Diagnosis and Natural History of HIV-Associated Nephropathy

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HIV-associated nephropathy (HIVAN) is a largely distinctive phenotype induced by HIV-1 infection and is the most recognized and detrimental kidney disease in HIV-infected patients. Host and viral characteristics have been implicated in the pathogenesis of HIVAN that may explain its exclusive predilection to patients of African descent. In untreated patients, the disorder is clinically manifested by an acute decline in kidney function, most often in conjunction with high-grade proteinuria and uncontrolled HIV-1 infection. Histologically, proliferating glomerular epithelial cells are the prominent feature of the disease. Data have evolved over the past decade suggesting that highly active antiretroviral therapy (HAART) can change the natural history of HIVAN, not only by preventing its development but also by halting its progression once developed. Consequently, with the widespread use of HAART, the prevalence of HIVAN is declining in Western countries. In contrast, the epidemiology of the disease is not well defined in the poorest areas in the world, which bear a disproportionate share of the HIV-1 epidemic's burden. Corticosteroids and inhibition of the renin-angiotensin axis are recommended as adjunctive agents in treating patients with established HIVAN and are potentially helpful in delaying the need for renal replacement therapy. However, the long-term value and potential risks of using corticosteroids in this population are unclear.

Key Words: HIV associated nephropathy, HIV 1, Kidney, ESRD, HAART

Originally named "acquired immune deficiency syndrome (AIDS) nephropathy," HIV-associated nephropathy (HIVAN) was first reported in 1984.[1-3] Rao and others[3] described focal and segmental glomerulosclerosis (FSGS) in 10 black patients among 92 diagnosed with AIDS who presented to King's County Medical Center in New York City over a 2-year period. The course of renal disease in those patients was marked by rapid progression to severe uremia. The existence of AIDS nephropathy was not readily accepted because of the low incidence of the disease in certain geographic, predominantly white, areas severely affected by the AIDS epidemic.[4] Since those initial reports, the prevalence of HIVAN over the past 25 years has been driven by the interaction of host factors, viral burden, and both the availability and use of HAART. The incidence of HIVAN peaked in the mid 1990s and has remained stable after an initial decline.[5] This decline can be attributed to the introduction of HAART in 1996. As an almost exclusive disorder of individuals of African descent,[6-12] the prevalence of HIVAN in this population has ranged from 3% to 12%. However, because of the lack of definitive diagnosis of HIVAN by kidney biopsy, most studies provide estimates of renal involvement in HIV-1–infected individuals rather than true prevalence of HIVAN. One autopsy study reported HIVAN prevalence of 12% (25 of 209 autopsies) in blacks.[13] The predilection of HIVAN for black race has also been reported in Europe.[14,15] This striking racial predilection for blacks is independent of any comorbid condition or intravenous drug use. In Western countries, as survival improves, the prevalence of HIV-infected individuals is likely to increase as well as the prevalence of individuals with HIV-associated kidney disease other than HIVAN.[16]

Pathogenesis

The mechanisms and cascade of events underlying susceptibility to HIVAN and its progression are not well established. Because only a subset of patients with HIV-1 infection develop HIVAN despite the presence of HIV-1

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DNA in the kidney,[17] additional factors, such as the responses of specific host characteristics to different HIV-1 gene products, are likely to play an important role in initiating the disease process.

Host Factors

The exclusiveness of HIVAN to individuals of African descent implied the existence of genetic variations. A genetic susceptibility locus has been identified in the Tg26 mouse model of HIVAN.[18] It has been suggested that HIVAN in this setting is linked to susceptibility alleles that induce latent perturbations in the podocyte gene expression network.[19] Similarly, in the human, using genome-wide mapping by admixture linkage disequilibrium, Kopp and associates[20] found several alleles centered on the *MYH9* locus (a functional gene expressed in kidney podocytes) of chromosome 22 occurring at higher frequency among blacks with HIVAN compared with European Americans. The frequency of these "risk alleles" in African Americans may provide insight for the predilection of HIVAN in this population. However, to date, no causal sequence variation in *MYH9* has been identified. It is also important to note that the vast majority of blacks with HIV-1 infection who carry these risk alleles at *MYH9* do not develop HIVAN, suggesting that other susceptibility factors or "multiple hits" must exist to initiate the disease process.

