

HIV/AIDS—DOMINANT PLAYER IN CHRONIC KIDNEY DISEASE

HIV-associated nephropathy (HIVAN) is now the third leading cause of end-stage renal disease (ESRD) in African Americans between the ages of 20 and 64 years. Statistics in the United States estimate the incidence of HIVAN to be between 3.5% and 12%. The estimated number of those living with HIV worldwide is 37.4 million, with 26 million in Africa. If the US data for HIVAN were extrapolated to Africa, between 0.9 and 3.1 million people would be predicted to have HIVAN. These figures predict an unprecedented (and possibly underestimated) burden of chronic kidney disease (CKD) in Africa, especially if we take into account the socioeconomic associations with CKD for the African continent. This potentially large number of patients poses daunting logistic, financial, and ethical issues for physicians and nephrologists practicing in Africa. Preventing chronic kidney disease due to HIV in Africa should become a major priority. This would enable early detection and treatment of HIVAN in order to prevent or delay progression to ESRD. As HIV infection is a risk factor for the development of CKD, the HIV Medicine Association of the Infectious Diseases Society of America recommends screening for CKD in HIV-infected patients; screening tests should be similar to those for patients with diabetes mellitus to detect early renal involvement. Preventive strategies need to be determined; prospective studies including antiretroviral therapy, angiotensin-converting enzyme inhibitors, and other therapeutic agents are required. (*Ethn Dis.* 2006;16[suppl 2]:S2-56–S2-60)

Key Words: HIV/AIDS, HIV-Associated Nephropathy (HIVAN), Chronic Kidney Disease (CKD), End Stage Renal Disease (ESRD), Preventive Strategies

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INTRODUCTION

This article reviews the impact of HIV/AIDS on chronic kidney disease (CKD) and the therapeutic modalities for HIV-associated nephropathy (HIVAN). Early diagnosis of CKD and treatment strategies to prevent or delay progression to end-stage renal disease (ESRD) in HIV infection should be a major priority.

The first sign of the HIV pandemic appeared in June 1981 when the Centers for Disease Control (CDC) reported 5 cases of *Pneumocystis carinii* pneumonia. Reports of AIDS in Africa started emerging in 1984, and 20 years later, data released by the Joint United Nations Programme on HIV and AIDS (UNAIDS) reveal the extent of the global burden of HIV (Fig. 1).¹ The estimated number of those living with HIV worldwide is 37.4 million, with 26 million in Africa. Sub-Saharan Africa has slightly >10% of the world's population but is home to >60% of those living with HIV. In Sub-Saharan Africa, an estimated 3.1 million people became newly infected with HIV in 2004, while 2.3 million died of AIDS.¹

HIV INFECTION AND THE KIDNEY

An association between HIV and renal disease was first reported in 1984 in New York City and Miami.^{2,3} These groups described HIV-positive individuals with proteinuria and progression to ESRD within 8–16 weeks; mortality approached 100% within 6 months of diagnosis. The existence of a specific HIVAN was subsequently confirmed as a distinct pathological entity. HIV-associated nephropathy (HIVAN) is

the most common lesion affecting the kidney in numerous biopsy series and was initially thought to be associated with AIDS. This lesion can occur at any stage of HIV infection, even prior to antibody seroconversion.⁴ Studies demonstrate a marked racial predilection for the development of HIVAN, as >90% of patients are Black, with a male predominance in both adults and children. The reasons for this racial predilection are as yet unexplained. Some have postulated a genetic predisposition, but candidate genes have not been identified.⁵ One study has shown a strong familial clustering of ESRD caused by hypertension or diabetes among Blacks commencing renal replacement therapy (RRT) because of HIVAN.⁶ In addition, HIVAN appears to follow a more severe clinical course in Black patients with a higher prevalence of severe glomerular lesions, such as focal glomerulosclerosis.⁷

In addition to the specific histologic lesion of HIVAN, a wide clinical and pathologic spectrum of acute and chronic renal disease occurs with HIV infection. For the purpose of this review, we shall not consider HIV and acute renal failure. Regarding CKD and HIV, glomerular involvement with HIV can be divided into four categories (Table 1). Chronic kidney disease in HIV infection, apart from being due to the direct or indirect effects of HIV and/or its treatment, may be compounded by common co-morbid conditions like diabetes mellitus and hypertension.

