

Renal Complications of HIV Infection

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Introduction

In the early 1980s, a unique kidney disease was described among HIV-infected patients.^{1,2} Patients usually presented with significant proteinuria and rapid progression to end-stage renal disease (ESRD).² When initially described, this renal failure was felt due to heroin nephropathy as it clinically appeared similar. As clinicians continued to see renal disease associated with HIV infection, the existence of a distinct disease called HIV-associated nephropathy (HIVAN) was debated. As more patients with HIV infection without a history of heroin use were noted to have renal disease, HIVAN was established as a unique entity.² From a once rare complication of HIV infection, HIVAN has emerged as the most common cause of ESRD in HIV-infected patients.³ In addition, as patients with HIV/AIDS are surviving longer, the prevalence of HIV-infected patients with chronic kidney diseases continues to rise.⁴ With up to 42 million people infected with HIV/AIDS worldwide and a prevalence of renal disease in HIV-infected black patients of 3.5–12%, up to 5 million people worldwide may be affected by HIV related kidney disease.^{2,5} This chapter will review the epidemiology and clinical course of HIV related renal disease using USA, European, and African studies to compare results based on regions of the world. Such a comparison requires initial insight into methods and infrastructure for delivery of healthcare within regions to provide a framework for the understanding of study comparisons.

Overview of Global Healthcare/Delivery

Healthcare and its delivery vary drastically around the world. In the USA and Europe, healthcare is available to a greater proportion of the population than in many other parts of the world. In Africa, unfortunately, the availability of health services is considerably more limited. The leading cause of death worldwide is infectious disease – 43% in the developing world compared with 1.2% in the developed world (The World Health Report). Many reasons are responsible for this difference including environmental exposures, lack of water treatment, a general lack of public health infrastructure and limited drug availability. Infectious diseases such as tuberculosis and malaria have been longstanding health problems; however, AIDS has recently become a significant epidemic particularly in sub-Saharan Africa and India. Despite the growing AIDS epidemic, limited resources are available for the majority of patients needing therapy. The financial limitations are significant and can be compared based on the annual *per capita* expenditure on healthcare in different regions. In 2001, annual *per capita* expenditure on healthcare in international dollars was 12 in the Democratic Republic of the Congo, 22 in the Congo, 34 in Afghanistan, 153 in Egypt, and 652 in South Africa; this is in contrast to >2800 in select European countries and >4000 in the USA.⁶ Due to limited preventive services in Africa, screening for renal disease is essentially non-existent and because of more pressing and immediate health concerns, screening

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assumes a lower priority. As a result, patients are often diagnosed late in the course of their disease after presenting to a hospital with another illness or overt nephrotic syndrome. Thus, treatment is limited by late diagnosis, comorbid conditions, and shortage of resources. In contrast, patients in the USA and Europe with known HIV may undergo screening for renal involvement and thus may be offered therapy earlier in the course of their disease.

Epidemiology

One of the first clinical reports of HIVAN occurred in 1984 in the USA.¹ Not surprisingly, the initial description engendered a debate that was focused mainly on whether or not this was a different entity from heroin nephropathy. As both children and patients without a history of heroin use were identified with renal disease and the disease became better defined histologically, the separate term HIVAN emerged to describe the combination of clinical and histological findings. In the early era of HIV, patients with HIVAN were diagnosed late in the course of HIV infection, usually already with AIDS. Predictably, renal survival for those diagnosed with HIVAN was 1–4 months without therapy.^{1,2,7,8} With the advent of highly active antiretroviral therapy (HAART) and the decline in mortality from AIDS, kidney diseases have become major contributors to HIV morbidity and mortality and are now the fourth leading cause of death in US AIDS patients.⁹