Role of HIV-1

Although HIVAN has been described during acute HIV-1 seroconversion as well as in a patient with well-controlled HIV-1 infection on HAART,[21-23] it is typically a late manifestation of uncontrolled HIV-1 infection, particularly in patients with high viral load.[24] It is extremely unusual for this disorder to develop in HIV-1 infected individuals with undetectable viral load. This finding suggests a direct role of the virus in the pathogenesis of HIVAN. Insights into which HIV-1 gene products are implicated in the pathogenesis of HIVAN have been provided by transgenic animal models.[25-28] In these experimental models, none of the structural gene products is necessary for the development of HIVAN. On the other hand, of the nonstructural gene products, *nef* (negative effector) and *vpr* (viral protein r) have been shown to be sufficient to produce the renal phenotype. Furthermore, Zuo and others[29] showed that podocyte-restricted transgenic expression of *nef* and *vpr* under the control of the nephrin promoter in murine models recapitulates the full clinical and morphologic features of HIVAN. Of interest, there is also evidence suggesting that the kidney is capable of supporting viral replication in a separate "compartment," in addition to accommodating distinctive HIV-1 quasispecies compared with those isolated from the blood of the same patients.[30] HIV-1 *nef* induces key podocyte actin cytoskeleton changes in infected host cells that are crucial to viral replication.[31] However, it is important to note that in the absence of a known mechanism by which HIV-1 might induce a productive infection in renal epithelial cells in vivo, the potential role of *nef* and *vpr* in human remains unclear. Another viral protein with a potential role in the pathogenesis in HIVAN is *tat* (trans-activating factor), which is a regulatory protein involved in HIV transcription that has been shown to induce cellular changes, including cytokine production and apoptosis, in podocytes.[32] The direct role of the virus in HIVAN is also supported clinically by the beneficial impact of HAART in the prevention and treatment of the disease.[33-35] Further support is provided by the observation that relapses of HIVAN can occur with the discontinuation of HAART.[36] Despite the evidence implicating a direct role of HIV-1 in the pathogenesis of HIVAN, the mechanism by which HIV-1 enters renal cells has not been determined. Renal epithelial cells lack the chemokine receptors CCR5 and CXCR4 that serve as cellular receptors in conjunction with CD4 for HIV-1 entry and infection of target cells.

Clinical Presentation

HIVAN characteristically presents in the setting of poorly-controlled HIV-1 infection manifested by elevated viral loads.[24,37] Very rarely, it presents as a manifestation of primary HIV-1 infection (within 6 months of infection) or as part of the acute HIV-1 syndrome.[21,23,38] As the most recognized and most aggressive

form of HIV-1–associated kidney disease, HIVAN typically presents with rapid decline in renal function, often with high-grade proteinuria. The proteinuria is typically in the nephrotic range (>3 g/24 h) with serum creatinine levels above 2 mg/dL and progressive kidney failure.[39,40] In one series of 25 black South Africans patients with biopsy-proven HIVAN, microalbuminuria was found in 6 (24%).[41] Of interest, 5 of those patients had an estimated glomerular filtration rate of >100 mL/min/1.73 m^2 and the sixth patient had a glomerular filtration rate of 82 mL/min/1.73 m^2. Because this indolent form HIVAN has not been described by others, further corroborating confirmation is needed. Lower-extremity edema and hypertension are uncommon in patients with HIVAN, and their absence may contribute to delayed diagnosis.[39] Urinalysis shows a bland sediment with varying numbers of proteinaceous casts and renal tubular epithelial cells.[39]

Morphologically, HIVAN is a variant of FSGS that is characterized by collapse of the glomerular tuft, often with concurrent tubular microcystic dilation and significant tubulointerstitial nephritis.[42] The unique feature of HIVAN, however, is the prominent glomerular epithelial cell hypertrophy and hyperplasia leading to "pseudo-crescents" (Fig 1).[43] Immunohistochemistry studies have revealed upregulation of proliferation markers of podocytes in conjunction with downregulation of differentiation markers.[44] By electron microscopy, endothelial tubuloreticular inclusions related to high plasma interferon levels can be detected.

