# HIV-Associated Nephropathy (HIVAN): Hope rising!

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## ABSTRACT

HIVAN, the commonest renal complication of HIV/AIDS is most prevalent among blacks of African descent. Before the advent of HAART, HIVAN was inevitably fatal within a short period. However, with the introduction of highly active anti-retroviral therapy (HAART), the prognosis of HIVAN has dramatically improved. Angiotensin-converting enzyme (ACE) inhibitors and corticosteroids have also improved the treatment outcome of HIVAN. Patients with HIVAN are now being offered renal replacement therapy (dialysis and transplantation) more readily than in the past and new therapeutic strategies against HIVAN are being devised. The racial predilection of HIVAN however, warrants further investigation.

## INTRODUCTION

HIVAN, formerly known as AIDS-associated nephropathy, was first described in 1984 [1] and it comprises a clinicopathological pentad (Table 1). HIVAN is the single most common and most well defined renal complication of human immunodeficiency virus (HIV) infection in black persons of African origin [2, 3, 4].

**Table 1:** Pentad of clinicopathological diagnosis of HIVAN

1. Significant proteinuria
2. Azotaemia with renal insufficiency
3. Normal blood pressure
4. Normal or large and highly echogenic kidneys on ultrasound
5. Collapsing form of focal segmental glomerulosclerosis on renal histology

At the beginning of the HIV/AIDS epidemic, and before the advent of HAART, HIVAN was inevitably fatal; progressing inexorably to death within a few months of the diagnosis [3]. The management of HIVAN then, was largely supportive. The recent advances in the knowledge of the epidemiology, pathogenesis and the management of HIVAN give hope for the containment of this disease with enhanced quality of life and longevity of the patients. The current advances are discussed further in this article.

## Epidemiology

HIVAN is the leading cause of chronic kidney disease (CKD) in HIV-1 seropositive patients with a reported prevalence of 5-10% [5]. No case of HIV-2 associated nephropathy without HIV-1 co-infection has thus far been reported.

Black patients are particularly vulnerable to HIVAN and more males than females. HIVAN was reported by the United States Renal Data Service (USRDS) as the third commonest cause of end-stage renal disease (ESRD) in African Americans between the ages of 20 and 64 years (after diabetes and hypertension) [6]. Unfortunately, the incidence of HIVAN in Africa with the largest concentration of blacks in the world is largely unknown, because of the paucity of published data on HIVAN cases.

HIVAN usually occurs late in the course of HIV infection [7], though cases of early onset occur. Many patients die relatively early of opportunistic infections in Africa probably before HIVAN becomes clinically evident. The incidence of renal diseases reported by USRDS [6], increased when mortality from opportunistic infections decreased among patients with AIDS. Similarly, the pool of patients in Africa at risk of developing HIVAN is expected to increase dramatically with improved survival from opportunistic infections.

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Racial predilection for HIVAN may be genetically determined. Blacks are more prone to kidney diseases in general than other races. Almost a quarter of patients with HIVAN volunteer a family history of renal disease and black patients with HIVAN are more than five times likely to have a

infection in their renal epithelium. The infection can remain transcriptionally active albeit, at low levels.

It is not yet certain whether the renal reservoir contributes to rebound of plasma viral loads in patients who had previously undetectable viral load with antiviral drugs. In addition, the renal reservoir

**Table 2:** Spectrum of renal diseases associate with HIV infection

| Acute Renal Failure | Chronic Renal Failure |
|---|---|
| *Pre-renal* | |
| • Hypovolemia | • Focal Segmental Glomerulosclerosis (Classic HIVAN) |
| • Sepsis | |
| • Hypoalbuminaemia | |
| | • Immune Complex Disease |
| *Intrinsic Renal* | (a) IgA Nephropathy |
| • Acute Tubular Necrosis | (b) Mixed sclerotic immune complex nephropathy |
| • Allergic Interstitial Nephritis | |
| • Crystal Deposition | (c) Proliferative glomerulonephritis |
| *Post Renal* | • Microangiopathies |
| • Extrinsic Obstruction | (a) Hemolytic Uremic Syndrome |
| • Intrinsic Obstruction | (b) Thrombotic thrombocytopenic purpura |

first-degree or second-degree relative with ESRD than are black patients without renal disease[8]. Unfortunately, no candidate gene has been definitely implicated.