While no data on global prevalence exists, HIVAN is likely to have the highest prevalence in Africa. According to the 2004 report on the global AIDS epidemic, almost 38 million (range 34.6–42.3 million) people are living with AIDS in the world.¹⁰ Within sub-Saharan Africa alone, nearly 30 million people are currently infected. In the USA, the prevalence of renal disease has been noted to be between 3.5–12% in HIV-infected African Americans.^{2,5} If one assumes a similar prevalence among persons of African descent, then up to 3 million patients may have renal disease in sub-Saharan Africa alone. Any estimate of prevalence, however, needs to account for the different mortality rates among HIV-infected patients and its variation by country. Without having an exact estimate, the prevalence of renal disease could be hypothesized to be quite high. One report in 2003 in the Nigerian Journal of Medicine studying the prevalence of renal disease in consecutive patients with AIDS seen in the infection unit suggests that these estimates are conservative. Of 79 patients with AIDS, renal disease was present in 51.8% (41 patients)

as compared with 12.2% (7 patients) of non-HIV-infected controls. Of these 79 patients, 19% ($n = 15$) had azotemia, 25% had proteinuria alone, and 7.6% had both proteinuria and azotemia.¹¹

The current leading cause of death from AIDS worldwide is infection; but as HAART becomes more available and survival is prolonged, renal disease will likely become a major secondary cause of mortality and morbidity as it has in the USA. As the mortality rate from AIDS declined in the early 1990s, the number of black patients living with HIV increased significantly. As a result, this 'at risk' group lived longer and HIVAN became one of the most rapidly increasing causes of end-stage renal disease in the USA.³

Patterns of Renal Disease in Africa

There is a large variation in the patterns of renal diseases reported in different geographic regions of Africa. Unfortunately, accurate and comprehensive statistics are not available.¹² For example, a single available study of 368 patients with chronic kidney disease (CKD) in Nigeria demonstrate that 62% had an undetermined etiology of renal failure.¹³ The prevalence of CKD in sub-Saharan Africa is not known. Data from the South African Dialysis and Transplant registry regarding etiologies of ESRD reflect only patients selected for dialysis. As only patients eligible for transplantation are offered dialysis and few patients with diabetic ESRD are offered dialysis or transplantation due to comorbid conditions, the available data likely does not reflect accurately the spectrum of renal diseases in the population as a whole.

In North Africa, the incidence of renal disease appears to be much higher than in the US, but the prevalence is lower due to higher mortality and fewer available treatment options.¹⁴ The reported annual incidence of ESRD ranges between 34 and 200 patients per million population (pmp) and the respective prevalence ranges from 30–430 patients pmp. Despite the high mortality from ESRD, the prevalence of CKD appears to be increasing. The principle causes of CKD are interstitial nephritis (14–32%), glomerulonephritis (11–24%), diabetes (5–20%), and nephrosclerosis (5–31%). Trends in Egypt suggest an increasing prevalence of interstitial nephropathies and diabetes.¹⁴ FSGS is reported in 23–34% of the glomerulonephritides and is mostly clustered in black patients.¹⁴

Overall, glomerular disease appears to be more prevalent and more severe in Africa than in Western

countries. It has been estimated that between 0.2–2.4% of medical admissions in tropical countries are due to renal disease (0.5% Zimbabwe, 0.2% Kwa Zulu Natal, South Africa; 2.0% in Uganda and 2.4% Nigeria).¹⁵ It has been observed that the majority of these admissions are related to glomerulonephritis which responds poorly to treatment and progresses to ESRD. In addition, glomerulonephritis in South Africa is more frequent in blacks and less frequent in Indians and Caucasians. This is a similar pattern to the distribution of HIVAN. Given the high prevalence of HIV/AIDS in South Africa, it can be postulated that some of these renal disorders may be caused by HIVAN or other HIV-related renal diseases.