Diagnosis

Definitive diagnosis of HIVAN requires a kidney biopsy, which should be performed promptly whenever possible, if not contraindicated. It is often difficult to distinguish HIVAN from other renal lesions on clinical grounds alone. Using clinical criteria in the diagnosis of HIVAN may increase the likelihood of inflating the number of cases by including patients with milder renal disease who may have different histological diagnoses. In a study by Post and colleagues,[45] the median glomerular filtration rate (interquartile range)

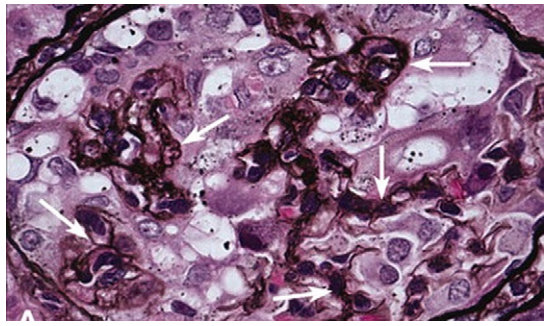

Figure 1. A silver-stained section from a human kidney biopsy showing collapse of the capillary tuft and pronounced podocyte hyperplasia and hypertrophy (ie, a "pseudocrescent") that is filling Bowman's space. The arrows point to the silver-stained remnants of the capillary tuft. (Reprinted with permission.[44])

was 21 (7-36) mL/min in 45 patients with biopsy-proven HIVAN compared with 36 (13-66) mL/min in 16 patients with clinically defined HIVAN ($P = .09$). As pointed out by the authors, although there was no statistical difference between both groups, the apparent discrepancy could result in misclassification bias.[45] Furthermore, because HIVAN may develop in patients with underlying kidney disease ("acute on chronic"), the diagnosis in this setting becomes more difficult without histological confirmation. Indeed, identifying valid noninvasive surrogate measures in the diagnosis of HIVAN has not been successful.[46,47] For example, nephrotic-range proteinuria, even in the presence of a low CD4 cell count, does not reliably predict HIVAN.[47] HIVAN was diagnosed in only 53% of 55 patients with nephrotic-range proteinuria, with a sensitivity of 73% and positive predictive value of 53%.[47] In individuals with nephrotic-range proteinuria without HIVAN, common diagnoses included classic FSGS (21%), membranoproliferative glomerulonephritis (5%), amyloid A amyloidosis (4%), diabetic nephropathy (4%), or other diagnoses (12%). Detectable viremia is a typical feature of HIVAN, and the diagnosis is very unlikely if HIV-1 RNA level is <400 copies/mL.[24] Estrelle and colleagues compared renal histopathological findings for 86 HIV1-infected patients according to HIV-1 RNA levels.[24] The group with viral loads of ≤400 copies/mL had only 1/23 patients having HIVAN. Conversely, the group with viral loads ≥400 copies/mL

included 23/63 HIVAN cases. Similarly, kidney size on ultrasound has not been found to predict HIVAN.[46] However, patients with HIVAN have significantly increased renal cortical echogenicity in comparison with HIV-infected individuals with other renal diseases at the time of renal biopsy.[46] In fact, normal or decreased echogenicity argues against the diagnosis of HIVAN. In summary, clinical criteria may be useful in excluding rather than establishing the diagnosis of HIVAN. The disorder is in unlikely in the setting of low-grade proteinuria, low or undetectable viral load on presentation, and low or normal echogenicity on ultrasound. Furthermore, HIVAN can be reasonably excluded if HIV-1 is well controlled on HAART.