## Pathogenesis of HIVAN
Many mechanisms have been suggested to explain the pathogenesis of HIVAN but increasing evidence now supports a direct role of HIV in its pathogenesis. HIV-1 infection of renal parenchymal cells in humans was demonstrated by Bruggeman *et al* in 2000 [9]. The infection of the epithelial cells of the glomerulus and tubules by HIV-1 overlaps the pattern of histologic disease in HIVAN, supporting a role for direct infection of the kidneys in the pathogenesis of HIVAN.

The kidneys may also be an important reservoir for HIV-1. The virus has been detected by both RNA *in situ* hybridization and DNA *in situ* Polymerase Chain Reaction (PCR) in some patients who had undetectable viral load in peripheral blood samples [9, 10]. This has very important implications for HIV-1 seropositive patients who despite an optimal response in viraemia to HAART and even clinical remission of HIVAN may have persistent HIV

of actively replicating HIV-1 may support the evolution of viral strains that differ significantly from virus present in the patient's blood. The virus strains may be drug-resistant and may not be susceptible to currently available anti-retroviral drugs.

The mechanism by which HIV-1 gains entry into renal epithelial cells is not entirely known. The receptor for HIV-1 (CD4) and the major co-receptors (CCR5, CXCR4) are not expressed in most normal renal epithelial cells. Direct infection of kidney cells resulting in proliferation and cellular apoptosis with the activation of cell-mediated immunity in patients who are genetically predisposed is likely to be the basis of HIVAN.

## Histopathology of HIVAN
Renal biopsy is the gold standard for the diagnosis of HIVAN. HIV is associated with a wide spectrum of renal diseases [Table 2]. However, HIVAN is the most common finding on renal histology in HIV-1 seropositive black patients with chronic kidney disease [1, 5]. Therefore, all HIV-infected patients with urine protein excretion in excess of one gram per day should have renal biopsy.
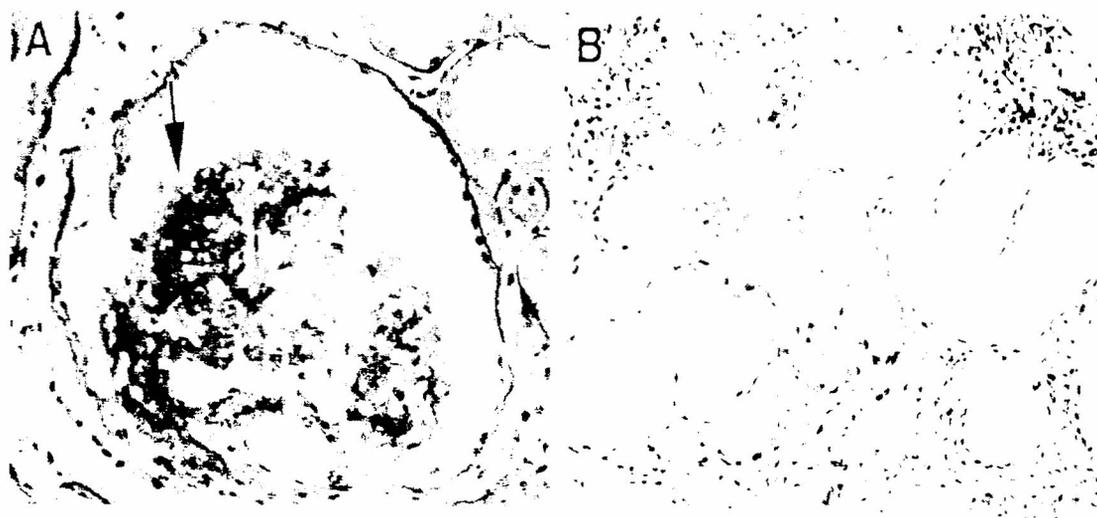
**Fig. 1:** Typical histopathologic findings in HIV-associated nephropathy (HIVAN).

**A:** Periodic acid-Schiff (PAS) staining showing focal segmental glomerulosclerosis (FSGS) with segmental collapse. Podocyte hypertrophy and hyperplasia are obvious overlying the area of collapse (arrow).

**B:** Tubular microcystic dilatations filled with proteinaceous material and interstitial lymphocytic infiltration and fibrosis in HIVAN. Hematoxylin and eosin.

