Gene-Gene and Gene-Environment Interactions in HIV-Associated Nephropathy: A Focus on the *MYH9* Nephropathy Susceptibility Gene

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HIV-associated nephropathy (HIVAN) is a leading cause of ESRD in African Americans. The HIV-1 virus infects podocytes, cells integral to formation of the glomerular filtration barrier, often leading to focal segmental glomerulosclerosis. HIVAN is typically a complication of late-stage HIV infection, associated with low CD4 cell counts and elevated serum HIV RNA levels. Highly active antiretroviral therapy is partially protective and has altered the natural history of HIV-associated kidney disease. Nonetheless, HIVAN remains an important public health concern among HIV-infected African Americans. Although polymorphisms in the *MYH9* gene on chromosome 22 are strongly associated with HIVAN, as well as with idiopathic focal segmental glomerulosclerosis and global glomerulosclerosis (historically labeled "hypertensive nephrosclerosis"), the majority of HIV-infected patients who are genetically at risk from *MYH9* do not appear to develop severe kidney disease. Therefore, we postulate that additional environmental exposures and/or inherited factors are necessary to initiate human HIVAN. Gene-environment interactions have also been proposed as necessary for the initiation of HIVAN in murine models. It is important that these novel risk factors be identified because prevention of environmental exposures and targeting of additional gene products may reduce the risk for HIVAN, even among those harboring 2 risk alleles in *MYH9*.

Key Words: African Americans, Focal segmental glomerulosclerosis, HIV-associated nephropathy, Kidney disease, MYH9

HIV-associated nephropathy (HIVAN) was initially described as "acquired immunodeficiency syndrome (AIDS) nephropathy" in 1984.[1] HIVAN is a common cause of CKD observed primarily in African Americans (AAs).[2-6] Pathologically, HIVAN is characterized by the collapsing variant of focal segmental glomerulosclerosis (FSGS) with microcystic tubular dilation, tubulointerstitial nephritis, and tubuloreticular inclusions.[7,8] HIVAN can be a rapidly progressive form of FSGS and is characterized by podocyte proliferation. Patients with pathologically proven HIVAN show poorer renal survival relative to HIV-infected individuals with other etiologies of CKD.[3,9,10] HIV infection and diabetes appear to convey similar risks for kidney disease in AAs.[11]

Epidemiology of HIVAN

The US Renal Data System reported that 0.97% of the 375,152 incident patients initiating chronic dialysis between January 1992 and June 1997 had HIVAN, and 87% were AA.[6] Four thousand new cases of ESRD were attributed to HIV in the United States in 2005,[12] making HIVAN the third leading cause of ESRD in AAs between the ages of 20 and 64 years. The incidence of HIVAN peaked in the United States during the mid-1990s[13] and declined by 50% in the 1998 to 2001 time period, relative to 1995 to 1997, in association with the widespread use of HAART.[2] Although the incidence of HIVAN decreased during the HAART era, its prevalence is now increasing because of the aging of patients as a result of improved survival among those with HIV infection.[14] The true prevalence

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Table 1. Incidence and Prevalence of HIVAN Among HIV-infected African Americans

Reference #	Location	Study Type	Definition of HIVAN	HIVAN Prevalence	HIVAN Incidence
15	Galveston, TX	Cross-sectional	Biopsy or clinical	3.5% (10/282)	
16	TDCCJI, TX	Cross-sectional, Postmortem	Autopsy	12% (25/209)	
2	Baltimore, MD	Longitudinal	Biopsy or clinical		10.1/100 person-years
9	Baltimore, MD	Longitudinal	Biopsy or clinical		1% per year

Abbreviation: TDCCJI, Texas Department of Criminal Justice Inmates.

of HIVAN remains unknown because the diagnosis requires viral testing and renal histologic analysis; more cases likely exist than are reported. In addition, non-HIVAN causes of kidney disease are often seen in HIV-infected patients, some of which result from HAART.[15] Table 1 summarizes the published incidence and prevalence rates of HIVAN among AA HIV-infected subjects. The prevalence of HIVAN in HIV-infected AAs ranges from 3.5% for proteinuria to 12% in postmortem studies.[16,17] A report in South Africans revealed higher frequencies of HIV immune complex kidney disease as well as membranous, mesangial hyperplasia, and IgA nephropathy, relative to AAs.[18]

HIVAN is most often a complication of the late stages of HIV infection and is associated with low CD4 cell counts and elevated serum HIV RNA levels.[2,3,9,10,19-21] However, HIVAN can develop in patients with undetectable viral loads and high CD4 cell counts.[3,22] Prior history of a low CD4 cell count (ie, nadir CD4 cell count <200 cells/mm^3) is a risk factor for HIVAN,[9] and there is a shorter time to initiation of renal replacement therapy in those with lower CD4 cell counts.[3] Before the availability of HAART, the prognosis for patients with HIVAN was dismal, and survival was measured in weeks to months.[23] There are several lines of evidence supporting a beneficial role of HIV treatment in improving survival and preserving kidney function, including the negative correlation between CD4 cell count and HIVAN, the decline in the incidence of HIVAN during the HAART era, and case reports of resolution of renal failure after initiation of HAART.[23-27] Nevertheless, HAART is only partially protective, and many patients with HIVAN ultimately progress to ESRD.[2,23,28] CD4 cell count restoration using HAART does not correlate with improved renal outcomes,[10,23] and 65% of patients who progress to ESRD after a diagnosis of HIVAN have had undetectable HIV RNA levels for median durations approaching 2 years.[23]

Pathogenesis of HIVAN

Although HIV-1 viral messenger RNA and DNA have been detected in renal glomerular and tubular epithelial cells, the mode of HIV-1 viral entry into kidney cells has not been determined.[29] Renal epithelial cells lack both CD4 and CD4 coreceptors CXCR4 and CCR5 used by HIV-1 for cellular entry.[30] However, the expression of CXCR5, an HIV-2 coreceptor, has been shown on podocytes.[31] A "renal reservoir" of HIV-1 has been described during primary viral infection.[32] Renal biopsies have revealed restoration of the architecture of the renal tubules and resolution of podocyte hypertrophy and glomerular collapse 3 months after the initiation of antiretroviral therapy. The number of podocytes expressing viral messenger RNA was unchanged. Similarly, Bruggeman and others[29] observed replication of HIV in renal cells of individuals with HIVAN despite treatment with antiretroviral agents and undetectable serum viral loads.

Local replication of HIV-1 in renal tubular cells has been confirmed.[33] DNA extracted from renal tubular cells in 2 patients with HIVAN was used to amplify HIV-1 V3-loop or gp120-envelope sequences. Sequences were compared with the corresponding sequences in monocytes obtained from these same individuals. Sequences obtained from kidney tissue formed tissue-specific subclusters, suggesting local (renal) replication of HIV-1.[33]

Normally, podocytes are postmitotic and do not proliferate. In HIVAN, podocytes appear to dedifferentiate and proliferate.