Differential Diagnosis

There is a multitude of glomerular disorders that may mimic HIVAN at presentation and are known to have significantly different management and outcomes. This fact is particularly important in patients who present with both nephrotic syndrome and acute renal failure, such as in the setting of minimal change disease and membranous glomerulopathy. Therefore, although kidney biopsy carries a small risk, the benefit of definitive diagnosis of HIVAN generally outweighs such risk. Other types of glomerular diseases that have been described in HIV-infected individuals are shown in Table 1. Although other nonglomerular renal disorders, such as acute kidney injury, present with a rapid decline in kidney function, high-grade proteinuria is not typical of these disorders. It is important to note that collapsing glomerulopathy has been reported in association with many conditions other than HIVAN.[44] Therefore, these conditions should be considered as potential causes of collapsing glomerulopathy in HIV-infected patients, particularly in the setting of coexisting viral infections, such as parvovirus B-19, cytomegalovirus, and hepatitis C, or with the use of certain medications, such as interferon-α or pamidronate.

Table 1. Differential Diagnosis of HIVAN

Noncollapsing "classic" FSGS
Diabetic nephropathy
Immune complex glomerulonephritis
Lupus like disease
Membranous glomerulopathy (associated with hepatitis B infection, syphilis)
Membranoproliferative glomerulonephritis (associated with hepatitis C infection, mixed cryoglobulinemia)
Immunoglobulin A nephropathy (where immunoglobulin A is directed against HIV 1 antigens)
Postinfectious glomerulonephritis
Minimal change nephropathy, primary or secondary (most often caused by NSAIDs)
Crescentic glomerulonephritis, primary or "postmembranous" glomerulopathy
Thrombotic microangiopathy
Renal amyloidosis

Abbreviation: NSAIDs, nonsteroidal anti inflammatory drugs.

Management

The lack of epidemiologic data on the scope of earlier stages of HIVAN deters the development of an early identification method for the syndrome and also the design of a risk stratification model that may guide the assessment of different intervention modalities. If left untreated, HIVAN almost uniformly progresses to ESRD within weeks to months. Several retrospective analyses have examined the clinical benefit of various therapies, including corticosteroids, inhibition of the renin-angiotensin-aldosterone system, and HAART.[35,48-52] National guidelines recommend initiating HAART once the diagnosis of HIVAN is made, regardless of the CD4 cell count.[53] Future clinical studies are needed to determine whether response to HAART regimens is class specific. If HIVAN is driven by viral replication, one may argue that antiretroviral regimens with the maximal suppression of viral replication as well as the maximal dose-response relationship would likely be optimal in treating HIVAN.

The efficacy of antiproliferative agents, such as all-trans retinoic acid,[54] has not been studied in humans with HIVAN. Suppression of HIV-1 infection may, in theory, allow renal epithelial cells to differentiate back to the mature phenotype, with improvement in glomerular filter characteristics and preservation of renal function. Improvement in the overall survival rate of HIV-1– infected individuals has resulted in organ transplantation emerging as a potential therapeutic option for those with end-stage organ failure. HIV-infected individuals with ESRD are considered renal

transplant candidates if the CD4 cell count is ≥200 cells/mm^3 and HIV-1 is undetectable. A multisite study sponsored by the University of California, San Francisco and supported by the National Institutes of Health is underway in the United States to explore the safety and efficacy of solid organ transplantation in HIV-1–infected individuals with end-stage organ damage.[55] This nationally coordinated effort will ultimately provide much-needed data on graft survival, drug interactions, optimal immunosuppressive therapy, and potential complications in this population. It will also provide the basis for future development of clinical practice guidelines in managing transplant recipients with HIV-1 infection.

