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Kidney Involvement in HIV Infection

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1. Introduction

Human immunodeficiency virus (HIV) infection can involve various organs of the body. Kidney involvement is frequently seen during course of human immunodeficiency virus infection and it has become fourth leading condition contributing to death in acquired immunodeficiency virus (AIDS) patients after sepsis, pneumonia, and liver disease. Rao first described the presence of focal segmental glomerulosclerosis and renal failure with HIV infection in 1984. This entity is now known as HIV-associated nephropathy (HIVAN). Renal involvement in HIV infection can manifest in a variety of clinical presentations. Renal manifestations can range from acute kidney injury to chronic kidney disease to end stage kidney disease. Various fluid and electrolyte disorders and acid base disturbances can also occur. Immune complex mediated glomerular involvement is also seen in these patients (see Table). HIVAN remains the most common form of kidney disease among HIV infected individuals which is usually associated with nephrotic range proteinuria. Treatment for HIVAN includes use of highly active anti-retroviral therapy (HAART), Angiotensin converting enzyme inhibitors and systemic steroid administration. End stage renal disease (ESRD) is common in HIV infected individuals and accounts for 1% of patients receiving dialysis in USA. Survival of ESRD patients with HIV disease has improved dramatically over last one decade due to use of HAART. Both hemodialysis and peritoneal dialysis can be dialysis options for ESRD patients due to HIV disease. One year survival rate of HIV infected patients is equivalent to that of general population. Renal transplantation recently has become a viable option for renal replacement therapy in patients with well controlled HIV disease.

Renal involvement can occur at all stages of HIV infection and can be initial clue to the presence of HIV infection in an undiagnosed patient. Renal involvement in HIV disease can also occur due to other causes seen in non -HIV infected population like exposure to nephrotoxic medications, hemodynamic changes during an acute illness, and obstruction. Treatment of HIV infection with highly active anti-retroviral agents itself can induce various renal abnormalities. Therefore, evaluation of renal abnormalities should be part of the comprehensive work up of a patient with newly diagnosed HIV infection and it should be periodically ruled out on subsequent follow up. Usually urinalysis, random protein to creatinine ratio, and comprehensive metabolic panel should be obtained as part of the initial work up. Patients on HAART should be monitored for potential renal toxicity of these agents. This chapter reviews details of various renal manifestations of HIV disease with special focus on presence of chronic kidney disease, pathogenesis and treatment of HIVAN, and

renal toxicity associated with use of HAART. Various options of renal replacement therapy including renal transplantation will also be discussed.

Acute kidney injury	Pre-renal azotemia Renal due to Acute tubular toxicity Acute interstitial nephritis Glomerulonephritis Vasculitis HUS/TTP Obstruction due to crystalluria, stones, papillary necrosis, BPH, and urethral strictures
Chronic kidney disease	HIVAN Can present as proteinuria only with or without renal failure. Degree of kidney disease can vary from stage 1-5. MDRD equation can be used to estimate eGFR. CKD related to other co morbid conditions like Hypertension, Diabetes Mellitus, or due to use of recreational drug use like cocaine and heroin.
End Stage Kidney Disease	Options for renal replacement therapy
Disorders of Potassium	Hyperkalemia or Hypokalemia
Disorders of Sodium and Osmolality	Hyponatremia and Hypernatremia Syndrome of inappropriate ADH secretion
Disorders of Calcium	Hypocalcemia and Hypercalcemia
Disorders of Magnesium	Hypomagnesemia
Disorders of Phosphate	Hypophosphatemia or Hyperphosphatemia
Disorders of acid-base disturbances	High anion gap metabolic acidosis Non anion gap metabolic acidosis
Immune complex mediated Glomerulonephritis	Membranoproliferative GN Membranous Nephropathy Minimal Change Disease SLE like GN Post infectious GN
Renal toxicity of HAART	Fanconi's syndrome Renal failure Diabetes insipidus Lactic acidosis

Table 1. Renal Manifestations of HIV

2. Acute Kidney Injury

Acute kidney injury (AKI) is abrupt impairment of renal function and is commonly seen in patients infected with HIV both in inpatient and outpatient settings. In era prior to HAART,

AKI was commonly due to opportunistic infections and heralded a poor outcome in hospitalized patients. The incidence of AKI defined as peak serum creatinine level of $\geq 2\text{mg/dl}$ was reported to be 20%.

An increased risk of inpatient AKI among HIV infected individuals has been reported in the modern era of highly active antiretroviral therapy (HAART). One study reported incidence of AKI in hospitalized patients with HIV to be 6% as compared with 2.7% in HIV uninfected patients. In a large population of hospitalized HIV-infected patients, incidence of cardiovascular disease and heart failure increased linearly with severity of AKI. Among HIV patients requiring dialysis for AKI, the risk for cardiovascular disease and heart failure were 1.96 and 4.20 fold greater than individuals who did not develop AKI during their hospitalization. The development of AKI in these patients is associated with high mortality rate. AKI is also seen in ambulatory HIV infected patients and its incidence has been reported to be 5.9/100 person years.

2.1 Causes of AKI

No study has assessed etiology of AKI in hospitalized HIV infected patients. The usual causes of AKI are commonly encountered in HIV infected individuals as in other hospitalized non- HIV infected patients (Table 1).

The causes of AKI can be divided into prerenal, renal, and post renal causes. Pre-renal azotemia and acute tubular necrosis (ATN) remain most common cause of AKI in HIV infected individuals (38% and 35% respectively). Patients with AIDS are at high risk of prerenal azotemia which results from vomiting, fever, and poor po intake due to underlying illness. ATN results from sepsis causing ischemic ATN in up to 50% of cases. Use of nephrotoxic agents like aminoglycosides, amphotericin, pentamidine, and intravenous administration of contrast agent can cause ATN in 25% of cases.

Acute interstitial nephritis can result from hypersensitivity reaction to use of certain medications or can be caused by certain infections in AIDS patients. Infections associated with interstitial disease in immunocompromised patients include cytomegalovirus, candida, tuberculosis, and histoplasmosis. Common medications associated with acute interstitial nephritis are penicillins, cephalosporins, macrolides, ciprofloxacin, cotrimoxazole, rifampin, and nonsteroidal anti-inflammatory drugs. Acute interstitial nephritis secondary to use of HAART is very rare. One study found 2/60 biopsy specimens had drug related interstitial nephritis. Cessation of offending agent usually leads to renal recovery. Sometimes a short course of corticosteroids may need to be given in patients with severe acute interstitial nephritis where withdrawal of offending agent fails to improve kidney function.

Vascular causes of AKI include hemolytic uremic syndrome/thrombotic thrombocytopenic purpura can be encountered in HIV seropositive patients. The clinical manifestations are similar to that seen in HIV seronegative patients. Laboratory examination reveals microangiopathic hemolytic anemia, thrombocytopenia, and impaired kidney function. Kidney biopsy reveals platelet and fibrin thrombi in renal and glomerular capillaries. Treatment with plasmapheresis and fresh frozen plasma replacement may be effective.