Racial Distribution of HIVAN

As demonstrated by US and European epidemiologic and pathologic data, HIVAN has an overwhelmingly higher prevalence in HIV-infected patients of African descent as compared with Caucasians.^{5,16–20} With the emergence of HIV throughout the world in the 1980s, a change in the pathologic findings in African patients with nephrotic syndrome was described. A study from Zaire in 1993 reported the pathologic findings of 92 patients with documented nephrotic syndrome systematically biopsied between 1986 and 1989. A total of 41% of these patients were found to have focal and segmental glomerulosclerosis (FSGS) which was a seven-fold increase from previous prevalence rates of FSGS of only 6%. The investigators were uncertain of the cause of the increase in FSGS but proposed that AIDS might be responsible.²¹ This study cannot assess the predisposition of blacks to HIVAN but does suggest that HIVAN has become an increasing health problem in this population. Early in the HIV epidemic, epidemiologic data from the United States and Europe noted HIVAN was diagnosed primarily in areas with large populations of HIV-infected black patients.¹⁹ Two series from France and London have reported that 97/102 and 17/17 of patients diagnosed with HIVAN were black, respectively.^{22,23}

In contrast to the high rate of HIV-related kidney diseases in predominantly black populated regions, Caucasians are noted to have a much lower prevalence of classic HIVAN. A post mortem analysis of 239 consecutive Swiss patients who died from AIDS between 1981 and 1989 demonstrated renal pathologic findings in 43% of patients, with HIVAN in only 1.7% (4/239) of the patients.¹⁸ Given that 95% of the patients were Caucasians, this study

emphasizes the low prevalence of classic HIVAN in Caucasians.

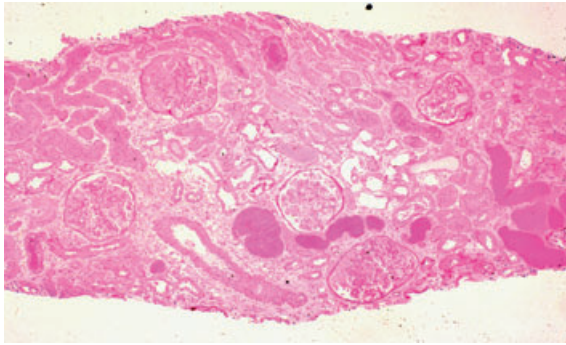
Another study reviewed the pathologic features of 120 consecutively autopsied HIV-infected Caucasian patients in Italy. Of these patients, 68% had pathologic renal changes and none of the renal specimens had classic HIVAN. The most common pathologic abnormality was immune-mediated glomerular diseases (25 patients) and tubulointerstitial lesions (19 patients).²⁰ A similar study of 26 Caucasian patients in northern Italy with HIV who underwent renal biopsy failed to reveal any lesions of HIVAN. The majority of diagnoses were immune complex-mediated glomerulonephritis.¹⁶ While patients of African descent are at the highest risk for HIVAN, other ethnic groups have renal disease related to other pathologic entities.

Pathologic Findings

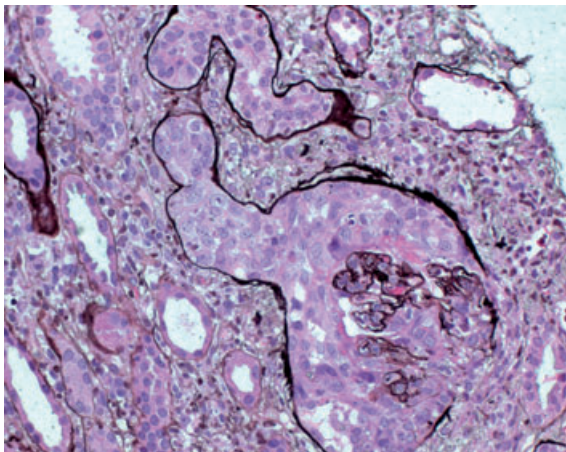
HIV-associated nephropathy has pathologic findings similar to idiopathic and heroin-related FSGS, however there are several unique findings that are suggestive of HIV infection.¹⁷ First, in HIVAN there is a tendency for the entire glomerular tuft to sclerose and collapse rather than finding only a segmental glomerular lesion (Fig. 28.1). In the tubules, there is often severe injury with proliferative microcyst formation and tubular degeneration. The tubular disease is characterized by the development of tubular dilation accompanied by flattening and atrophy of the tubular epithelial cells. Electron microscopy can reveal the presence of numerous tubuloreticular structures in the glomerular endothelial cells. The tubuloreticular inclusions are composed of ribonucleoprotein and membrane structures; their synthesis is stimulated by α -interferon. The only other disorder in which these structures are prominently seen is lupus nephritis, which is also associated with chronically high levels of circulating α -interferon. The finding of tubuloreticular inclusion had been noted to be a common pathologic abnormality in the pre-HAART era; however this pathologic abnormality is now found less frequently potentially related to the advent of effective antiviral therapy resulting in reduced levels of plasma interferon.^{17,24} In patients with human immunodeficiency virus-1 (HIV-1) infection and kidney disease, several different glomerular syndromes have been described (Box 28.1). The most common pathologic finding is HIVAN. In the USA, the second most common pathologic findings are membranoproliferative GN (often with HCV coinfection) or mesangioproliferative