*Adapted from Ross MJ, Klotman PE. Recent Progress in HIV-Associated Nephropathy. J Am Soc Nephrol 2002; 13:2997-3004*



**Fig. 1C:** Histopathologic characteristics of HIV-associated nephropathy in humans. Ultrastructural analysis shows a collapsed glomerular capillary with wrinkling of the glomerular basement membrane. Podocytes (P) have lost foot processes, and their cell body sits directly on the glomerular basement membrane and new matrix deposition (asterisks).
*Adapted from: Kimmel, PL, Barisoni L, Kopp JB. Ann Intern Med 2003; 139:214-226*

Histologic, immunologic and ultrastructural features of renal tissue from a biopsy specimen in HIVAN are distinctive. A collapsing form of focal segmental glomerulosclerosis on light microscopy is typical [Figure 1A] but not pathognomonic of HIVAN. Collapsing glomerulopathy has also been described in certain other conditions such as systemic autoimmune disorders (e.g. systemic lupus erythematosus, adult Still's disease), viral infections (e.g. parvovirus B19 infection), and effects of drugs like interferon and pamidronate [11, 12, 13, 14, 15, 16].

Light microscopy shows collapsed glomerular capillary tuft which is either segmentally or globally sclerosed. There is hypertrophy of visceral epithelial cells (podocytes) which form a pseudocrescent in the Bowman's space (Fig 1A). Tubulo-interstitial disease such as tubular degeneration is also common. Tubular atrophy as in Figure 1B, is associated with enlargement of the kidneys in patients with HIVAN. There is interstitial expansion by edema, fibrosis and markedly dilated tubules filled with proteinaceous casts.

Immunofluorescence microscopy demonstrates deposits of immunoglobulin (Ig) G, IgM, C3. Occasionally, there is positive staining for albumin in the mesangial and sclerotic areas. Typical features on electron microscopy include wrinkling of the

basement membranes, epithelial cell proliferation, and focal foot process effacement [Figure 1C].

Tubuloreticular inclusions which consist of ribonucleoprotein and membrane within the glomerular and arterial endothelial cells, interstitial leucocytes and capillary are highly suggestive of HIVAN [17]. The synthesis of the tubuloreticular inclusions is stimulated by alpha-interferon; however, these tubuloreticular inclusions are less commonly seen these days perhaps, due to the efficiency of HAART in reducing plasma concentrations of interferon.

## Clinical Manifestations

The typical picture of HIVAN clinically, is of progressive proteinuria usually within the nephrotic range (>3g/24 hours) and rapidly deteriorating renal function, if untreated. Despite the nephrotic range proteinuria and hypoalbuminaemia, edema is strangely uncommon [7]. The absence of edema may be due to the salt-losing propensity and high oncotic pressure contributed by marked hyperglobulinemia in patients with HIVAN. Hypertension is unusual in these patients probably also due to the salt wasting tendency of HIVAN [18]. There may or may not be associated hyperlipidaemia. Some electrolyte abnormalities such as hyponatremia and hyperkalemia occur in HIVAN patients and may result from an increase in total body water from the nephrotic syndrome, syndrome of inappropriate secretion of antidiuretic hormone [SIADH] or hyporeninemic hypoaldosteronism, respectively.

Serum complement levels are normal. Urinalysis reveals proteinuria, microscopic hematuria sometimes, and hyaline casts but no cellular casts. The kidneys on ultrasound are highly echogenic and normal-to-large despite progression to ESRD. A highly dense renal parenchyma on computerized tomography (CT) scan without contrast media has been reported in HIVAN [19].

The prognosis of HIVAN is worse with higher degrees of proteinuria, severe renal impairment, low CD4 lymphocyte count, high viral load, and severe anemia.

## Management of HIVAN

There was a sense of therapeutic nihilism in the pre-HAART era over the management of HIVAN because of the dismal prognosis. The management of HIVAN should involve collaboration between a nephrologist and an HIV specialist. HAART has

however revolutionized the treatment of HIVAN and significantly improved the prognosis [18, 20, 21]. There are reports of dramatic improvement of dialysis-dependent patients with biopsy-proven HIVAN who after the commencement of aggressive management with HAART, no longer required dialysis [20, 21]. Indeed, it has been estimated that HAART since its introduction in 1995, has retarded the progression of HIV-associated renal diseases including HIVAN to ESRD by 38% [22].

Though no formal management guidelines exist currently, all patients with HIVAN should be treated with HAART as soon as the diagnosis is made except in cases where there are compelling contraindications. Strict adherence to HAART treatment by the patients is required to obtain and sustain improvement.

Doses of nucleoside analogues should be adjusted according to renal function because of their potential toxicity. However, protease inhibitors, non-nucleoside reverse transcriptase inhibitors which are metabolized by the liver are relatively safe while Enfuvirtide (Fuzeon®) which belongs to a new class of fusion inhibitors has no known adverse renal effects. Nephrotoxic drugs such as Tenofovir should be avoided.