Obstruction should be considered in differential diagnosis of AKI among HIV infected patients. Certain drugs are associated with obstructive nephropathy. These include sulfadiazine, acyclovir, atazanavir, and indinavir. Volume depletion with sluggish urine flow is the most important risk factor allowing crystallization. Reduced glomerular filtration rate is also a risk factor for crystallization. Normal dosing of drugs in patients with reduced

GFR is associated with high urinary concentration of insoluble drug and pH of urine. Sulfadiazine can cause intratubular obstruction by causing crystal formation. It can also cause stone formation which may give rise to ureteral obstruction. Acyclovir can cause crystalluria and AKI especially when given intravenously rapidly without concomitant hydration. Protease inhibitor indinavir has been reported to cause crystalluria in 20% of the patients receiving indinavir at normal dose. The use of this medication has declined significantly and has been replaced by less nephrotoxic protease inhibitors. Atazanavir can cause nephrolithiasis in up to 0.97% of the individuals taking the drug. Atazanavir stones appear to form in alkaline urine. No risk factors have been associated with stone formation from atazanavir use. One should keep in mind possibility of atazanavir stones in HIV patient who develops renal colic. Ciprofloxacin associated crystal formation commonly occurs in HIV infected patients and should be considered as cause of AKI in patients taking this antibiotic. Ciprofloxacin induced nephropathy occurs usually in patients with reduced renal function with hypovolemia and having urine pH above 6.0. One should adjust dose of ciprofloxacin in patients with reduced renal function and urine alkalinization should be avoided. Treatment of obstructive nephropathy secondary to crystalluria requires discontinuation of offending agent, intravenous hydration, and close monitoring of renal function.

Treatment of AKI in HIV positive individuals is similar to HIV seronegative individuals with renal failure. Indications of renal replacement therapy remain the same for both groups of patients.

3. Chronic Kidney Disease

Chronic kidney disease (CKD) is an important complication of HIV infection. The prevalence of impaired renal function defined as estimated glomerular filtration rate (eGFR) of $<60\text{ml/min/1.73m}^2$ varies from 2.4 to 10% depending upon the social and demographic characteristics of the studied population. 10-30% of HIV- infected individuals have microalbuminuria or proteinuria. A variety of renal abnormalities on renal biopsy have been described in these patients. These abnormalities seen on renal biopsy can be HIV associated Nephropathy (HIVAN), HIV associated immune complex kidney disease (HIVICK), non collapsing focal and segmental glomerulosclerosis, thrombotic microangiopathy, nephropathy secondary to use of HAART, and diseases related to common comorbidities such as amyloidosis, diabetic nephropathy, hypertensive renal disease etc can be seen on renal biopsy.

HIV infected individuals with glomerular disease present clinically with significant proteinuria, hematuria, or reduced kidney function. Work up should focus on work up for possible secondary causes of glomerular diseases along with good history and physical examination. The work up should focus on evidence of hepatitis B or C infection, syphilis, evidence of malignancy or collagen vascular disease. A kidney biopsy is usually indicated in for tissue diagnosis and future management of the disease.

3.1 Epidemiology

HIVAN is a histopathological diagnosis based on kidney biopsy only. The true prevalence of HIVAN is unknown as many patients with HIV infection do not undergo renal biopsy routinely in clinical practice. In kidney biopsy series among HIV infected individuals;

HIVAN is seen in 40-60% of renal biopsy specimens. Autopsy studies on organs from HIV infected persons have reported prevalence of HIVAN to be 6.9%. HIVAN is the most important cause of milder forms of kidney disease in South Africa where it is commonly manifested clinically by microalbuminuria. Infectious Diseases Society of America (IDSA) guideline recommends urinalysis and estimation of kidney function for all HIV-infected persons at the time of HIV diagnosis.

HIVAN commonly occurs in African American individuals. With 90% of cases of HIVAN occurring in African Americans. The remaining 10% of cases are observed in mixed heritage or Hispanic patients. This entity is rarely seen in HIV seropositive white patients. HIVAN progresses very fast in African Americans and risk of End Stage Renal Disease (ESRD) is similar to diabetes in African American patients with HIVAN. In Caucasians, the risk of ESRD associated with HIV is not increased.

3.2 Pathogenesis

HIV is pathogenic through direct infection of epithelial cells of the nephron including the glomerulus, the tubules and the collecting duct. In situ hybridization studies have found the HIV genome in the tubular and glomerular epithelial cells in patients with HIVAN. The pattern of epithelial cell infection determines histological abnormalities seen with HIVAN. Transgenic mice expressing a replication-defective HIV-1 construct develop proteinuria, reduced renal function, and histologically characteristic HIVAN. Reciprocal transplantation studies using this mouse model demonstrate that HIVAN develops only in kidneys expressing the transgene. HIV RNA and DNA have been detected in podocytes and renal tubular epithelial cells of patients with HIVAN. The mechanism of entry of HIV into renal epithelial cells is unknown. Studies have shown that renal epithelial cell is able to support a productive viral life cycle, and renal epithelium is an important reservoir for HIV infection. Despite undetectable viral load in the serum, HIV can still be present in renal epithelial cells where it may undergo rapid replication. This may produce HIV stains in the kidney microenvironment that differ from HIV circulating in the blood.

3.3 Clinical features

Patients with HIVAN typically present with proteinuria. This proteinuria is variable in magnitude, usually is heavy in nephrotic range ($>3\text{gm/day}$), but can be mild and sometimes present only as microalbuminuria. HIVAN is associated with rapidly deteriorating renal function with high rate of progression to ESRD. These patients usually have poorly controlled HIV infection characterized by low CD4 count and high HIV RNA load. Besides heavy proteinuria, many patients with HIVAN do not exhibit significant edema or Hypertension. A recent study noted that 43% of patients with biopsy proven HIVAN did not have Hypertension. The serum albumin levels remain above 3 gm/dl besides heavy proteinuria. On the contrary, patients with early HIVAN lesions may have normal renal function, microalbuminuria or mild proteinuria. Renal function may remain stable for many years in these patients. Urinalysis usually shows bland sediment with varying number of proteinaceous casts, oval fat bodies, and renal tubular epithelial cells. Abdominal ultrasound reveals relatively large, echogenic kidneys. Ultrasound findings are limited predictive value. Serologic markers are usually negative in these patients on work up. A diagnostic renal biopsy is usually indicated for diagnosis.

3.4 Histopathology

HIVAN is associated with characteristic glomerular, tubulointerstitial, and electron micrographic lesions. The characteristic findings on histopathology include presence of focal segmental glomerulosclerosis, cystic tubular dilatation, interstitial edema, cellular infiltrates, and dilated tubules filled with pale staining amorphous casts. Collapsing glomerulosclerosis is a common variant in patients with HIVAN due to hypercellularity of the cells lining the Bowman's capsule. Proliferation of tubular epithelial cells contributes to micro cyst formation and may account for the bigger size of the kidneys. Increased proliferation of podocytes is also present and plays an important role in lesions of collapsing FSGS found in HIVAN. Immunofluorescence staining is non specific. Electron microscopy reveals tubuloreticular inclusions in the endothelial cells of glomerular capillaries. Collapsing FSGS is not pathognomonic of HIVAN and can be seen in non- HIV related collapsing focal segmental glomerulosclerosis, heroin nephropathy, and as complication of bisphosphonate therapy.