HIV INFECTION AND CHRONIC KIDNEY DISEASE

In the United States, African Americans develop hypertension-associated

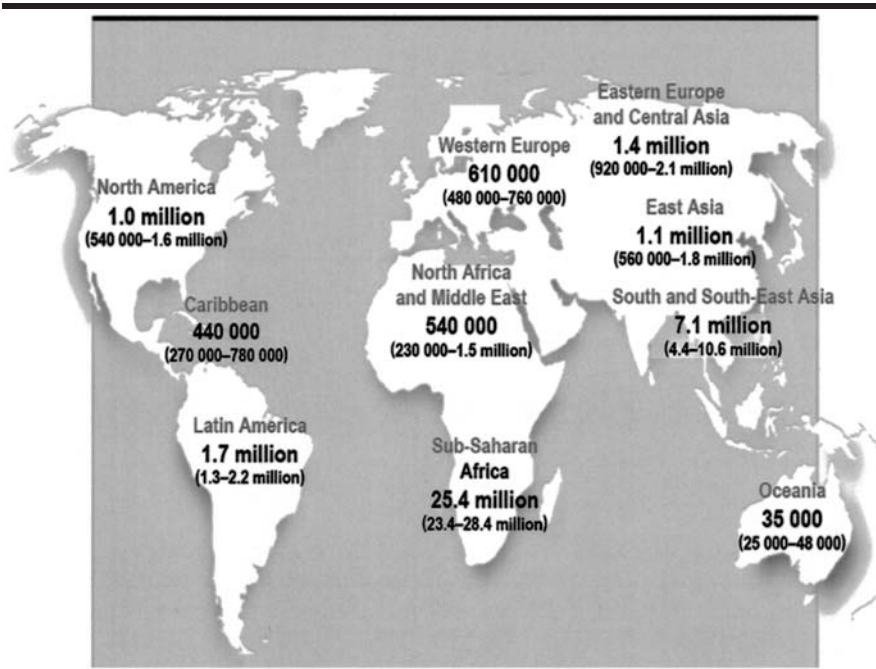


Fig 1. Adults and children estimated to be living with HIV at the end of 2004¹

ESRD seven times more often and all-cause ESRD four times more often than White individuals. Having a close relative with ESRD gives an African American an eight-fold increased risk of developing ESRD compared with Caucasians, who have an increased risk of 2.7-fold.⁸ African Americans in the United States have the highest rates of ESRD, 988 per million population (pmp). In the United Kingdom, the rates of ESRD in the African Caribbean and Indian populations are 163 and 221 pmp respectively, as compared with

58 pmp for Caucasians.⁹ In both the United States and United Kingdom, the most common causes of ESRD in these populations are diabetes mellitus and hypertension, with presentation of ESRD at a relatively earlier age. These groups of patients with ESRD are often of lower socioeconomic status, have low levels of educational attainment, reside in low-income areas, and have more limited access to health care. Unfortunately, statistical data on ESRD in African countries are scarce. Access to RRT for patients with ESRD in African

countries varies widely and is a gross underestimate of the true incidence of ESRD. Dialysis treatment rates (pmp) in the following countries reveal the marked variation within the African continent: Algeria 78.5, Egypt 129.3, Libya 30, Morocco 55.6, Tunisia 186.5, South Africa 99.¹⁰

