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In-Depth Review of Human Immunodeficiency Virus-Associated Nephropathy

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ABSTRACT

Human Immunodeficiency Virus (HIV)-Associated Nephropathy (HIVAN) is one of the most important renal complications found in HIV-infected individuals. Morbidity and mortality in this group of patients increases due to End-Stage Renal Disease (ESRD). Classic histological characteristics of HIVAN are collapsing Focal Segmental Glomerulosclerosis (FSGS), microcystic tubular dilation and interstitial inflammation and fibrosis. High prevalence of HIVAN among people of African descent can be explained by host genetic susceptibility, which is associated with several genes on human chromosome 22. HIV can infect renal epithelial cells via unconventional mechanisms and cause changes in multiple host cellular pathways, especially in renal tubular cells and podocytes. Accurate diagnosis of HIVAN relies mainly on renal biopsy. Antiretroviral therapy is the mainstay treatment for HIVAN and current standard guidelines recommend the initiation of Highly Active Antiretroviral Therapy (HAART) in all HIV-infected individuals with HIVAN, regardless of CD4 level. Other possible treatments for HIVAN including steroids, Angiotensin Converting Enzyme (ACE) inhibitors, renal replacement therapy and renal transplantation are reviewed in this chapter.

Keywords: Human Immunodeficiency Virus, Glomerulosclerosis, Transplantation, End-Stage Renal Disease, Associated Nephropathy

1. INTRODUCTION

Human Immunodeficiency Virus (HIV)-associated nephropathy or HIVAN was first described in patients with Acquired Immunodeficiency Syndrome (AIDS) in (Pardo *et al*., 1984; Rao *et al*., 1984). Originally, it was named AIDS-nephropathy; however, because renal histopathologic defective findings were demonstrated in asymptomatic patients, the name was changed to HIVAN. Collapsing Focal Segmental Glomerulosclerosis (FSGS) with tubulointerstitial lesions, the classical histopathologic pattern in HIVAN is more prevalent in patients of African descent (Lucas *et al*., 2004; Lescure *et al*., 2012; Schwartz *et al*., 2005). At present, medical laboratories and clinical societies have focused on host genetic factors and complex host-viral genetic interactions to understand the pathogenesis of this disease among various populations and to develop potentially effective therapy.

1.1. Pathogenesis

1.1.1. Host Genetic Susceptibility

Human genetic factors are important to determine an individual's degree of susceptibility to the development

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of HIVAN from HIV infection. Data from the United States Renal Data System (USRDS) shows that almost 90% of patients with End-Stage Renal Disease (ESRD) from HIVAN are African-American (USRDS, 2010).

Studies in animal models have improved our understanding of the pathogenesis of HIVAN. Among all animal models, the HIV-transgenic mouse model, which expresses HIV genes on their murine genetic background ("transgenic 26" or "Tg26"), is the most studied one. Based on the existence of different renal phenotypes depending on the mice's genetic background, "HIVAN1" and "HIVAN2", the two susceptibility loci associated with HIVAN in Tg26 mice were identified (Gharavi *et al*., 2004; Chan *et al*., 2009).

HIVAN1 is on murine chromosome 3. This locus strongly associates with renal disease in mice (Gharavi *et al*., 2004). It correlates with human chromosome 3q25-27, which was previously linked to diabetic nephropathy (Imperatore *et al*., 1998; Moczulski *et al*., 1998) and hypertensive nephropathy (DeWan *et al*., 2001). HIVAN1 also increases susceptibility to the development of HIVAN (Chan *et al*., 2009).

HIVAN2 is on murine chromosome 13. Together with HIVAN1, both loci are involved in the transregulation of podocyte genes including Nephrosis 2 homolog (Nphs2) gene which encodes podocin, a protein component in the slit diaphragm of podocytes (Papeta *et al*., 2009). This finding adds to the evidence that podocyte genes are regulated by a network of other genes. In the presence of host susceptibility alleles, this network can be altered by HIV infection (Medapalli *et al*., 2011).

In human, several loci associated with HIVAN were identified. Myosin Heavy chain-9 (MYH9) and Apolipoprotein L1 (APOL1) are the two most important loci studied.