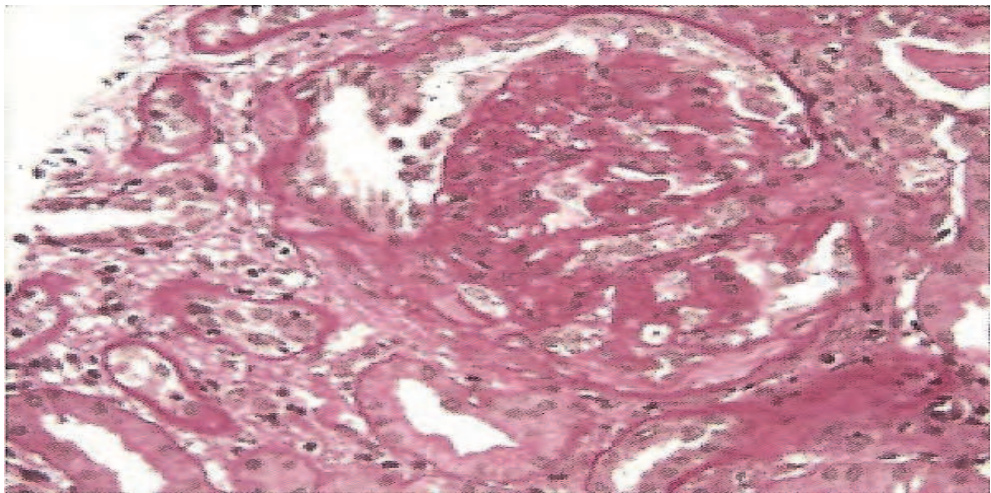


Fig. 1. Collapsing FSGS

It shows collapsing focal segmental glomerulosclerosis in a patient with HIV showing global collapse of the glomerular capillary loops and proliferation of visceral epithelial cells.

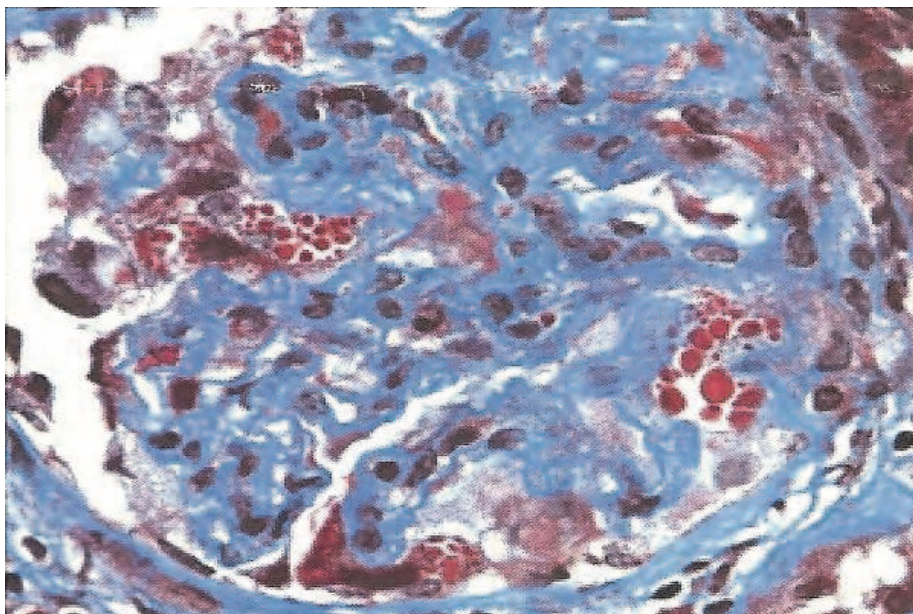


Fig. 2. Collapsing FSGS

It shows podocyte hypertrophy.

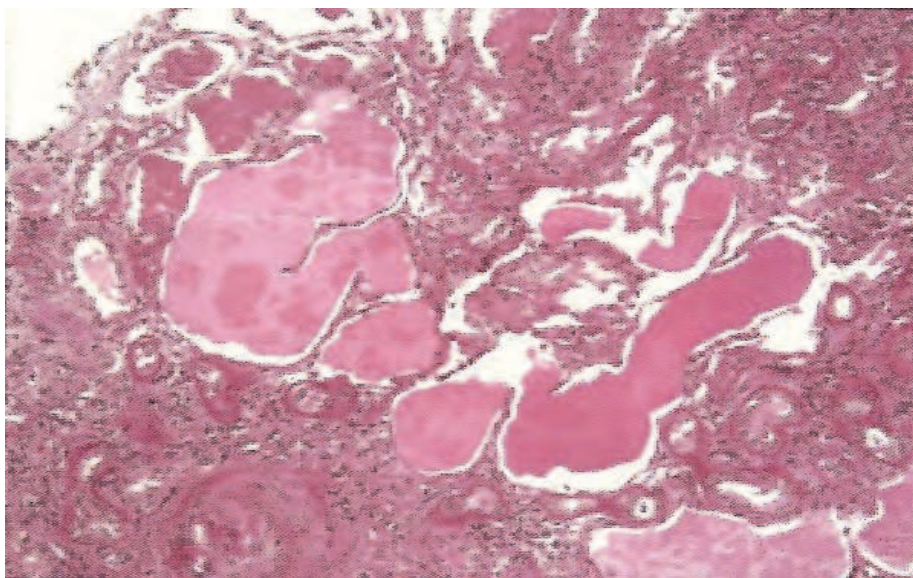


Fig. 3. Tubulointerstitial involvement in HIV associated Nephropathy

It shows microcystic dilatation of tubules, proteinaceous material casts within tubular lumina, and interstitial inflammation.

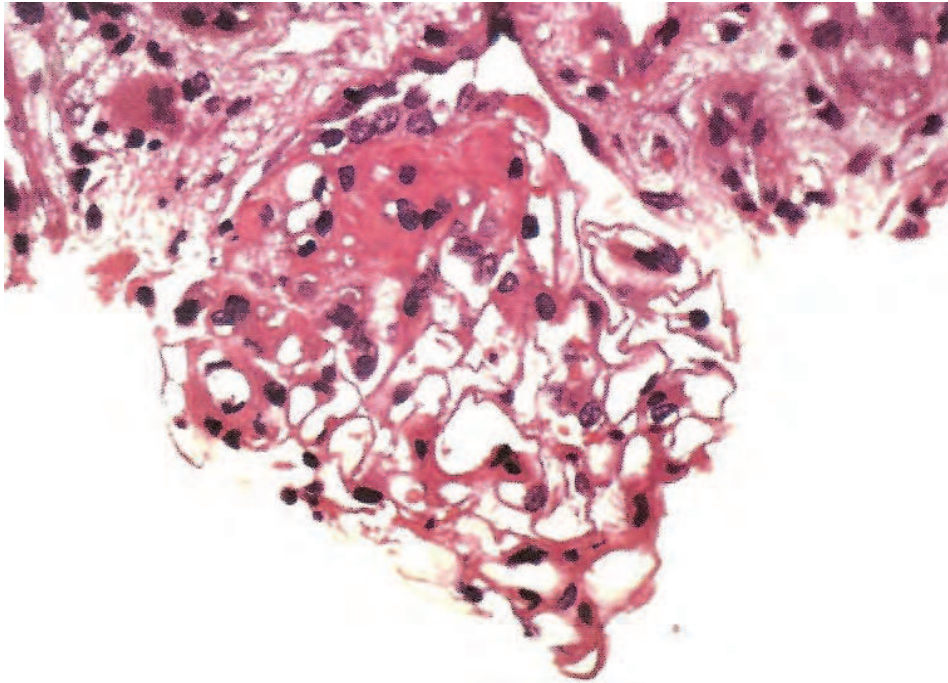


Fig. 4. Non-Collapsing FSGS

It shows focal segmental glomerulosclerosis at 12 o'clock position in an HIV infected patient.