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A



B

Figure 28.1 Kidney biopsy specimens. (A) Low-power view of a biopsy specimen from a patient with HIVAN in the USA. There are 5 glomeruli with collapsing sclerosis and podocyte hyperplasia. The tubules are separated by edema, mild fibrosis and patchy interstitial inflammatory infiltrates. Some tubules show degenerative changes with focal tubular microcysts containing large casts. (B) High-power view of a biopsy specimen from a patient with HIVAN in Brazil. Note the collapsing sclerotic glomerulus, tubular atrophy, and interstitial inflammation. (Courtesy of C.E. Poli de Figueiredo, MD, DPhil, Medical School PUCRS, Porto Alegre, Brazil.)

(GN), followed by immune complex GN, membranous, and IgA nephropathy.^{17,25} Less commonly, patients with HIV have been found to have thrombotic microangiopathy, minimal change disease, and amyloidosis.^{25,26} This is in comparison to patients seen in Baragwanath, South Africa. Among 64 HIV-infected patients, 39% had classic HIVAN; 14% had immune complex rich 'lupus-like' disease; 38% had other glomerulonephritides (GN) including 13% membranous, 9% post-infectious GN, 6% IgA nephropathy, 5% mesangioproliferative GN, 5%

Box 28.1

Diagnosis in HIV-infected patients with proteinuria

- HIV-associated nephropathy^a
- Membranoproliferative GN (often with HCV)^a
- Mesangioproliferative GN
- Immune complex GN
- Membranous nephropathy
- IgA Nephropathy
- Post-infectious GN
- Minimal change disease
- Diabetic nephropathy
- Tubulointerstitial nephritis
- Thrombotic microangiopathy
- Amyloidosis

^aMost common pathologic findings.

other GN; 3% had tubulointerstitial nephritis; 3% had acute tubular necrosis and 3% other.²⁷ However, among hospitalized HIV-infected patients with acute renal failure, the most common diagnosis is acute tubular necrosis.

Clinical Manifestations and Diagnosis

Among patients with HIVAN, severe proteinuria (often in the nephrotic range >3 g/day) with progression to ESRD within 1–4 months of diagnosis was initially described.^{1,2,7,8,28} Subsequent data in the setting of monotherapy with zidovudine and HAART suggests a much slower progression.^{25,28,29} While early reports suggested that HIVAN was a late manifestation of AIDS, occurring when CD4 counts were well below 200×10^6 cells/L, subsequent data suggests that a lower CD4 count may be associated with a faster progression and greater likelihood of biopsy.^{22,25} A case report of HIVAN demonstrates its presence as early as the time of acute HIV seroconversion.³⁰ Most patients with HIVAN do not have significant peripheral edema and despite the high prevalence of hypertension in blacks, patients with HIVAN are not usually hypertensive. Laboratory data are nonspecific in HIVAN. Serologic studies for glomerular diseases (i.e. ANA, complements, Anti-streptolysin O antibodies, ANCA, anti-GBM, cryoglobulins) are usually negative except for in patients with Hepatitis C co-infection. Ultrasonography will typically reveal bilaterally echogenic and enlarged kidneys in contrast to other conditions where the