Prognosis

Before the introduction of HAART, the initial experience in patients with HIVAN who presented with high-grade proteinuria was largely progression to ESRD within 8 to 16 weeks, as first reported in 1984.[3] Mortality in these patients approached 100% within 6 months of the onset of uremia.[56]

Risk factors for progression to ESRD are uncontrolled HIV-1 replication (particularly, detectable viremia), the lack of treatment with HAART, and the histological index of chronic damage of renal tissue.[45,57] Initial reports suggested a dismal prognosis for HIV-infected individuals undergoing maintenance dialysis.[58,59] Furthermore, using the United States Renal Data System, Abbott and colleagues[10] reported poor survival in individuals with HIVAN who were dependent on hemodialysis between January 1992 and June 1997. The 2-year all-cause unadjusted survival was 36% compared with 64% for all other patients with ESRD.[10] Unfortunately, the United States Renal Disease System does not provide data on the difference in survival among HIV-infected individuals on maintenance dialysis with or without HIVAN. During the HAART era, there have been reports of improved survival among HIV-infected individuals undergoing maintenance dialysis.[60,61] Conversely, in resource-limited areas in which HAART is not universally used, improvement in survival has not been shown.[62] Furthermore, survival among those HIV-infected individuals undergoing maintenance dialysis remains significantly lower than among those dialysis patients not infected with HIV-1.[60] In a study by Atta and others,[62] the 1- and 2-year survival of HIV-infected blacks undergoing hemodialysis during the HAART era was 63% and 43%, respectively; these rates are significantly lower than the 1- and 2-year survival of 80% and 68%, respectively, among non–HIV-infected blacks undergoing dialysis.[63]

Summary

HIVAN is the most aggressive type of kidney disease in HIV-infected patients and typically occurs in the setting of uncontrolled HIV-1 infection in individuals of African descent. Although the role HIV-1 structural genes in the pathogenesis of HIVAN in humans has not been excluded, nonstructural HIV-1 genes, particularly *nef* and *vpr*, have been implicated as playing prominent and synergistic roles in the pathogenesis of this disorder. In addition, animal and human genetic studies have identified potential genetic loci that may confer susceptibility to HIVAN. In untreated patients, the disease presents with a rapid decline in renal function, often with high-grade proteinuria with morphologic features of collapsing FSGS and significant tubulointerstitial injury with microcystic tubular dilation. Response to therapy requires prompt diagnosis in light of the aggressiveness of this disorder. Only renal biopsy is diagnostic and should be performed whenever feasible because no one clinical criterion, including nephrotic-range proteinuria or kidney size by ultrasound, has adequate predictive value in the diagnosis of HIVAN. First-line treatment of HIVAN is HAART, which has been shown to reduce the development of HIVAN and slow progression to ESRD. In addition, short-term treatment with corticosteroids in conjunction with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may also be of benefit as adjunctive therapy. Future potential therapies that have not yet been studied in humans include antiproliferative agents, such as cyclin-dependent kinase inhibitors and all-trans retinoic acid. Patients who develop ESRD are considered renal transplant

candidates if the CD4 cell count is ≥200 cells/mm^3 and HIV-1 is undetectable. With the projected progressive declines in both morbidity and mortality attributable to HIVAN in Western countries, the spectrum of kidney diseases encountered in HIV-infected individuals is changing, whereby both the incidence and prevalence of HIVAN have declined during the HAART era.[34,40,64] As the prevalence of HIVAN declines, the HIV-infected population may be increasingly faced with accelerated rates of other risk factors for CKD, including diabetes mellitus, hypertension, and dyslipidemia.