ACE inhibition has been found to be effective at preserving renal function in patients with biopsy-proven HIVAN [23]. ACE inhibitors are most beneficial when initiated as soon as the diagnosis of HIVAN is established. Patients receiving ACE inhibitors should be monitored for hyperkalemia, progressive azotaemia, or volume depletion. In black patients who may not respond adequately to ACE inhibitors, non-potassium sparing diuretics may be added with caution and where appropriate.

The probable mechanisms of ACE inhibitors' actions include changes in renal hemodynamics resulting in the reduction of transglomerular passage of serum proteins, an anti-proliferative effect mediated by the inhibition of transforming growth factor- beta (TGF-â), or interference with ACE-mediated pathways involved in antigen processing and presentation between macrophages and T-lymphocytes [24]. The role of Angiotensin II receptor blockers in human HIVAN has not yet been established but may be similar to the renoprotective effect of ACE inhibitors.

Improved renal function and reduction of interstitial inflammation but not overall survival have been reported in patients treated with corticosteroids [25]. Therapy with corticosteroids may however,

increase the incidence of sepsis and opportunistic infections. Prednisone should be used in association with HAART in treatment of HIVAN in patients with aggressive renal disease and no active infectious complications. Cyclosporine has limited use in the management of HIVAN [26].

Renal support for patients who present with severe renal failure may still be necessary before HAART takes effect. Survival rates are similar between patients on hemodialysis and peritoneal dialysis though the incidence of peritonitis due to fungi and pseudomonas may be more common in HIVAN patients treated with peritoneal dialysis. The choice of dialysis should however, be based on patient preference, resources and the treatment centre.

The vastly improved prognosis of HIV-1 infected patients treated with HAART, has led to kidney transplantation being increasingly offered to patients with ESRD due to HIVAN. Conditions for transplant include compliant and stable patients with no active opportunistic infections and who have undetectable viral load and a CD4 count more than 300 cells/$\mu$L. The outcome of graft and patient survival is said to be comparable to other high-risk populations receiving kidney transplant.

## Future Therapeutic Strategies
Experimental studies involving the use of cyclin–dependent kinase inhibitor and blockade of nuclear factor kappa beta (a cell signaling pathway), in mice have reported decreased renal visceral epithelial cell proliferation and increased longevity respectively in HIV-infected mice [27, 28]. Further studies are required to define their role in humans with HIVAN.

## CONCLUSION
Recent advances in the understanding of HIVAN as a distinct clinical entity and the obvious benefit of HAART in the management of this disease bring hope to the legion of people suffering from HIVAN who before now were hopeless.

It is gratifying that HAART is now more readily available and accessible to patients even in resource-poor settings such as exist in Sub-Saharan Africa. More studies and data from Africa with regard to HIVAN are required. The characteristics of HIVAN and the response to therapy in African-Americans in whom most studies have been done may not necessarily be the same in blacks of Sub-Saharan Africa because of the influence of environment, life-styles, et cetera.

The factors that predispose blacks to HIVAN need to be explored in future studies while optimum strategy for the management of HIVAN should be established. The future however, looks bright for patients with HIVAN.

## REFERENCES
1. Gardenswartz MH, Lerner CW, Seligson GR, Zabetakis PM, Rotterdam H, Tapper ML, Michelis MF and Bruno MS: Renal disease in patients with AIDS: a clinicopathological study. Clin Nephrol 1984; 21: 197-204.

2. Cantor ES, Kimmel PL and Bosch JP: Effect of race on expression of acquired immunodeficiency syndrome-associated nephropathy. Arch Intern Med 1991; 151: 125-128.

3. Abbot KC, Hypolite I, Welch PG and Agodoa LY: Human immunodeficiency virus/acquired immune deficiency syndrome-associated nephropathy at end-stage renal disease in the United States: patient characteristics and survival in the pre-highly active antiretroviral therapy era. J Nephrol 2001 Sep-Oct; 14: 377-383.

4. Szczech LA, Gupta SK, Habash R, Guasch A, Kalayjian R, Appel R, Fields TA, Svetkey LP, Flanagan KH, Klotman PE and Winston JA: The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. Kidney Int 2004 Sept; 66(3):1145-1152.

5. D'Agati V and Appel GB. HIV infection and the kidney. J Am Soc Nephrol. 1997; 8:138-152.

6. US Renal Data System (USRDS): USRDS 2001 Annual Data Report. Bethesda MD. The National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases, 2001.

7. Winston JA, Klotman ME and Klotman PE. HIV-associated nephropathy is a late, not early, manifestation of HIV-1 infection. Kidney Int 1999 Mar; 55(3): 1036-1040.