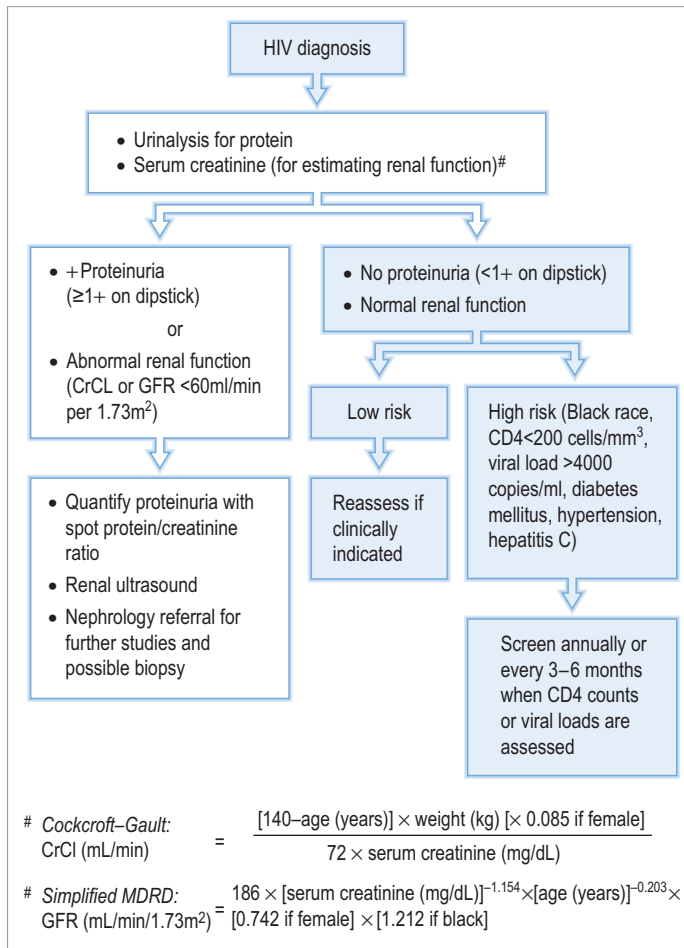


Figure 28.2 Screening algorithm for kidney disease in HIV-infected patients. (Adapted from Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005; 40:1559–1585.)

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kidneys shrink in size as function deteriorates. Diagnosis of specific histology requires a renal biopsy. Figure 28.3 proposes a screening algorithm for kidney disease in HIV-infected patients.

Pathogenesis

Early in the description of HIVAN, it was uncertain whether HIV-1 caused injury through a direct effect on renal cells or an indirect effect from immune dysregulation. Studies by Bruggeman and co-workers using a murine model of HIVAN, demonstrated that HIV-1 expression in renal epithelial cells is necessary for the development of the HIVAN phenotype.³¹ They went on to demonstrate that both tubular and glomerular epithelial cells are infected by HIV-1 in patients with HIVAN.³² Furthermore, Marras and co-workers demonstrated that the renal

tubular epithelial cells support viral replication, subsequent divergence, and act as a separate compartment from blood.³³ Based on a study by Winston and co-workers, renal parenchymal cells can serve as a reservoir for HIV and the presence of the virus can persist in glomerular and tubular epithelial cells despite antiviral therapy.³⁴

The mechanisms by which HIV-1 gains entry into epithelial cells remains unclear. The major co-receptors for HIV-1 have not been detected using immunocytochemistry but more sensitive methods including PCR suggest that CD4 and CXCR4 can be detected in cultured renal epithelial cells.³⁵ The data are less clear for the other co-receptors. Whether the receptors are in sufficiently high density or functional enough to mediate entry into the cell also remains unknown.³⁵

The observation that HIV DNA has been found in glomeruli of HIV-infected patients without HIVAN

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suggests that some additional factor (such as a genetic predisposition) may be required.³⁶ The pathologic findings of collapsing focal glomerulosclerosis combined with tubular microcystic disease has been thought to be specific to HIVAN. However, a recent report of collapsing GN in seven Caucasian HIV negative patients who were treated with high dose pamidronate suggests that other environmental agents can also induce collapse.³⁷ Thus, Caucasian patients can develop a collapsing phenotype but the mechanism appears to be different from those observed in response to HIV infection in blacks.