References

1. Gardenswartz MH, Lerner CW, Seligson GR, et al: Renal disease in patients with AIDS: A clinicopathologic study. Clin Nephrol 21:197 204, 1984
2. Pardo V, Aldana M, Colton RM, et al: Glomerular lesions in the acquired immunodeficiency syndrome. Ann Intern Med 101:429 434, 1984
3. Rao TK, Filippone EJ, Nicastri AD, et al: Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. N Engl J Med 310:669 673, 1984
4. Mazbar SA, Schoenfeld PY, Humphreys MH: Renal involvement in patients infected with HIV: Experience at San Francisco General Hospital. Kidney Int 37:1325 1332, 1990
5. Ross MJ, Klotman PE: Recent progress in HIV associated nephropathy. J Am Soc Nephrol 13:2997 3004, 2002
6. Carbone L, D'Agati V, Cheng JT, et al: Course and prognosis of human immunodeficiency virus associated nephropathy. Am J Med 87:389 395, 1989
7. Cantor ES, Kimmel PL, Bosch JP: Effect of race on expression of acquired immunodeficiency syndrome associated nephropathy. Arch Intern Med 151: 125 128, 1991
8. Laradi A, Mallet A, Beaufils H, et al: HIV associated nephropathy: outcome and prognosis factors. Groupe d' Etudes Nephrologiques d'Ile de France. J Am Soc Nephrol 9:2327 2335, 1998
9. Williams DI, Williams DJ, Williams IG, et al: Presentation, pathology, and outcome of HIV associated renal disease in a specialist centre for HIV/AIDS. Sex Transm Infect 74:179 184, 1998
10. Abbott KC, Hypolite I, Welch PG, et al: Human immunodeficiency virus/acquired immunodeficiency 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 14:377 383, 2001
11. Kopp JB, Winkler C: HIV associated nephropathy in African Americans. Kidney Int Suppl 83:S43 S49, 2003
12. Eggers PW, Kimmel PL: Is there an epidemic of HIV Infection in the US ESRD program? J Am Soc Nephrol 15:2477 2485, 2004
13. Shahinian V, Rajaraman S, Borucki M, et al: Prevalence of HIV associated nephropathy in autopsies of HIV infected patients. Am J Kidney Dis 35:884 888, 2000
14. Nochy D, Glotz D, Dosquet P, et al: Renal disease associated with HIV infection: A multicentric study of 60 patients from Paris hospitals. Nephrol Dial Transplant 8:11 19, 1993
15. Nochy D, Glotz D, Dosquet P, et al: Renal lesions associated with human immunodeficiency virus infection: North American vs. European experience. Adv Nephrol Necker Hosp 22:269 286, 1993
16. Lucas GM, Mehta SH, Atta MG, et al: End stage renal disease and chronic kidney disease in a cohort of African American HIV infected and at risk HIV seronegative participants followed between 1988 and 2004. AIDS 21:2435 2443, 2007
17. Bruggeman LA, Ross MD, Tanji N, et al: Renal epithelium is a previously unrecognized site of HIV 1 infection. J Am Soc Nephrol 11:2079 2087, 2000
18. Gharavi AG, Ahmad T, Wong RD, et al: Mapping a locus for susceptibility to HIV 1 associated nephropathy to mouse chromosome 3. Proc Natl Acad Sci U S A 101:2488 2493, 2004
19. Papeta N, Chan KT, Prakash S, et al: Susceptibility loci for murine HIV associated nephropathy encode trans regulators of podocyte gene expression. J Clin Invest 119:1178 1188, 2009
20. Kopp JB, Smith MW, Nelson GW, et al: MYH9 is a major effect risk gene for focal segmental glomerulosclerosis. Nat Genet 40:1175 1184, 2008
21. Winston JA, Bruggeman LA, Ross MD, et al: Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med 344:1979 1984, 2001
22. Szabo S, James CW, Telford G: Unusual presentations of primary human immunodeficiency virus infection. AIDS Patient Care STDS 16:251 254, 2002
23. Izzedine H, Wirden M, Launay Vacher V: Viral load and HIV associated nephropathy. N Engl J Med 353: 1072 1074, 2005
24. Estrella M, Fine DM, Gallant JE, et al: HIV type 1 RNA level as a clinical indicator of renal pathology in HIV infected patients. Clin Infect Dis 43:377 380, 2006
25. Zhong J, Zuo Y, Ma J, et al: Expression of HIV 1 genes in podocytes alone can lead to the full spectrum of HIV 1 associated nephropathy. Kidney Int 68:1048 1060, 2005
26. He JC, Husain M, Sunamoto M, et al: Nef stimulates proliferation of glomerular podocytes through activation of Src dependent Stat3 and MAPK1,2 pathways. J Clin Invest 114:643 651, 2004
27. Hanna Z, Kay DG, Rebai N, et al: Nef harbors a major determinant of pathogenicity for an AIDS like disease induced by HIV 1 in transgenic mice. Cell 95:163 175, 1998
28. Hanna Z, Kay DG, Cool M, et al: Transgenic mice expressing human immunodeficiency virus type 1 in immune cells develop a severe AIDS like disease. J Virol 72:121 132, 1998
29. Zuo Y, Matsusaka T, Zhong J, et al: HIV 1 genes vpr and nef synergistically damage podocytes, leading