In the 1980s, HIVAN was an uncommon cause of ESRD in the United States, in part because of the high mortality in infected persons and the absence of antiretroviral therapy (ART). With improved survival after the introduction of ART, HIVAN became the most rapidly increasing cause of ESRD in the United States by 1990. In 1995, although the decline in mortality from AIDS was dramatic, the number of new cases of ESRD due to HIVAN did not decline. Instead, mortality data have shown a steady plateau in the African American population, which is regarded as the population at highest risk for HIVAN in the United States (Figure 2). HIVAN is now the third leading cause of ESRD in African Americans between the ages of 20 and 64 years, preceded only by diabetes and hypertension. Statistics in the United States estimate the incidence of HIVAN to be 3.5%–12%.¹¹

Regarding the impact of HIV on the increasing global burden of CKD, no published data from African countries exist. With increasing accessibility to ART in Africa, one may postulate that the epidemiologic pattern of HIVAN that has evolved in the United States over the last 20 years may predict events in Africa. Hypothetically, if the US data for HIVAN were extrapolated to Africa, 0.9–3.1 million people would be predicted to have HIVAN. These figures predict an unprecedented (and possibly underestimated) burden of CKD in Africa, especially if socioeconomic consequences of CKD are taken into account. This potentially large number of patients poses daunting logistic, financial, and ethical issues for physicians and nephrologists practicing in

Table 1. Classification of glomerular disease in HIV

1. "Classic" HIV-associated nephropathy
2. HIV-immune complex-mediated disease (often have hepatitis C co-infection)
 - Mesangial proliferative
 - Membranoproliferative (type I, III)
 - Lupus-like
 - Exudative-proliferative and crescentic IgA
 - Membranous
3. Various glomerulonephritides (heterogeneous group with different etiologies)
 - Minimal change
 - Immunotactoid
 - Amyloidosis
4. Thrombotic microangiopathy/hemolytic uremic syndrome

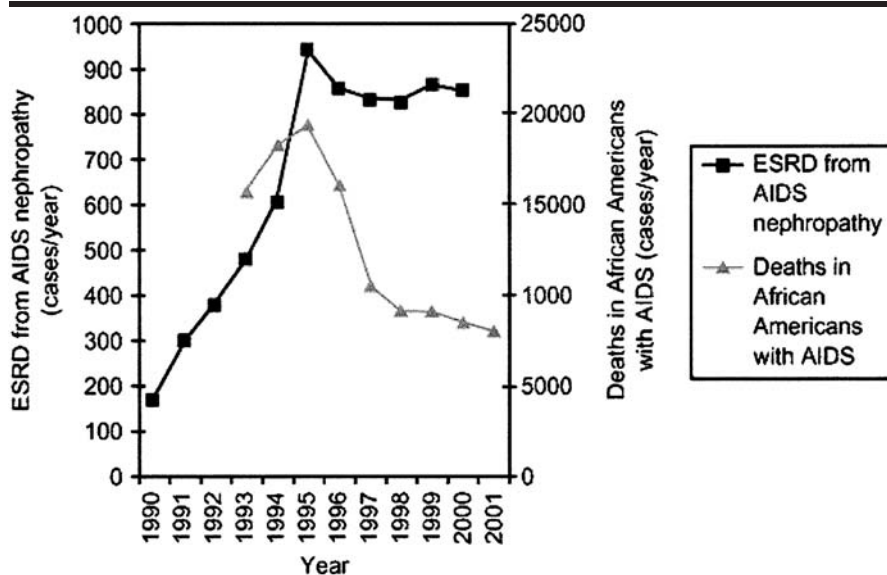


Fig 2. End-stage renal disease due to AIDS nephropathy and deaths in African Americans with AIDS¹¹

Africa. Emphasis on the prevention of CKD due to HIV in Africa should become a major priority.

TREATMENT OF HIVAN

No prospective, randomized, controlled studies with any form of therapy for HIVAN have taken place to date. Drugs that have been used in the treatment of HIVAN include corticosteroids, angiotensin-converting enzyme inhibitors (ACEI), cyclosporine, and highly active ART (HAART). Treatment options for patients who have reached ESRD include hemodialysis, peritoneal dialysis, and renal transplantation.