The racial predilection for HIVAN in blacks strongly suggests that genetic factors play an important role in the pathogenesis of HIVAN. In support of this, Gharavi and co-workers assessed the influence of genetic background on the development or progression of HIVAN by crossing the HIVAN transgenic mouse with mice of different genetic backgrounds.³⁸ These investigators found that the HIVAN phenotype varied from severe renal disease to no renal disease based on the background strain of the mice. In addition, genome-wide analysis of linkage in 185 heterozygous transgenic backcross mice identified a locus on chromosome 3A1-3, HIVAN1, that showed highly significant linkage to renal disease. This locus, HIVAN1, is syntenic to human chromosome 3q25-27, which is an interval showing suggestive evidence of linkage to various nephropathies.³⁸

Treatment

Despite the high prevalence of kidney disease in HIV-infected patients, no prospective randomized controlled trials have been performed to assess the effect of various treatments on outcome. However, a number of retrospective analyses have been performed to assess the association between antiretroviral therapy, angiotensin-converting enzyme inhibitors, and steroids and outcomes (Box 28.2).

Antiretroviral Therapy

Initial reports of the efficacy of monotherapy with zidovudine on HIVAN were conflicting. FSGS was noted to develop in many patients despite treatment with zidovudine and thus it was suggested to be of little benefit.³⁹ Other studies suggested that zidovudine might delay the progression of HIV nephropathy if begun when patients had mild proteinuria and near normal renal function.²⁸ In a retrospective cohort of 19 patients with a clinical diagnosis of

Box 28.2

Management of kidney disease in HIV-infected patients^a

- Control blood pressure to <130/80, initial agents should be ACE inhibitors for patients with proteinuria
- Prepare for dialysis by placing dialysis access
- Discuss renal transplantation
- If proven HIVAN, treat with HAART
- If patient with HIVAN fails to respond to HAART, consider adding ACE inhibitor (if not already initiated) and/or prednisone

^aAdapted from Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005; 40:1559–1585.

HIVAN, protease inhibitor usage has also been associated with a slower decline in creatinine clearance (–0.08 mL/min per month versus –4.30 mL/min per month for those not administered one of these drugs).²⁹ In another analysis, among patients with HIVAN, the use of antiretroviral therapy (ART) was associated with a slower progression to end-stage renal disease (HR 0.24, $P = 0.03$).²⁵ Despite a variety of study designs, it would appear that these reports are generally consistent in that either suppression of viral replication or ART slows the progression of renal disease among patients with HIVAN.

Among HIV-infected patients with renal disease other than HIVAN, a single study suggests that antiretroviral therapy may not be associated with a similar benefit.²⁵ Additional studies to confirm this are required.

Angiotensin-converting Enzyme Inhibitors

ACE inhibitors have been shown to be efficacious in a variety of renal disorders associated with proteinuria, such as diabetes mellitus. In patients with HIVAN, retrospective analyses suggest that the use of ACE-I is associated with improved renal survival. Kimmel and co-workers reported a delayed progression of renal failure in a retrospective cohort of nine patients with HIVAN compared with a group of controls.⁸ Burns and co-workers prospectively evaluated 20 patients with ‘early’ HIVAN (baseline creatinine <2.0 mg/dL, 177 $\mu\text{mol/L}$) all of whom were offered fosinopril.⁷ In the 12 patients who were compliant

with treatment, renal function remained stable at 12 and 24 weeks of follow-up. In the eight untreated patients, serum creatinine increased from 88.4 to 433.2 $\mu\text{mol/L}$. Long-term effects have also been reported with ACE inhibitors. In a single-center prospective study, 44 patients with biopsy-proven HIVAN and early renal disease (mean serum creatinine <2.0 mg/dL, <177 $\mu\text{mol/L}$, $<50\%$ with proteinuria >3 g/day) were all offered treatment with fosinopril.⁴⁰ In the 28 patients who consented to fosinopril, serum creatinine remained stable after a median of 479.5 days of follow-up in all but one patient who progressed to ESRD. All of the 16 patients who refused treatment progressed to ESRD after a median period of 146 days. Initial serum creatinine and proteinuria were similar in both groups but exposure to antiretroviral therapy prior to the study appeared different (57% in the ACE-I group versus 31%, $P=0.12$) as was CD4 count (172 versus 120 $P=0.06$).

