular dysfunction, and nephrogenic diabetes insipidus. Patients with tenofovir toxicity may present with glycosuria, hypophosphatemia, acidosis, proteinuria, and ARF.⁹⁻¹²

Nonsteroidal anti-inflammatory drugs (NSAIDs), trimethoprim-sulfamethoxazole, and rifampin are often used in HIV-infected patients and are known to cause acute interstitial nephritis.^{8,13} In addition, there have been case reports of interstitial nephritis in patients taking indinavir or ritonavir.^{14,15}

Sulfadiazine crystal formation causing tubular obstruction, and sulfadiazine stones causing ureteral obstruction, has been reported in volume-depleted, HIV-infected patients.¹⁶⁻¹⁸ Acyclovir and indinavir can also cause crystalluria and ARF, and dose adjustments should be made in patients with preexisting chronic kidney disease to avoid neurotoxicity.¹⁹

To conclude, HIV-infected patients with ESRD need to be managed according to the K/DOQI guidelines, besides the special issues related to the drugs, control of infection and electrolyte disturbances.

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