MYH9 is on human chromosome 22. It is expressed in podocytes and encodes non-muscle myosin heavy chain IIA. Despite being proven to be associated with many renal diseases (e.g., hypertensive ESRD (Kao *et al*., 2008), idiopathic FSGS and HIV-associated FSGS in HIVAN (Kopp *et al*., 2008)), the role of MYH9 in the pathogenesis of HIVAN still remains unclear.

APOL1 is also on human chromosome 22. This gene was identified later than MYH9; however, it has been proven to possess a stronger association with HIVAN. This apolipoprotein L1-encoding gene was found to be present only among African participants in the 1,000 Genome Project. Its product has an ability to lyse Trypanosome brucei brucei, an African parasite. Therefore, the high prevalence of APOL1 in people of African descent was hypothesized to be a result of positive selection, in which people with APOL1 gene tend to live longer (the same way that individuals with sickle-cell heterozygotes have a selective advantage in malaria-endemic regions) (Freedman *et al*., 2009). To date, two alleles in the APOL1 locus, named G1 and G2, have been identified as risk alleles. These risk alleles follow an autosomal recessive pattern of inheritance and are in strong linkage disequilibrium with the most important MYH9 risk haplotype. Thus, the association between MYH9 and renal disease may be explained by the presence of APOL1 risk allele which is linked with that MYH9 risk haplotype (Freedman *et al*., 2009).

1.2. Role of HIV

The introduction of combined Antiretroviral Therapy (cART) thus helps decrease its incidence, resulting in a plateau in the incidence of ESRD from HIVAN in the United States (USRDS, 2010; Wyatt *et al*., 2008).

The role of HIV in the pathogenesis of HIVAN was initially studied in HIV-transgenic mice. Reciprocal transplantation studies between Tg26 and wild-type mouse focusing on podocyte-specific expression of HIV genes showed that viral gene expression within the kidney itself played an important pathologic role in the development of HIVAN (Rosenstiel *et al*., 2009a; Bruggeman *et al*., 1997). Subsequent studies confirmed that HIV has an ability to infect renal epithelial cells (Marras *et al*., 2002) and HIV nucleic acid was found in podocytes, parietal epithelial cells, tubular epithelial cells, T-cells and macrophages in human HIVAN renal biopsies (Bruggeman *et al*., 2000; Tanji *et al*., 2006).

Phylogenetic comparative analysis of HIV nucleic acid sequences derived from renal epithelial cells and peripheral blood mononuclear cells showed a divergent pattern, suggesting that the kidney probably acts as a separated compartment where kidney-specific viral evolution takes place (Marras *et al*., 2002). Some pieces of evidence even suggested the existence of renal tropic strains of HIV (Ray *et al*., 1998). HIV has been proven to be able to replicate in the kidney even though the patients had achieved serological viral suppression from the combination antiretroviral therapy (Medapalli *et al*., 2011).

How can HIV infect kidneys? Since renal epithelial cells possess no traditional HIV surface receptors (CD4) or co-receptors (CXCR4 or CCR5) (Marras *et al*., 2002; Eitner *et al*., 2000), other pathways must be used by the virus to enter those cells. Several mechanisms for cell-free

HIV infection of tubular epithelial cells (Hatsukari *et al*., 2007) and podocytes (Mikulak and Singhal, 2010; Mikulak *et al*., 2010) have been proposed. In one study, tubular epithelial cells were co-cultured with infected T-cells. The result showed efficient viral nucleic acid transfer which required direct cell-cell contact and cell surface heparin sulfate proteoglycans (which helped HIV to attach on macrophages and dendritic cells), but did not depend on an interaction with CD4 (Chen *et al*., 2011). Comparing the cell to cell contact mechanism and cell-free mechanism (exposure of tubular epithelial cells to a large amount of cell-free virus), the former mechanism resulted in a greater number of transferred viral nucleic acids. Moreover, de novo viral protein synthesis following this cell-cell contact could not be blocked by reverse transcriptase, protease or integrate inhibitors (Chen *et al*., 2011). Theoretically, HIV infection of renal epithelial cells may occur via direct cell-cell contact with lymphocytes infiltrating the renal parenchyma (Wyatt *et al*., 2012).