The potential benefit of ACE-I was also demonstrated by Gerntholtz among 64 patients with HIV who underwent renal biopsy in South Africa.²⁷ In 26 patients with HIVAN, use of an ACE-I was associated with improved renal survival ($P=0.00026$). All patients progressed to ESRD by 15 weeks of follow-up in the absence of ACE-I compared with 30% with ESRD at 160 weeks of follow-up in the ACE-I treated group. As patients were not randomized to treatment groups, baseline characteristics were different and included a lower creatinine (448 $\mu\text{mol/L}$ versus 1082 $\mu\text{mol/L}$), higher albumin, and higher cholesterol level in the ACE-I group. ACE-I therapy appeared to have no effect on proteinuria.²⁷ As only six patients in this cohort were taking antiretrovirals, further research is required to define the benefit of ACE-I among patients using HAART.

Steroids

Initial observations in children with HIVAN suggested corticosteroids to be ineffective. However, later research has found that select patients may respond to therapy.^{4,41} In a retrospective cohort, 13 of 21 patients with biopsy proven HIVAN received corticosteroids for one month followed by a steroid taper over several months. Seven patients treated with corticosteroids stayed off dialysis at 6 months of follow-up compared with only one of the non-corticosteroid group ($P=0.06$).⁴ A second group reported a series of 20 patients (17 with biopsy proven HIVAN) who were treated with prednisone 60 mg/day for 2-11 weeks followed by a slow taper.

After a mean follow-up of 44 weeks, eight patients required maintenance dialysis, 11 died from AIDS-related complications, and seven were alive and free from dialysis.⁴¹ Unfortunately, in both groups, infectious related complications were high. Gerntholtz retrospectively analyzed patients in South Africa with kidney disease and HIV and found that prednisone had no effect on outcome.²⁷ Szczech and co-workers retrospectively studied 19 patients with suspected HIVAN or other HIV-related lesions. The five patients who received prednisone experienced an increase in creatinine clearance of 5.57 mL/min per month, whereas the 14 patients who did not receive prednisone experienced a decline in creatinine clearance of 3.32 mL/min per month ($P=0.003$).²⁹ Given the small number of observational studies, the short follow-up and the likelihood of relapse and adverse events, definitive conclusions cannot be made regarding the efficacy or safety of steroids for the treatment of HIVAN.

Renal Replacement Therapy

With the rapid progression of renal failure in patients with HIVAN, renal replacement therapy (RRT) becomes the major therapeutic option. Unfortunately, the availability of RRT to patients with ESRD is not uniform globally. The availability of dialysis and transplantation are particularly variable in Africa. According to the Dialysis registry (1994-1998), only 32 patients were on renal replacement therapy in the Congo, seven in Namibia, 350 in Sudan, and >3000 in South Africa. Treatment rates in South Africa are 99 per million population as compared with treatment rates in North Africa which are 30-186.5 per million population (pmp).^{12,15} This is in contrast to the 2002 treatment rates in the USA at 1432 per million population³ and Europe at 438 pmp (Iceland) to 1081 pmp (Spain).²⁶ Dialysis services are predominantly available only in urban regions in Africa and are thus inaccessible to poorer, rural patients.¹²

In South Africa, there is strict rationing of dialysis due to the lack of resources and funding. The National Health Department has formalized a protocol for the management of ESRD: state facilities will only offer patients long-term dialysis if they are eligible for a kidney transplant. Currently, HIV-infected patients with acute renal failure may be supported by dialysis on a short-term basis but HIV-infected patients are not candidates for renal transplantation and subsequently are not offered long-term dialysis.¹²