3.5 Treatment

There have been no randomized controlled trials with any type of therapy in treatment of HIVAN. US department of Health and Human Services recommends use of HAART for diagnosis of HIVAN regardless of CD4 count. Other medications used in the treatment of HIVAN in patients with suboptimal response to HAART include angiotensin converting enzyme inhibitors and corticosteroids. A summary of the trials conducted in HIVAN is given in Table 2.

3.5.1 Highly Active Antiretroviral Agents (HAART)

The use of antiretroviral agents has slowed down progression of HIVAN to ESRD and reports of patients dependent on dialysis becoming dialysis free have been published after use of HAART. In one study, a patient with HIVAN and dialysis dependent renal failure became dialysis free after 15 weeks of HAART. Repeat renal biopsy revealed significant histologic recovery from fibrosis and infrequent collapsing glomerulosclerosis.

The rationale for using HAART is based on the direct role of the HIV virus itself in the pathogenesis of HIVAN. The effect of HAART on kidney disease progression has been characterized by observational studies. The evidence for effectiveness of HAART is from the retrospective cohort of biopsy proven HIVAN. In this study, renal survival benefit was

noted in 26 patients treated with antiretroviral agents compared with ten patients who did not receive anti-retroviral therapy. Median renal survival was significantly improved for the treated group compared with the untreated group (18.4 months vs. 3.9 months respectively). Complete viral suppression was associated with better renal outcome than partial viral suppression. Continuous therapy with HAART is recommended in preventing and slowing the progression of kidney disease due to HIVAN as evidenced by Strategies for Management of Antiretroviral Therapy (SMART) study.

3.5.2 Corticosteroids

The rationale for using corticosteroids is based on presence of significant tubulointerstitial inflammation seen in histology of renal biopsy of patients with HIVAN. In vitro studies have shown up regulation of proinflammatory genes in renal tubular cells of individuals with HIVAN as a possible explanation for development of tubulointerstitial disease. The use of corticosteroids decreases this inflammation markedly in these patients. There is improvement in kidney function and reduction in mean urinary protein excretion in patients with HIVAN with use of corticosteroids. There are no long term studies supporting efficiency and safety of corticosteroid use in patients with HIVAN. Most of the studies supporting use of corticosteroids in patients with HIVAN have been short term, non randomized and retrospective in design. In a single center cohort study, 20 patients with HIVAN were prospectively enrolled to receive treatment with corticosteroids. 17 out of 20 patients manifested improvement in kidney function and had significant reduction in proteinuria. Another study of steroid therapy employed control group and found similar results with no increased risk of infection in the steroid group. Based on this evidence, steroids are considered as second line of therapy for patients with HIVAN especially in patients with a rapidly deteriorating renal function despite use of HAART. Usually a dose of 1mg/kg (up to maximum dose of 60mg/day) with a taper over 2 months is recommended. Simultaneous use of HAART is essential to suppress viral replication.

3.5.3 Inhibition of the renin-Angiotensin – Aldosterone system

Angiotensin- Aldosterone system activation has been shown to play a role in development and progression of HIVAN in animal models. The rationale for the use of ACE-inhibitors in HIVAN is based on their favorable efficacy in most other renal glomerular diseases, resulting from their renal hemodynamic effect and their modulation of profibrotic cytokines such as transforming growth factor-beta. Two prospective studies support use of ACEI for the treatment of HIVAN. In a case control study of 18 patients with HIVAN prior to discovery of HAART, 9 were treated with captopril , and matched with 9 controls. The captopril treated group had improved renal survival compared with controls. Another prospective single center study of 34 patients with HIVAN was treated with fosinopril 10mg/day and was compared with group of patients who refused treatment over a period of 5 years. The patients treated with fosinopril had better median renal survival as compared to untreated patients. All untreated patients progressed to ESRD over a median period of 5 months. This is limited data showing efficacy of ACEI in these non randomized trials. There are no trials on use of angiotensin receptor blockers. Usually ACEI may be used in halting the progression of HIVAN especially as first choice therapy in a patient with coexisting hypertension.

Medication used	Study Name	Number of patients	Study Design	Diagnosis of HIVAN (Biopsy proven or clinical diagnosis)	Outcome (change in renal function, effect on proteinuria)
HAART	Cosgrove	23 13 patients received HAART and remaining 10 patients received nothing	retrospective	Clinical and biopsy proven HIVAN	S/Cr stabilized in treated group as compared to untreated group
HAART	Szczech	42 patients with HIVAN. 27 patients with HIVAN took HAART	retrospective	Biopsy proven HIVAN.	Slower progression to ESRD in HAART treated group
Corticosteroids	Eustace	21 patients of which 13 patients received steroids	Retrospective Systemic steroids in dose of 60mg for one month followed by several month taper	Biopsy proven HIVAN	Reduction in proteinuria and stabilization of renal function at 3, 6, and 12 months
	Smith 1994	4 patients	Case series of Systemic corticosteroids given at dose of 60mg/ day for 2-6 weeks	Biopsy proven HIVAN	Improvement of renal function but no effect on proteinuria
	Smith 1996	20 patients Given systemic steroids at 60mg/ day for 2-11 weeks followed by taper over 2-26 weeks	Prospective, no control group	Clinical and biopsy diagnosis of HIVAN	Improvement in serum creatinine and improvement in proteinuria. Serum albumin increased. 25% rate of relapse seen on withdrawal of steroids
Angiotensin converting enzyme inhibitors	Wei	44 patients Fosinopril 10mg/day was given for HIVAN	Single center prospective with control group which received nothing	Clinical and biopsy proven HIVAN	Improvement of renal function with reduction in risk of kidney failure
	Kimmel	18 9 patients treated with captopril three times daily and 9 patients were untreated	Single center prospective	Biopsy proven HIVAN	Stabilization of renal function

Table 2. Trials of Various Agents Used in Treatment of HIVAN

3.6 Other glomerular diseases in HIV infection

HIV-related immune complex mediated kidney disease (HIVICK) can occur in HIV infected individuals of non-African descent due to deposition of or in situ development of HIV antigen specific immune complexes. HIV infected individuals are likely to develop non-HIV related kidney diseases related to various comorbidities as their age matched counterparts in the general population. Due to use of HAART, the aging HIV infected individuals with Diabetes Mellitus (DM) and Hypertension (HTN) can develop renal disease due to Diabetic Nephropathy or Hypertensive Nephrosclerosis. The incidence of diabetes mellitus, hypertension, and dyslipidemia is increased fourfold in HIV infected individuals on HAART as compared with HIV uninfected persons. The treatment of CKD due to either DM or HTN is similar to treatment of CKD due to these co morbid conditions in non- HIV infected individuals.

Hepatitis C related kidney disease can also occur in patients with HIV who are co infected with Hepatitis C virus. This is commonly seen in intravenous drug users. Approximately a third of HIV infected individuals are co infected with Hepatitis C. Membranoproliferative glomerulonephritis(usually with cryoglobulins) is seen on histopathology of kidney biopsy of the coinfectd patients. These patients have circulating immune complexes of antigen-antibody with low complement levels and circulating cryoglobulins. They present clinically with proteinuria, hematuria, renal insufficiency, and maculopapular non blanching rash usually over the lower extremities. The treatment includes treatment of underlying Hepatitis C infection with interferon and Ribavarin.

Other glomerular diseases can be seen in HIV infected individuals which includes classic FSGS, IgA Nephropathy, Lupus like glomerulopathy, AA amyloidosis, Membranous Nephropathy, and immune complex mediated Glomerulonephritis.