to glomerulosclerosis. J Am Soc Nephrol 17:2832 2843, 2006
30. Marras D, Bruggeman LA, Gao F, et al: Replication and compartmentalization of HIV 1 in kidney epithe lium of patients with HIV associated nephropathy. Nat Med 8:522 526, 2002
31. Lu T C, He JC, Wang Z H, et al: HIV 1 nef disrupts the podocyte actin cytoskeleton by interacting with diaphanous interacting protein. J Biol Chem 283: 8173 8182, 2008
32. Conaldi PG, Bottelli A, Baj A, et al: Human immuno deficiency virus 1 tat induces hyperproliferation and dysregulation of renal glomerular epithelial cells. Am J Pathol 161:53 61, 2002
33. Wali RK, Drachenberg CI, Papadimitriou JC, et al: HIV 1 associated nephropathy and response to highly active antiretroviral therapy. Lancet 352:783 784, 1998
34. Lucas GM, Eustace JA, Sozio S, et al: Highly active antiretroviral therapy and the incidence of HIV 1 associated nephropathy: A 12 year cohort study. AIDS 18:541 546, 2004
35. Atta MG, Gallant JE, Rahman MH, et al: Antiretroviral therapy in the treatment of HIV associated nephropa thy. Nephrol Dial Transplant 21:2809 2813, 2006
36. Scialla JJ, Atta MG, Fine DM: Relapse of HIV associ ated nephropathy after discontinuing highly active antiretroviral therapy. AIDS 21:263 264, 2007
37. Winston JA, Klotman ME, Klotman PE: HIV associ ated nephropathy is a late, not early, manifestation of HIV 1 infection. Kidney Int 55:1036 1040, 1999
38. Levin ML, Palella F, Shah S, et al: HIV associated nephropathy occurring before HIV antibody serocon version. Am J Kidney Dis 37:E39, 2001
39. Ross MJ, Klotman PE, Winston JA: HIV associated ne phropathy: Case study and review of the literature. AIDS Patient Care STDS 14:637 645, 2000
40. Berliner AR, Fine DM, Lucas GM, et al: Observations on a cohort of HIV infected patients undergoing native renal biopsy. Am J Nephrol 28:478 486, 2008
41. Han TM, Naicker S, Ramdial PK, et al: A cross sectional study of HIV seropositive patients with varying degrees of proteinuria in South Africa. Kid ney Int 69:2243 2250, 2006
42. D'Agati V, Suh JI, Carbone L, et al: Pathology of HIV associated nephropathy: A detailed morphologic and comparative study. Kidney Int 35:1358 1370, 1989
43. D'Agati V, Appel GB: HIV infection and the kidney. J Am Soc Nephrol 8:138 152, 1997
44. Albaqumi M, Soos TJ, Barisoni L, et al: Collapsing glomerulopathy. J Am Soc Nephrol 17:2854 2863, 2006
45. Post FA, Campbell LJ, Hamzah L, et al: Predictors of renal outcome in HIV associated nephropathy. Clin Infect Dis 46:1282 1289, 2008
46. Atta MG, Longenecker JC, Fine DM, et al: Sonography as a predictor of human immunodeficiency virus asso ciated nephropathy. J Ultrasound Med 23:603 610, 2004
47. Atta MG, Choi MJ, Longenecker JC, et al: Nephrotic range proteinuria and CD4 count as noninvasive indi cators of HIV associated nephropathy. Am J Med 118: 1288.e1221 1288.e1226, 2005