Of all HIV genes that were studied, nef, vpr and tat are three HIV genes that have potential roles in the development of pathology in HIVAN.

Nef is important in the development of glomerular lesion in HIVAN. It is involved in de-differentiation and proliferation of podocytes, which normally are terminally differentiated (Husain *et al*., 2002; 2005; He *et al*., 2004; Zhong *et al*., 2005; Zuo *et al*., 2006).

Vpr plays a role in the development of tubular lesion in HIVAN. Its expression in tubular epithelial cells is associated with G2 cell cycle arrest, impaired cytokinesis and finally apoptosis (Zhong *et al*., 2005; Rosenstiel *et al*., 2008; 2009b; Snyder *et al*., 2010; Vashistha *et al*., 2008). A synergistic effect of nef and vpr was observed in a study which showed that mice with both nef and vpr expression developed more severe nephropathy (Zuo *et al*., 2006).

That may have a role in podocyte de-differentiation (Doublier *et al*., 2007), however, its role is unclear since mice with podocyte-specific expression of that did not develop pathology. It might be possible that circulating tat released from HIV infected cells may have an effect on podocytes in vivo (Zuo *et al*., 2006).

1.3. Host Response to HIV Infection

HIV infection causes multiple changes in host cellular pathways, resulting in pathological changes observed in HIVAN. Those histological characteristics of HIVAN are collapsing form of FSGS, microcystic tubular dilation and interstitial inflammation and fibrosis (Medapalli *et al*., 2011).

Tubular epithelial cells infected with HIV have changes including up-regulation of cellular pathways mainly involved in cell cycle arrest and apoptosis. HIV vpr gene induces an up-regulation of FAT10 (ubiquitin-like protein), resulting in apoptosis of tubular epithelial cells and finally the tubular dilation and atrophy characteristic of HIVAN (Vashistha *et al*., 2008; Kapasi *et al*., 2002; Ross *et al*., 2005; 2006a; 2006b). Furthermore, HIV infection of tubular epithelial cells also induces expression of multiple inflammatory mediators which may contribute to the prominent tubulointerstitial inflammation feature of HIVAN (Ross *et al*., 2006b). This justifies potential benefit from corticosteroid in the treatment of HIVAN (Yahaya *et al*., 2013).

Podocytes infected with HIV also have changes in cellular pathways. They have decreased expression of typical markers (such as synaptopodin and Wilm's tumor-1) and Cyclin-Dependent Kinase (CDK) inhibitors (p27, p67); the latter indicates that they re-enter the cell cycle. On the other hand, they have increased expression of desmin (intermediate filament protein) and some proliferation markers such as Ki-67 and cyclins (A, D1) (Barisoni and Kopp, 2002; Barisoni *et al*., 1999; 2000; Schwartz *et al*., 2001).

HIV also induces MAPK 1,2 activation and Stat-3 pathway in podocytes. These pathways are induced mainly by HIV nef gene and correlate with podocyte proliferation seen in vitro studies (He *et al*., 2007). All-Trans Retinoic Acid (ATRA) was shown to suppress HIV-induced activation of these pathways in cultured podocytes (He *et al*., 2007).

Homophilic adhesion molecule sidekick-1 (sdk-1) is a mediator of cellular adhesion that is up-regulated in HIV infected podocytes (Kaufman *et al*., 2004) and is proven to have a crucial role in the development of FSGS (podocyte clustering in classical pseudo crescent formation) (Kaufman *et al*., 2007; 2010).

More recently, a mammalian Target of Rapamycin (mTOR) pathway was also found to be up-regulated in HIV-transgenic mice (Kumar *et al*., 2010).

Several possible therapeutic agents targeting at each host pathway in the pathogenesis of HIVAN are being investigated. This includes CDK inhibitor, Stat-3 inhibitor, ATRA, mTOR inhibitor sirolimus, corticosteroid, ACEI and ARB (Wyatt *et al*., 2012).