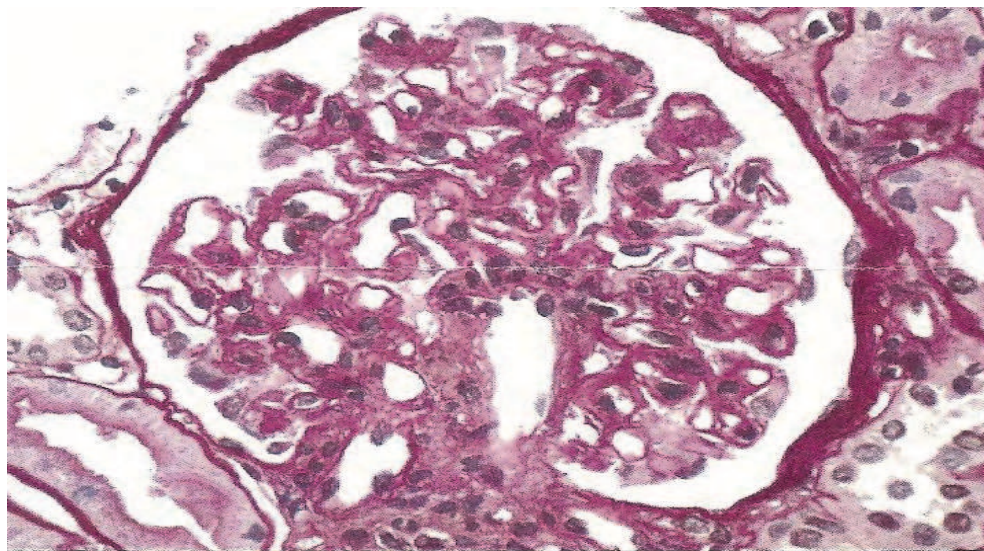


Fig. 5. Membranoproliferative Glomerulonephritis in HIV patient

It shows segmental glomerular basement duplication of Membranoproliferative glomerulonephritis seen in a patient coinfectd with HIV and Hepatitis C.

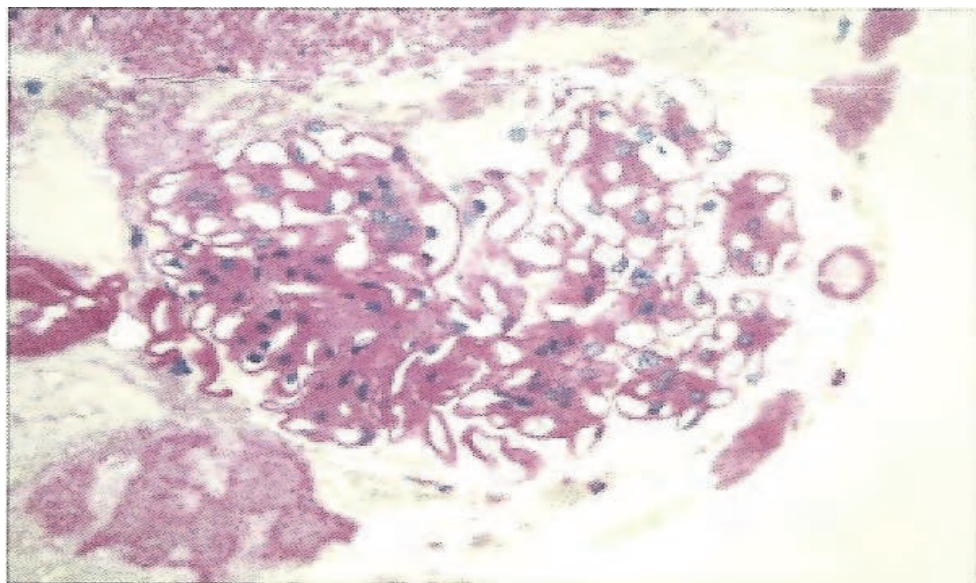


Fig. 6. Nodular Diabetic Nephropathy

It shows mesangial sclerosis consistent with Diabetic Nephropathy in an HIV infected patient with Diabetes Mellitus.

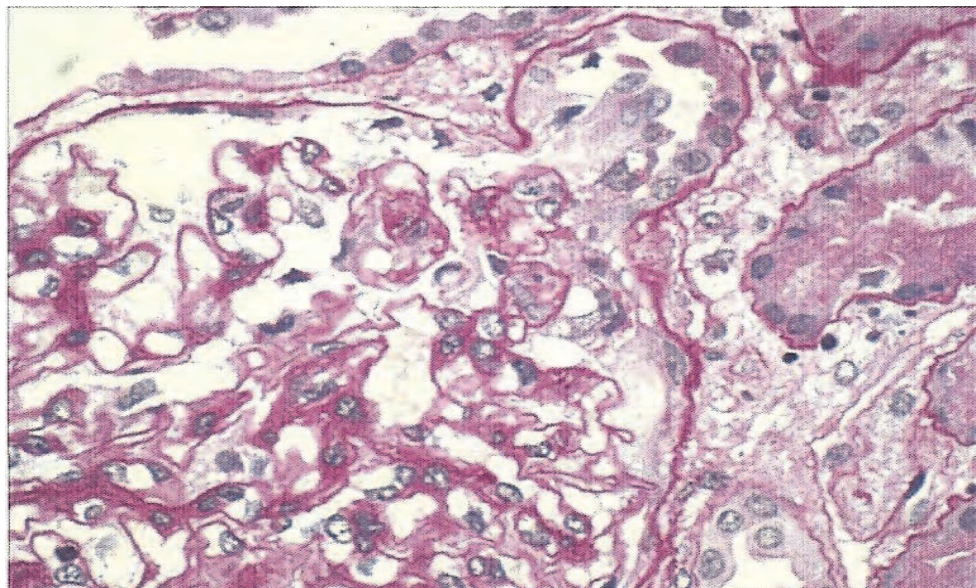


Fig. 7. FSGS with Tip lesion

It shows glomerular tip lesion of FSGS in a patient with HIV.

3.7 Supportive measures in chronic kidney disease

All supportive measures need to be employed to halt the progression of renal disease in patients with chronic kidney disease due to HIVAN. These measures include strict blood pressure control especially with blockade of renin angiotensin system in proteinuric patients. Use of nephrotoxic agents like aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs), and radiocontrast agent for computerized tomography should be minimized. Hyperlipidemia should be treated with lipid lowering drugs with target goal of low density lipoprotein level to $<100\text{mg/dl}$. Cessation of smoking should be emphasized. Complications of CKD like anemia, hyperparathyroidism should be treated accordingly to Dialysis Outcome Quality Initiative (DOQI) guidelines. Options for renal replacement therapy should be discussed with the patients and appropriate referrals made during chronic kidney disease stage 4. Option for renal transplantation should be discussed with HIV infected patients with CKD.

4. End Stage Renal Disease (ESRD)

End Stage Renal Disease is common in HIV infected African Americans. According to United States Renal Data System (USRDS) more than 4000 incident cases of ESRD secondary to AIDS Nephropathy were reported to initiate dialysis from 2000-2004. Epidemiological studies have characterized the marked racial differences in the ESRD incidence among HIV-infected individuals. Blacks are the largest and fastest growing racial group with HIV in the United States. African Americans account for 63% of all persons with HIV infection in Africa. Prevalence of ESRD may rise very high in future.