8. Freedman BI, Soucie JM, Stone SM and Pegram S: Familial clustering of end-

stage renal disease in blacks with HIV-associated nephropathy. Am J Kidney Dis 1999; 34:254-258.

9. Bruggeman LA, Ross MD, Tanji N, Cara A, Dikman S, Gordon RE, Burns GC, D'Agati VD, Winston JA, Klotman ME and Klotman PE: Renal epithelium is a previously unrecognized site of HIV-1 infection. J Am Soc Nephrol 2000 Nov; 11 (11): 2079-2087.

10. Winston JA, Bruggeman LA, Ross MD, Jacobson J, Ross L, D'Agati VD, Klotman PE and Klotman ME: Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med 2001; 344:1979-1984.

11. Amoura Z, Georgin-Lavialle S, Haroche J, Merrien D, Brocheriou I, Beaufils H and Piette J-C. Collapsing glomerulopathy in systemic autoimmune disorders: a case occurring in the course of full blown systemic lupus erythematosus (letter). Ann Rheumatic Dis 2006; 65: 277-278

12. Kumar S, Sheaff M and Yaqoob M. Collapsing glomerulopathy in adult Still's disease. Am J Kidney Dis 2004; 43: 4-10

13. Tanawattanacharoen S, Falk RJ, Jennette JC and Kopp JB. Parvovirus B 19 in kidney tissue of patients with focal segmental glomerulosclerosis. Am J Kidney Dis 2000; 35:1166-1174.

14. Hammar, SP, Luu, JY, Bockus, DE, Remington, FL, Luu, JW, Friedman, S and Bean, MA: Induction of tubuloreticular structures in cultured human endothelial cells by recombinant interferon alpha and beta. Ultrastruct Pathol 1992 16:211–218.

15. Laurinavicius A, Hurwitz S and Rennke HG. Collapsing glomerulopathy in HIV and non-HIV patients: A clinicopathological and follow-up study. Kidney Int 1999; 56:2203-2213.

16. Kunin M, Kopolovic J, Avigdor A, Holtzman EJ. Collapsing glomerulopathy induced by long-term treatment with standard-dose pamidronate in a myeloma patient (case report). Nephrol Dial Transplant 2004; 19:723-726.

17. D'Agati, Appel GB. Renal pathology of human immunodeficiency virus infection. Semin Nephrol 1998; 18:406-421.

18. Klotman PE: HIV-associated nephropathy. Kidney Int 1999 Sep; 56(3):1161-76.

19. Hulot J-S, Beaufils H and Mercadal L. Spontaneous renal CT-scan hyperdensity of an HIV-associated nephropathy. Nephrol Dial Transplant 2003; 18: 2678-2679.

20. Kirchner JT: Resolution of renal failure after initiation of HAART: 3cases and a discussion of the literature. AIDS Read 2002 Mar; 12(3): 103-105, 110-112.

21. Scheurer D: Rapid reversal of renal failure after initiation of HAART: a case report. AIDS Read 2004 Aug; 14(8): 443-447.

22. Schwartz EJ, Szczech LA, Ross MJ, Klotman ME, Winston JA and Klotman PE. Highly Active Antiretroviral Therapy and the Epidemic of HIV+ End-Stage Renal Disease. J Am Soc Nephrol 2005; 16: 2412-2420.

23. Wei A, Burns GC, Williams BA, Mohammed NB, Visintainer P and Sivak SL. Long-term survival in HIV-associated nephropathy with angiotensin-converting enzyme inhibition. Kidney Int 2003 Oct; 64(4):1462-1471.

24. Odaka C and Mizuochi T. Angiotensin-converting enzyme inhibitor captopril prevents activation-induced apoptosis by interfering with T cell activation signals. Clin Exp Immunol 2000; 121:515-522

25. Eustace JA, Nuermberger E, Choi M, Scheel PJ, Jr, Moore R and Briggs WA: Cohort study of the treatment of severe HIV-associated nephropathy with corticosteroids. Kidney Int 2000; 58: 1253-1260.

26. Singh A and Tejani A. One-center experience with cyclosporine in refractory nephrotic syndrome in children. Pediatr Nephrol 1999; 13: 26-32.

27.   Gherardi D and D'Agati V: Reversal of collapsing glomerulopathy in mice with the cyclin- dependent kinase inhibitor CYC202. J Am Soc Nephrol 2004; 15(5): 1212-1222.

28.   Heckmann A and Waltzinger C: IKK2 inhibitor alleviates kidney and wasting diseases in a murine model of human AIDS. Am J Pathol 2004; 164(4): 1253-1262.