1.4. Diagnosis

HIVAN is characterized by the presence of heavy proteinuria and collapsing focal segmental glomerulonephritis with microcystic tubular dilatation in renal pathology (Ray, 2012). Data from many

retrospective studies showed that almost 40% of biopsy-proven renal diseases in HIV patients with clinical backgrounds of massive proteinuria and progressively worsening renal function were not HIVAN (Schwartz *et al*., 2005; Atta *et al*., 2006; Wearne *et al*., 2012); therefore, histopathologic diagnosis is crucial for definitive diagnosis. Considering new taxonomy for podocytopathies, HIV-1 could induce at least three different podocytopathies including focal segmental glomerulonephritis, collapsing glomerulopathy and diffuse mesangial sclerosis (D'Agati *et al*., 2004; Barisoni *et al*., 2007).

1.5. Treatment

Several therapeutic strategies have been proposed to treat HIV-infected patients with HIV-Associated Nephropathy (HIVAN). Treatment modalities include steroid, Angiotensin Converting Enzyme (ACE) inhibitors and antiretroviral medications could slow down the progression of HIVAN to ESRD or improve renal survival time. However, the major drawback of the evidence is that there are currently no randomized clinical control trials to demonstrate effective treatment of HIVAN.

1.6. Antiretroviral Therapy

The introduction of HAART in 1995-1996 was associated with dramatically decreased in mortality rates from AIDS and End Stage Renal Disease (ESRD) in HIV-infected patients. This information suggests a possible beneficial role of antiretroviral drugs in HIVAN. The first 12-year observational cohort study (1989-2001) showed the 50% decreased incidence of HIVAN in 1998-2001 compared to 1995-1997 which was associated with increased HAART use (Lucas *et al*., 2004). This conclusion has been supported by another 12-year retrospective study (1995-2007) of biopsy-proven glomerular disease in HIV population (total 88 renal biopsies), which showed decreased prevalence of HIVAN compared to classic FSGS in 2004-2007 which had the highest proportion of HAART-treated patients (Lescure *et al*., 2012).

In addition, there are a few studies demonstrating the effect of HAART and renal survival time. Schwartz *et al*. (2005; 2001) demonstrated mathematical model to calculate the effect of HAART and ESRD using data from Centers of Disease Control and Prevention (CDC) and USRDS which suggested HAART could slow the progression of ESRD in HIV-infected individuals by 38% (Schwartz *et al*., 2005). Atta *et al*. (2006) found that ARV-treated patients, either with monotherapy, combination ART or HAART regimens, had significantly higher renal survival time than patients who did not receive treatment. Subgroup analysis trended towards better renal survival in patients with complete virologic response (Atta *et al*., 2006). The largest renal biopsy series (221 renal biopsies in HIV-positive patients) in South Africa emphasized most untreated HIV-related renal diseases patients with combined antiretroviral therapy died of renal failure (Wearne *et al*., 2012). Interestingly, the benefit of HAART on HIVAN was contradicted by one retrospective study (total 61 HIVAN with 45 biopsy-confirmed). The study demonstrated that once severe HIVAN was diagnosed, HAART and HIV viral suppression could not prevent progression towards ESRD (Post *et al*., 2008).

Considering the data from observational, prospective multicenter cohort studies and retrospective studies; 2012 US Department of Health and Human Services (DHHS) and International AIDS Society treatment guidelines recommended starting Highly Active Antiretroviral Therapy (HAART) in HIV-infected individuals with HIV-associated nephropathy regardless of CD4 level (Thompson *et al*., 2012; PAGAA, 2003).

1.7. Renin-Angiotensin-Aldosterone System Inhibitors

The possible efficacy of ACEI was proposed for the first time in a case report. Burns *et al*. (1994) reported that fosinopril had a positive effect in decreasing proteinuria in biopsy-proven HIVAN (Burns *et al*., 1994). Two years later, Burns *et al*. (1997) conducted a non-randomized prospective cohort study to demonstrate the efficacy of fosinopril in 20 biopsy-proven HIVAN (11 presented with non-nephrotic-range proteinuria and 9 presented with nephrotic-range proteinuria). The preliminary report showed that fosinopril may stabilize serum creatinine and decrease proteinuria up to 24 weeks in patients with non-nephrotic range proteinuria, but only 12 weeks in nephrotic range patients (Burns *et al*., 1997). In the same year, the effect of captopril was shown to improve renal survival time in 18 biopsy-proven HIVAN, compared to controls matched for age, gender, race and baseline serum creatinine. The median length of survival was 83 and 30 days in treated group and untreated group, respectively (Kimmel *et al*., 1996). Another 5-year nonrandomized prospective cohort study supported the concept of fosinopril-improved renal survival time in both non-nephrotic range and nephrotic range groups. Total 44 treated and controlled patients