4.1 Survival of HIV infected ESRD patient

Patients with HIV and ESRD had very high mortality rate in early 1980s before era of highly reactive anti-retroviral agents (HAART). These patients had advanced HIV disease with multiple opportunistic infections. Currently, with use of HAART, survival of HIV patients with ESRD has improved drastically over past decade. One year survival rate of HIV-infected patients was equivalent to that of general population in both US and French database.

All options of renal replacement therapy (RRT) should be offered to a patient who develops ESRD with HIV infection due to any etiology. This includes hemodialysis, peritoneal dialysis, and renal transplantation. Each modality of RRT has its own advantages and disadvantages.

4.2 Hemodialysis

It is the most commonly utilized modality of renal replacement therapy in HIV infected patients. Indications of initiation of hemodialysis are the same as in non-HIV infected individuals with kidney disease. Early surgical referral for placement of an arteriovenous fistula should be made so that a working access is available for use at time of initiation of chronic hemodialysis. Arteriovenous grafts (AVG) and permanent catheters are less favorable accesses in HIV infected individuals. AVG infection rate is high in patients with AIDS, asymptomatic HIV infection as compared to HIV negative patients. AVF survival rates are similar between HIV seropositive and HIV negative individuals with ESRD. Usually isolation of HIV infected patient with ESRD is not needed in dialysis unit. Reuse of

properly sanitized dialyzer is permissible in HIV infected ESRD individuals. There is risk of transmission of HIV to dialysis staff through blood and needle stick exposure. Universal precautions of infection control need to be observed by the dialysis staff taking care of HIV ESRD patients. Routine cleaning with sodium hypochlorite solution of dialysis equipment and commonly touched surfaces are sufficient measures with regard to treating HIV infected individuals on hemodialysis. There is very small removal of HIV particle during hemodialysis to dialysate and hence dialysate should be handled as a potentially contaminated body fluid.

4.3 Peritoneal dialysis

This modality is preferred mode of dialytic therapy due to greater independence of life style and preservation of residual renal function as compared to patients on hemodialysis. Outcome of patients between hemodialysis and peritoneal dialysis is similar and therefore should be offered to HIV patients with ESRD. This modality minimizes exposure of healthcare workers to contaminated blood and needles. Peritoneal dialysis is associated with increased losses of protein in the dialysate and can cause protein malnutrition. Peritonitis is seen in patients on peritoneal dialysis. The risk of peritonitis in HIV infected with ESRD is higher than the HIV negative individuals on peritoneal dialysis particularly peritonitis caused by pseudomonas species and fungi. HIV is eliminated in the peritoneal dialysate is handled as a contaminated body fluid product. Peritoneal dialysis patients are instructed to pour dialysate into the home toilet. They should dispose off dialysate bags and lines by tying them in plastic bags and disposing these bags with conventional home garbage.

4.4 Kidney transplantation

It is an available modality for RRT in HIV infected individuals with well controlled HIV infection. HIV RNA must be undetectable using an ultra-sensitive assay. Individual and graft kidney survival rates are comparable with those of other population groups. Usually HIV infected individuals have high incidence of acute rejection after kidney transplantation. Studies have shown a 94% 3-year kidney transplant recipient survival but 67% of the patients in the study experienced acute rejection. The high incidence of acute rejection has not affected the graft survival rate due to use of immunosuppressive therapy. HIV disease does not progress in patients with kidney transplantation due to use of immunosuppressive therapy. HIV RNA levels and CD4 counts remain stable with use of immunosuppressive drugs. There is drug interaction of HAART with immunosuppressive drugs like Cyclosporin, Tacrolimus, and Sirolimus. These drugs are metabolized by cytochrome P450 system in the liver and hence raise level of immunosuppressive drugs. Usually doses of immunosuppressive agents used are usually 20% of the immunosuppressive dose administered to renal transplant recipients without HIV because concomitant HAART tends to raise serum levels of Cyclosporin and Tacrolimus.

5. Disorders of potassium

Both hyperkalemia and hypokalemia can be seen in HIV infected individuals. Hyperkalemia is very common in HIV infected patients and can be due to multiple

causes. It can be medication induced (see Table 3) due to use of Trimethoprim/ Sulphamethoxazole or Pentamidine use for *Pneumocystis Carinii* pneumonia prophylaxis or treatment respectively.

Hyperkalemia can also occur due to mineralocorticoid deficiency resulting from adrenal insufficiency or the syndrome of hyporenin hypoaldosteronism. Hyperkalemia can also occur with acute or chronic kidney disease. Usually treatment of Hyperkalemia includes discontinuation of any offending drug if possible, dietary potassium restriction especially in advanced kidney disease, and treatment of underlying cause of Hyperkalemia. Administration of certain medications like loop diuretics, fludrocortisone, and administration of corticosteroids in patients with adrenal insufficiency can be considered.

Hypokalemia is usually seen in conditions of gastrointestinal secretory losses like vomiting, diarrhea or nasogastric tube drainage. It is also seen in patients with severe wasting syndrome in advanced HIV disease. Certain medications also can cause hypokalemia like diuretics, amphotericin, foscarnet, and use of anti-retroviral agents like tenofovir and didanosine. Some HIV infected patients have distal tubular renal tubular acidosis and can present with severe hypokalemia with metabolic acidosis.

PCP prophylaxis or treatment	Trimethoprim/ Sulphamethoxazole Pentamidine
Potassium sparing diuretics	Amiloride or Triamterene
Mineralocorticoid antagonists	Spirolactone and Eplerenone
Renin angiotensin blockade with angiotensin converting enzyme inhibitors or angiotensin receptor blockers	Captopril, Fosinopril, Lisinopril, Losartan, Telmisartan
Non steroidal anti-inflammatory medications	Ibuprofen, Naproxen, Indomethacin
Immunosuppressive drugs especially in patients who undergo renal transplantation	Cyclosporin, Tacrolimus
DVT prophylaxis or treatment	Heparin(both unfractionated and low molecular weight heparin)
Congestive Heart failure	Digoxin

Table 3. Drugs Causing Hyperkalemia in HIV Infected Patients

6. Disorders of osmolality

Hyponatremia is very common in HIV infected patients and can be seen in 30-60% of hospitalized patients. It is a marker of severe illness which is associated with increased mortality in HIV- infected patients. In one study of 212 HIV infected patients hospitalized patients, the mortality rate was higher in hyponatemic group as compared to patients with normal serum sodium (36% vs. 19%).

Hyponatremia is usually due to multiple reasons in HIV infected patients. The commonest causes are volume depletion, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and adrenal insufficiency. Volume depletion causing hyponatremia is usually due to gastrointestinal losses in HIV infected patients like vomiting or severe diarrhea. Volume

depletion is associated with low urinary sodium, high urine osmolality, increased BUN/Cr ratio. Hypovolemia usually responds well to intravenous hydration, along with measures to treat the underlying cause of volume losses. Syndrome of inappropriate antidiuretic hormone secretion can occur due to variety of intrapulmonary or intracranial causes like pneumocystis carini pneumonia, pulmonary tuberculosis, cerebral toxoplasmosis, and histoplasmosis etc. SIADH is treated with free water restriction and treatment of underlying infection or malignancy. In some cases, one may have to use specific medications to treat SIADH like demeclocycline or ADH receptor antagonists like conivaptan.