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Dialysis and transplant programs in the rest of Africa are dependent of the availability of funding and donors. Nigeria, Tanzania, Ethiopia, Cote d'Ivoire, and Cameroon offer very limited dialysis to a small number of patients for short time periods. Peritoneal dialysis is limited due to the high cost of peritoneal fluids and the high rate of peritonitis.¹⁴

Course and Outcome

In the absence of treatment with antiretroviral therapy, reports from the early 1990s suggest patients' progress to ESRD within 1–4 months of diagnosis.^{7,8,28} Subsequent data in the setting of monotherapy with zidovudine and HAART suggests a much slower progression.^{25,28,29} Clinical variables associated with increased risk of progressive renal failure include decreased CD4 count^{22,25} elevated serum creatinine,²⁵ increased proteinuria,²² higher viral HIV-1 viral load^{22,25} and the presence of Hepatitis C co-infection.²⁵

Patients with a pathologic diagnosis of HIVAN had worse renal survival compared with patients with lesions other than HIVAN. In a cohort of 89 HIV-infected patients with renal disease biopsied between 1995 and 2000, 17 of 47 patients with lesions other than HIVAN required the institution of renal replacement therapy at an average time of 731 days (± 642 days) from renal biopsy as compared to 25/42 patients with HIVAN who required initiation of renal replacement therapy at an average time of 254 days (± 331 days) from renal biopsy ($P = 0.0003$ comparing time with initiation of renal replacement therapy).²⁵ The prolonged renal survival of patients with HIVAN as compared to earlier reports is arguably related to a number of factors including the use of ART and HAART.

In a retrospective review of 64 HIV-infected patients in Baragwanath, Africa, who underwent renal biopsy, the investigator could not distinguish a difference in renal or overall survival between patients with HIVAN and those with other pathologic findings. In the 25 South African patients with biopsy proven HIVAN at 28 weeks of follow-up, 9/25 (36%) died, 8/25 (32%) were lost to follow-up and the remaining 8/25 (32%) were free of dialysis. In 27 HIV-infected patients with other pathologic diagnosis at an average of 10–30 weeks of follow-up, 15/27 (55%) died, 3/27 (11%) were lost to follow-up, and the remaining 9/27 (33%) were free of dialysis.²⁷ Further research to understand the effect of international differences in populations is required to reconcile these conflicting results.

In the USA, ESRD patients with HIVAN have decreased overall survival when compared with other patients with ESRD. In an analysis of 3374 incident patients with ESRD in 1996, patients with a diagnosis of HIVAN ($n = 36$) had a 4.74-fold increased risk of mortality after adjusting for clinical variables other than HIV. The 1-year survival in this cohort of patients with HIVAN was 53%, however more recent data from 1999–2000 report a 1-year survival of up to 74% in dialysis patients with HIVAN which may reflect the benefit of HAART in this patient population.⁴² Unfortunately, dialysis is not always available for HIV-infected patients with renal failure; thus, in the absence of other life-threatening illnesses, life expectancy can be drastically shortened.

Conclusion

Kidney disease in HIV-infected patients is common, and HIVAN is the leading cause of CKD, particularly in patients of African descent. Patients with HIVAN are often diagnosed late in the course of their HIV illness and present with proteinuria and renal insufficiency. Without treatment, renal survival is only a few months. However, small clinical trials and epidemiologic data strongly suggest a benefit of HAART therapy in the treatment of HIVAN.^{25,28,29} In addition, similar studies have noted ACE-I therapy is associated with improved renal survival.^{7,8,27,40} Based on the best available data, if ACE-I and HAART are available, they should be utilized to try to prolong renal survival in these patients. As countries become more developed and HAART becomes more widely available through the World Health Organization AIDS initiative, patients can be anticipated to live longer and an increasing number of HIV-infected patients will have advanced kidney failure. Decisions regarding renal replacement therapy including transplantation are going to become significant issues as cost and resources are limited in a significant number of geographic areas.

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