Corticosteroids

Several uncontrolled studies have been conducted to assess the benefit of corticosteroids in patients with HIVAN.^{12,13} Patients with renal insufficiency and heavy proteinuria due to HIVAN who were treated with prednisone experienced an improvement in renal function and reduction of proteinuria. However, the rate of relapse after steroid withdrawal was high, and

several patients developed serious opportunistic infections. Other case reports showed only short-term beneficial effects of corticosteroids in patients with HIVAN. Thus, the role and efficacy of corticosteroids in HIVAN remains unclear. Further prospective, randomized, controlled studies are warranted.

ACEI

Angiotensin-converting enzyme inhibitors (ACEI) have been shown to be effective in reducing proteinuria and progression of renal disease in patients with diabetic and nondiabetic renal disease. In case-control studies of HIVAN,^{14,15} an increase in renal survival was associated with the use of ACEI with significantly lower levels of serum creatinine and proteinuria than those who were not on ACEI treatment. Several patients in the study were on nucleoside reverse-transcriptase inhibitor monotherapy.¹⁵ A prospective study to determine the long-term effects of ACEI on renal survival in HIVAN patients showed a median renal survival of treated patients of 479.5 days, with only one patient progressing to ESRD, compared to a median renal survival of 146.5 days in untreated patients who all

developed ESRD.¹⁶ Further prospective studies are needed to determine the optimal role of ACEI therapy in patients with HIVAN.

Cyclosporine

The effectiveness of cyclosporine in inducing remission of proteinuria was reported in children with HIVAN.¹⁷ However, larger studies and studies in adults are required to evaluate its usefulness in HIVAN.

HAART

ART was first used in a patient with HIVAN in 1989, with remission of nephrotic syndrome for 11 months before relapse. Various investigators have subsequently evaluated the use of ART for the treatment of HIVAN. Patients treated with zidovudine who were compliant with treatment did not have worsening of renal function; however, noncompliance with zidovudine treatment resulted in ESRD.¹⁸

The effectiveness of ART in HIVAN patients has also been documented by other investigators as isolated case reports. Two patients with biopsy-proven HIVAN who had renal failure requiring hemodialysis were treated with HAART with dramatic improvement, resulting in discontinuation of dialysis. Renal biopsies done before and after HAART showed resolution of the histologic features of HIVAN in these patients. Patients with biopsy-proven HIVAN who presented with heavy proteinuria and renal impairment had improvement in renal function and proteinuria after treatment with HAART and ACEI. The contribution of individual drugs was unclear, as a combination of HAART and ACEI was used.

With the advent of ART and improved survival of patients with HIV infection, HIVAN has become the third most common cause of ESRD among young African Americans. Prospective studies evaluating the efficacy of HAART in preventing or delaying disease progression are needed.

Renal Replacement Therapy

Although rates of HIV-related opportunistic infections and diseases decreased dramatically from 1995 to 1999, coincident with the introduction of HAART, rates of HIVAN remain stable. Without any treatment, HIVAN rapidly progresses to ESRD.

Dialysis

The prevalence of HIV infection in various dialysis centers is variable and is dependent on the demographics of the population. The US Renal Data System (USRDS) report for 2001 showed that 6179 patients with HIV infection had received RRT in the United States before May 2000. In France, a much lower prevalence of 0.36% was reported in a survey of 260 dialysis facilities serving 22,707 patients. In an Italian survey of 27,000 patients, a prevalence of 0.13% was found.

During hemodialysis, various cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor- α , are released. These cytokines increase viral replication in vitro.¹⁹ Therefore, HIV-infected patients on hemodialysis appear to be at a theoretical risk of increased morbidity. However in the HAART era, the survival of hemodialysis patients on HAART has been better than that of patients on less aggressive therapy (one or two antiretroviral medications); the plasma viral load was also significantly lower in patients who were on HAART therapy.