Adrenal insufficiency is an uncommon cause of hyponatremia as compared to hypovolemia and SIADH. Hyponatremia results from cortisol deficiency leading to urinary salt wasting. The adrenal insufficiency can result from adrenalitis, an abnormality that may be infectious in etiology caused by cytomegalovirus, mycobacterium avium intracellulare, or HIV itself. Adrenal hemorrhage and infiltration with Kaposi's sarcoma may also be seen.

Hypernatremia is seen uncommonly and results from loss of water from the body in excess of salt. This is seen usually in HIV infected patients admitted to the hospital due to opportunistic infections accompanied by high fevers. It occasionally can occur as consequence of loss of massive amounts of water in the urine due to development of Diabetes Insipidus or adipsia.

7. Disorders of acid-base disturbances

Acid base disturbances in HIV infected patients are commonly caused by infections or drugs. Both metabolic and respiratory acid base disorders are encountered in HIV infected patients. Respiratory alkalosis and respiratory acidosis may occur in opportunistic infections of the lungs or central nervous system. Metabolic acidosis can be of both anion and nonanion type. Nonanion gap metabolic acidosis can occur as a result of several different processes taking place in the body. These include gastrointestinal losses due to diarrhea, renal acid loss due to adrenal insufficiency or syndrome of hyporeninemic hypoaldosteronism, or nephrotoxicity of the drugs used to treat HIV infected patients.

High anion gap metabolic acidosis in HIV infected patients occur due to multiple causes. These patients are prone to multiple opportunistic infections especially in untreated HIV individuals which can be serious and can result in sepsis induced lactic acidosis (type A lactic acidosis). Type B lactic acidosis can result from mitochondrial dysfunction in the absence of sepsis, hypoperfusion or hypoxia. Type B Lactic Acidosis has been reported with use of nucleoside reverse transcriptase inhibitors like zidovudine, didanosine, zalcitabine, and stavudine. Life threatening lactic acidosis is rare; 5-25% of HAART treated patients may develop mildly elevated lactate levels without acidosis. It is not recommended to screen HIV positive patients for presence of lactic acidosis, but lactic acid level should be measured in patients who present with low bicarbonate level, an elevated anion gap, or abnormal liver enzymes.

8. Disorders of calcium

Both hypercalcemia and hypocalcemia can be seen in patients infected with HIV. It is present in 6.5% of HIV infected patients. Hypocalcemia is usually due to presence of vitamin D deficiency, pancreatitis, hypoparathyroidism, use of certain drugs like foscarnet,

tenofovir, pentamidine for treatment of pneumocystis carinii pneumonia. Hypomagnesemia can accompany hypocalcemia in these patients.

Hypercalcemia can occur due to use of certain drugs like high doses of vitamin D and calcium supplements. Certain diseases like pulmonary tuberculosis, sarcoidosis, Mycobacterium avium intracellulare infection, Hyperparathyroidism, monoclonal gammopathy, human T lymphotropic virus (HTLV-1) associated Lymphoma, and other malignancies have been associated with hypercalcemia in HIV infected individuals. Hypercalcemia can be severe in HTLV -1 associated lymphoma which needs urgent treatment. Hypercalcemia may be associated with kidney failure due to its vasoconstrictive effects which is often reversible. Hypercalcemia is managed usually with IV hydration followed by forced diuresis, calcitonin, and bisphosphonates. Hemodialysis against low calcium bath may be needed in patients presenting with severe hypercalcemia with CNS manifestations.

9. Disorders of magnesium

Hypomagnesemia is encountered frequently in HIV infected individuals. It usually results from the use of certain medications like foscarnet or pentamidine especially if both are used together. Hypomagnesemia has been associated with nonrecovery of renal function and high inpatient mortality in AIDS patients with acute kidney injury.

10. Disorders of phosphate

Hypophosphatemia is seen usually as a result of drug therapy in HIV infected patients. The drugs usually involved with hypophosphatemia are tenofovir, foscarnet and other antiretroviral agents. Hypophosphatemia results from fanconi's syndrome in these patients which cause phosphaturia and hence hypophosphatemia.

Hyperphosphatemia is seen usually in patients who develop chronic kidney disease due to HIV related or non-HIV related causes. It is usually seen in advanced stages of chronic kidney disease usually stage 4 & 5. The management of hyperphosphatemia includes dietary phosphate restriction, use of non calcium based phosphate binders etc. Hyperparathyroidism resulting from chronic kidney disease is managed on the same principles as in non-HIVrelated CKD.

11. Nephrotoxicity of anti-retroviral agents

Nephrotoxicity is commonly encountered with use of anti-retroviral medications used for treatment of HIV infected individuals. Kidneys are involved in the excretion of these drugs and hence are exposed to high concentrations of these drugs, their metabolites or both. These medications require dose adjustment in patients with reduced GFR. Drug induced nephrotoxicity is seen in clinical practice and accounts for 2-15% cases of acute kidney injury (AKI). The exact frequency of nephrotoxicity induced by anti-retroviral agents in HIV infected patients is unknown. The dose recommendations by the pharmaceutical manufacturers are based on creatinine clearance and clinical validity of Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault equations in HIV patients is not available. A brief overview of commonly used groups of drugs is given below.

11.1 PI (Protease Inhibitors)

Protease inhibitors are metabolized primarily in the liver. Urinary excretion accounts for approximately 10% of parent drug clearance for indinavir and 5% or less for other drugs in this class. PI's are highly protein bound (60-90%) and have large volume of distribution. None of the currently available PI requires dose adjustment for patients with reduced GFR. These medications are not cleared significantly by dialysis (both hemodialysis and peritoneal dialysis) although studies supporting this evidence recruited small number of patients. Some of the commonly used protease inhibitors are given in Table 4. No adjustment of dose is needed in patients with reduced GFR or on dialysis.

Brand Name	Generic Name	Normal Dose
crivan	Indinavir	800mg q8hour
Invirase	Saquinavir	1000mg bid with ritonavir 100mg bid
Norvir	Ritonavir	600mg bid
Viracept	Nelfinavir	750mg tid
Kaletra	Lopinavir/Ritonavir	Lopinavir 400mg/ritonavir 100mg bid
Reyata	Atazanavir	1400mg bid
Lexiva	Fos-amprenavir	1400mg bid
Fortovase	Saquinavir(soft gel)	1200mg tid

Table 4. Commonly Used Protease Inhibitors with Doses in HIV

11.2 NRTI (Nucleoside /Nucleotide Reverse Transcriptase Inhibitors)

These drugs are eliminated by the kidney except abacavir which is mostly metabolized by the liver (Table 5 & 6). Urinary excretion ranges from 20-70% for various formulations except abacavir which is eliminated by 1% through the kidney. All the agents need dose

Brand Name	Generic Name	Normal Dose	Dose Adjustment Needed for Reduced GFR
Emtriva	Emtricitabine	200mg qd	Dose interval needs to be increased depending on GFR
Epivir	Lamivudine	150mg bid or 300mg /day	Dose needs to be decreased based on level of GFR
Hivid	Zalcitabine	0.75mg tid	Dose interval needs to be increased based on GFR
Retrovir	Zidovudine	300mg bid or 200mg tid	Dose needs to be decreased in dialysis patients
Videx	Didanosine	≥60kg: 200mg bid ≤ 60kg:125mg bid	Dose needs to be reduced in patients with compromised GFR
Viread	Tenofovir	300mg /day	Dose interval needs to be increased in patients with reduced GFR
Ziagen	abacavir	300mg bid	No dosage adjustment needed
Zerit	Stavudine	≥60kg:40mg q12h ≤60kg:30mg q12h	Dose needs to be reduced in patients with reduced GFR

Table 5. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors Dosing in Patients with Normal and Impaired Renal Function

adjustment except abacavir in patients with reduced GFR. In dialysis patients, these drugs should be given after dialysis session. Unlike PI, these drugs have low protein binding and small volume of distribution. These drugs are eliminated by both glomerular filtration and tubular secretion. Nucleoside RTIs are less nephrotoxic than Nucleotide RTIs.