were matched for age, baseline median CD 4 count, serum creatinine level, proteinuria; however, fosinopril-treated groups had higher rate of HAART exposure. The median survival time was 146.5 and 479.5 days in untreated groups and treated groups, respectively (Wei *et al*., 2003). It is unclear if there is a class effect from other ACEIs for treatment in HIVAN as recent clinical studies we have reviewed only demonstrated potential benefits in fosinopril and captopril (Burns *et al*., 1997; Kimmel *et al*., 1996; Wei *et al*., 2003).

In brief, even though the available data regarding the efficacy of fosinopril in decreasing proteinuria and improving renal survival time came from a group of researchers and might have had bias due to lack of randomization, given fosinopril with HAART in selected patients without hyperkalemia, hypotension or other contraindications for ACEI may provide benefits more than risks.

1.8. Corticosteroids

Most of the available information for corticosteroids in HIVAN was published in pre-HAART era. Most of evidence came from case reports or small cohort study without controlled groups and the majority of population in every study were already treated with ARVs or had a history of prior ARV exposure which could affect outcomes (Smith *et al*., 1994; Watterson *et al*., 1997). Smith *et al*. (1994) prospectively evaluated the effect of prednisone in 20 HIVAN patients and concluded that prednisone was able to improve serum creatinine and proteinuria. Duration of treatment varied for each patient (range 2 to 26); it was based on the response of serum creatinine, development of steroid-induced side effects or opportunistic infections. However, 19 patients in this study had exposed to at least ARV monotherapy (Smith *et al*., 1996). Another retrospective study in 21 biopsy-proven HIVAN, treated and controlled groups had non-significant baseline characteristics in term of co-morbidities, renal functions, CD4 level, HIV viral load and potential co-founding medications use including ARVs and ACEI, demonstrated preserved renal function and no difference in the incidence of infection or hospitalization in treatment (Eustace *et al*., 2000).

1.9. Renal Replacement Therapy and Renal Transplantation

Though AIDS-defining illnesses have decreased after the introduction of antiretroviral drugs and HIV-infected individuals have longer life expectancy, late-stage organ diseases including End Stage Renal Disease (ESRD) have increased (Mocroft *et al*., 2002). Currently, renal transplantation and renal replacement therapy (hem dialysis and peritoneal dialysis) are valid options in selected patients. Renal transplantation was absolute contraindication in the past, due to a concern of drug-drug interactions of immunosuppressive drugs and ARVs and risks of Opportunistic Infections (OIs) in the setting of post-transplant immunosuppression.

Criteria for including HIV-infected patients on the transplant list (Trullas *et al*., 2011):

- Clinical criteria: Ideally, patients should not have OIs or AIDS-defining diseases. However, some OIs (previous tuberculosis, Pneumocystis jiroveci pneumonia, esophageal candidiasis) are not exclusion criteria in United States.
- Immunological criteria: CD4 should be more than 200 cells/mm^3
- Virological criteria: Patients should have undetectable HIV-1 RNA viral load.
- Other criteria: Patient should have favorable psychiatric evaluation and not actively use alcohol or substance.

2. CONCLUSION

HIVAN is an aggressive form of FSGS in HIV-infected patients, particularly in African-American population. Apart from HIV, host genetic susceptibility and host response to HIV infection also play a crucial role in the development of the disease. Only renal biopsy is definitive for diagnosis because no clinical criteria could provide accurate diagnosis of HIVAN. The information about treatment is still inconclusive; however, all standard treatment guidelines recommend initiating HAART in every HIV-infected individual with HIVAN, regardless of CD4 count. Other adjunctive therapy including ACEI might be considered in selected patients.

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