Data on the role of peritoneal dialysis in the treatment of HIV-infected patients with ESRD are limited. Cumulative technique survival of 43% and 27% and patient survival of 58% and 54% at one and two years, respectively, was reported in HIV-infected patients with ESRD on continuous ambulatory peritoneal dialysis (CAPD). Higher rates of peritonitis (3.9 episodes/outpatient CAPD year) occurred, compared to non-HIV-infected patients (1.5 episodes/CAPD year), especially for *Pseudomonas* and

fungal infections. Some investigators have also suggested that increased protein losses with CAPD in these patients may lead to increased illness and death. Other studies found no difference in survival between patients on hemodialysis and peritoneal dialysis in the USRDS database, when adjusted for confounding variables.²⁰ The dialysis modality is not an established factor in predicting survival among HIV-infected patients with ESRD.

Transplantation

Before the introduction of HAART, an analysis of the USRDS showed that HIV-infected recipients were at increased risk of death and graft loss compared with uninfected recipients of cadaver kidneys. As the survival of HIV-infected patients has improved remarkably in the HAART era, renal transplantation as a form of RRT is now being offered to HIV-infected patients with ESRD in some centers. Rejection occurred in 5 of 10 kidney transplant recipients but did not occur in any of the four liver transplant recipients who were HIV-infected. No evidence of significant HIV progression and no adverse effect of HIV on allograft function were seen.²¹ A retrospective study of 27,851 kidney transplant recipients with a positive HIV serologic test result in the United States found that 47 patients (0.2%) were HIV-infected. All patients in the study were on HAART, had CD4 counts >200 were free from opportunistic infections, and had undetectable viral loads. HIV-infected recipients had improved survival compared with HIV-uninfected recipients, although it was not statistically significant in the adjusted analysis.²² However, this study had limitations. Healthier recipients were selected for transplantation; the use of HAART therapy or the clinical stage and other manifestations of disease in HIV-infected patients could not be determined; none of the HIV-infected recipients had HIVAN; and White patients were over-

represented. Although no broad consensus about improved post-transplantation survival for HIV-infected recipients in the modern era should be drawn from this study, HIV-infected patients appear to enjoy successful outcomes after transplantation.

Other factors may improve post-transplantation survival as well. The commonly used immunosuppressive agents have effects that favor HIV-infected recipients. Sirolimus inhibits HIV replication at the transcriptional level and down-regulates the CCR5 receptor. Mycophenolate mofetil has inhibitory effects on HIV, works synergistically with many antiretroviral agents, and has been used to treat resistant strains of HIV. Certain calcineurin inhibitors such as cyclosporine have anti-HIV activity. However, HAART interacts with most immunosuppressive therapies; therefore, careful monitoring and dose adjustment is crucial.

In conclusion, analysis of USRDS transplant populations indicates that kidney transplantation in HIV-infected patients is plausible and ongoing. However, the appropriate use of immunosuppression and HAART still awaits the results of properly designed prospective clinical trials.

PREVENTION OF CHRONIC KIDNEY DISEASE IN HIVAN

As HIV infection is a risk factor for the development of CKD, the recommendations of the HIV Medicine Association of the Infectious Diseases Society of America suggesting screening for CKD in HIV-infected patients should be implemented;²³ screening tests should be similar to those for patients with diabetes mellitus to detect early renal involvement. Early detection and treatment of HIVAN to prevent or delay progression to ESRD is crucial.

Preventive strategies need to be determined; prospective studies includ-

ing ART, ACEI, and other therapeutic agents are required as a matter of urgency for developing countries in Africa, where the high burden of HIV disease coexists in stark contrast with limited healthcare resources.

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Data analysis interpretation: Naicker, Han
Manuscript draft: Naicker, Han, Fabian
Acquisition of funding: Naicker
Administrative, technical, or material assistance: Naicker, Han, Fabian
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