Other drugs such as Cimetidine and Trimethoprim can reduce their elimination by competing for tubular secretion by organic cation pathway.

Fixed drug combination should be avoided in patients with GFR <50ml/min. The reader should refer to individual package inserts for guidance with dosing of antiretroviral combinations.

Brand Name	Generic Name	Usual Dose
Combivir	Lamivudine/ Zidovudine	One tablet bid
Trizivir	Abacavir, Lamivudine, Zidovudine	One tablet bid
Truvada	Emtricitabine, Tenofovir	One tablet daily
Epzicom	Abacavir, Lamivudine	One tablet daily

Table 6. Nucleoside Reverse Transcriptase Inhibitors Fixed Dose Combinations

11.3 NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitors)

These drugs are eliminated primarily by the liver. These drugs are protein bound and they do not require drug adjustment in patients with reduced GFR. These drugs are removed to some extent by dialysis and should be dosed after hemodialysis. Nevirapine is removed significantly by peritoneal dialysis but it remains unclear if a dosage adjustment is needed for patients on peritoneal dialysis as its trough plasma level remains unaffected.

Efavirenz and Delavirdine have not been studied in patients with reduced GFR or on dialysis.

11.4 Pathogenesis of nephrotoxicity

Nephrotoxicity results from mitochondrial dysfunction induced by NRTIs since they inhibit nuclear or mitochondrial DNA polymerase from host cell along with inhibition of reverse transcriptase of HIV. NRTIs affects DNA polymerase of mitochondria with subsequent deficits in mitochondrial DNA encoded enzymes of the mitochondrial respiratory chain. Oxidative phosphorylation is disrupted with deficits in energy production. This leads to production of lactate from anaerobic respiration which results in clinical effects like lactic acidosis, cardiomyopathy, peripheral neuropathy, fatty liver, and pancreatitis. Clinically it manifests as tubular injury to proximal tubular cells. Histologically is characterized by tubulointerstitial nephropathy with mitochondrial cytopathy. Protease inhibitors induce kidney injury by causing crystalluria, renal stones, and tubulointerstitial disease.

11.5 Renal manifestations of toxicity of antiretroviral agents

Various lesions caused by anti-retroviral agents as cause of AKI are acute tubular necrosis (ATN), crystalluria, Fanconi's syndrome, distal tubular acidosis (RTA), nephrogenic

diabetes insipidus (NDI), and lactic acidosis. Chronic kidney disease can also result from long term HAART use.

AKI secondary to acute tubular necrosis (ATN) is commonly seen in patients with HIVinfection(up to 10%) and regarding HAART, tenofovir and indinavir are most commonly associated with nephrotoxicity.

Tenofovir is taken up into renal epithelial cells by basolateral membrane human organic anion transporters, then secreted into the urine across the apical membrane by transporters called multidrug resistance associated protein. Tenofovir toxicity was first reported by Verhelst et al in 2002. Tenofovir is associated with reversible Fanconi's syndrome, nephrogenic diabetes insipidus and they occur within 5-12 months after starting therapy with tenofovir. These abnormalities resolve within few months of discontinuation of tenofovir. Renal biopsy reveals cytoplasmic vacuolization, apical localization of nuclei, and reduction of brush border on proximal tubular cells. Clinically, it is manifested by glucosuria, aminoaciduria, hyperuricosuria, hypouricemia and hypophosphatemia due to phosphaturia. Most patients who develop tenofovir related renal dysfunction also have concomitant use of ritonavir. Patients taking tenofovir should have close monitoring of renal function especially if ritonavir is used concomitantly. Glucosuria and hypophosphatemia are early manifestations of tenofovir induced injury and tenofovir should be discontinued promptly. Nephrotoxicity improves upon discontinuation of tenofovir in most cases although in some patients serum creatinine levels remain above baseline levels.

Indinavir has been associated with crystalluria, nephrolithiasis, and obstructive nephropathy which can occur anytime after initiation of drug and has been reported in as many as 33% of patients on chronic therapy. Obstructive nephropathy may be mild to severe and may need urologic intervention. It is recommended to monitor patients on indinavir periodically during the first 6 months of therapy and then biannually. The use of indinavir has declined recently in patients with HIV.

Renal calculi have been reported with use of nelfinavir and saquinavir. Ritonavir has been associated with AKI in few reports. Atazanavir can induce AKI secondary to interstitial nephritis.

Some NRTI can induce interstitial nephritis and proximal tubular dysfunction like abacavir. Fanconi's syndrome has also been reported in patients using DDI and stavudine/lamivudine.

Lactic Acidosis has been described with use of NRTI. The development of lactic acidosis can range from asymptomatic chronic hyperlactemia to acute life threatening lactic acidosis. Lactic acidosis was first described with didanosine and zidovudine. It is believed to be caused by inhibition of mitochondrial DNA polymerase by intracellularly generated triphosphate metabolites of these drugs. Approximately 20-30% of patients who are treated with these drugs can be found to have asymptomatic hyperlactemia that develops several months after institution of therapy. Severe lactic acidosis (lactate acid level >5mmol/L) is clinically characterized by fatigue, nausea, vomiting, anorexia, and abdominal pain is rare and is associated with 80% mortality rate. Risk factors associated with lactic acidosis include longer duration of treatment with HAART, older age, female, pregnancy, hypertriglyceridemia, impaired renal function, and use of alcohol. Most patients with asymptomatic hyperlactemia remain stable. Stavudine and didanosine (alone or in

combination) have been associated with hyperlactinemia and lactic acidosis, although all of NRTI have been implicated. Routine monitoring of lactic acid is not recommended except in patients with symptoms of lactic acidosis.

NNRTI can rarely be associated with AKI in association with rash and eosinophilia. HAART treated patients may develop chronic kidney disease especially in patients with partial recovery of renal function after an episode of AKI. These medications are excreted through kidneys and may be involved in causation of chronic kidney disease in HIV patients.

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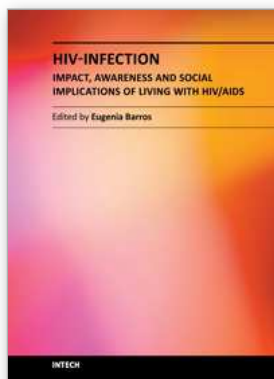
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HIV-infection - Impact, Awareness and Social Implications of living with HIV/AIDS

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The past few decades have seen the escalation of HIV-infections and the 'frantic' search for new drugs to treat the millions of people that live with HIV-AIDS. However because HIV-AIDS cannot be cured, but only controlled with drugs, and the Antiretroviral (ARV) treatment itself results in some undesirable conditions, it is important to generate wider awareness of the plight of people living with this condition. This book attempts to provide information of the initiatives that have been used, successfully or unsuccessfully, to both prevent and combat this 'pandemic' taking into consideration the social, economic, cultural and educational aspects that involve individuals, communities and the countries affected.

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