48. Eustace JA, Nuermberger E, Choi M, et al: Cohort study of the treatment of severe HIV associated nephropathy with corticosteroids. Kidney Int 58: 1253 1260, 2000
49. Burns GC, Paul SK, Toth IR, et al: Effect of angioten sin converting enzyme inhibition in HIV associated nephropathy. J Am Soc Nephrol 8:1140 1146, 1997
50. Smith MC, Austen JL, Carey JT, et al: Prednisone improves renal function and proteinuria in human immunodeficiency virus associated nephropathy. Am J Med 101:41 48, 1996
51. Briggs WA, Tanawattanacharoen S, Choi MJ, et al: Clinicopathologic correlates of prednisone treatment of human immunodeficiency virus associated nephropathy. Am J Kidney Dis 28:618 621, 1996
52. Burns GC, Matute R, Onyema D, et al: Response to inhibition of angiotensin converting enzyme in hu man immunodeficiency virus associated nephropa thy: A case report. Am J Kidney Dis 23:441 443, 1994
53. Hammer SM, Eron JJ Jr, Reiss P, et al: Antiretroviral treatment of adult HIV infection: 2008 recommenda tions of the International AIDS Society USA panel. JAMA 300:555 570, 2008
54. He JC, Lu TC, Fleet M, et al: Retinoic acid inhibits HIV 1 induced podocyte proliferation through the cAMP pathway. J Am Soc Nephrol 18:93 102, 2007
55. Available at: http://www.hivtransplant.com/. Accessed May 28, 2009
56. Rao TK, Friedman EA, Nicastri AD: The types of renal disease in the acquired immunodeficiency syndrome. N Engl J Med 316:1062 1068, 1987
57. Szczech LA, Gupta SK, Habash R, et al: The clinical epidemiology and course of the spectrum of renal dis eases associated with HIV infection. Kidney Int 66: 1145 1152, 2004
58. Ortiz C, Meneses R, Jaffe D, et al: Outcome of patients with human immunodeficiency virus on maintenance hemodialysis. Kidney Int 34:248 253, 1988
59. Tebben JA, Rigsby MO, Selwyn PA, et al: Outcome of HIV infected patients on continuous ambulatory peri toneal dialysis. Kidney Int 44:191 198, 1993
60. Ahuja TS, Grady J, Khan S: Changing trends in the survival of dialysis patients with human immunode ficiency virus in the United States. J Am Soc Nephrol 13:1889 1893, 2002
61. Macrae J, Friedman AL, Eggers P, et al: Improved sur vival in HIV infected African Americans with ESRD. Clin Nephrol 64:124 128, 2005
62. Atta MG, Fine DM, Kirk GD, et al: Survival during re nal replacement therapy among African Americans infected with HIV type 1 in urban Baltimore, Mary land. Clin Infect Dis 45:1625 1632, 2007
63. US Renal Data System (USRDS): 2006 Annual Data Report: National Institutes of Health, National Insti tute of Diabetes and Digestive Diseases and Kidney Diseases, Bethesda, MD. http://www.usrds.org Accessed January 8, 2008
64. Ahuja TS, Borucki M, Funtanilla M, et al: Is the prev alence of HIV associated nephropathy decreasing? Am J Nephrol 19:655 659, 1999