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Pharmacotherapy and Treatment Options for HIV-Associated Nephropathy

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Abstract

Introduction: Human immunodeficiency virus (HIV) remains a worldwide disease with significant mortality and morbidity. There are a multitude of HIV-related kidney diseases including HIV-associated nephropathy (HIVAN) most prominently. The risk of developing HIVAN increases with decreasing CD4 count, higher viral load, and based on genetic factors. The mortality rate for those with HIVAN-end stage renal disease (ESRD) remains 2.5–3 times higher than ESRD patient without HIVAN.

Areas Covered: The epidemiology of HIVAN, particularly risk assessment will be explored in this review. Further, the pathogenesis of HIVAN, from viral-specific renal expression to the role of genetics as well as characteristic renal pathology will be described. Diagnosis and treatment of HIVAN focusing on ESRD progression, will be addressed with an emphasis on various treatment strategies, including medication, dialysis, and kidney transplantation.

Expert Opinion: HIVAN is associated with a high risk for progression to ESRD and increased mortality. The backbone of HIVAN therapy remains cART, while adjunctive therapies including RAAS blockade and prednisone, should be considered. In those who progress to ESRD, dialysis remains the mainstay of management, though increasing evidence has demonstrated that kidney transplantation can be effective in those with controlled HIV disease.

Keywords

ESRD; dialysis; HIV; HIVAN; kidney biopsy; transplantation

1. Introduction

Human immunodeficiency virus (HIV) remains a worldwide disease, and despite advances in combined anti-retroviral therapy (cART) over the past several decades, the mortality and morbidity associated with HIV remain staggering, especially in the developing world.(1, 2) The most updated World Health Organization (WHO) data regarding the global burden of

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Declaration of interest

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this disease from 2015 notes that 36.7 million people worldwide are living with HIV infection, with the vast majority (25.5 million) in Africa. There were an estimated 1.1 million deaths in 2015 attributed to AIDS-related illnesses.(3)

There are a multitude of HIV-related kidney diseases including HIV-associated nephropathy (HIVAN), immune complex kidney disease in the setting of HIV, thrombotic microangiopathy, and drug-induced kidney disease from medications such as tenofovir (Table 1).(2, 4) Further, it is clear that kidney disease is a common cause of morbidity and mortality in HIV-positive patients, with the risk of death in HIV-positive patients significantly higher in those with acute kidney injury (AKI).(5–7) In order to determine the prevalence of HIVAN, it is imperative to understand the predictors of HIVAN or its major risk factors. Those include African ancestry particularly with the presence of apolipoprotein-1 (*APOLI*) gene variants, high viral load, low CD-4 count indicating lack of therapy, nephrotic-range proteinuria, and increased renal echogenicity on ultrasound, suggestive of parenchymal disease, which in the presence of HIVAN correlates with severity. (4, 8–11) In a clinical cohort from Baltimore, MD from 1989 to 2001, the overall incidence of HIVAN was 8.0 per 1000 person-years but was 26.4 per 1000 person-years in those not receiving cART.(10)Originally named "acquired immune deficiency syndrome (AIDS) nephropathy," HIV-associated nephropathy (HIVAN) was first reported in 1984.(12) Rao and colleagues described focal and segmental glomerulosclerosis (FSGS) in 11 patients (10 of whom of African ancestry) among 92 diagnosed with AIDS who presented to King's County Medical Center in New York City over a 2-year period. Those 11 patients were found to have proteinuria, 9 of whom with overt nephrotic syndrome. Overall, the course of kidney disease in those patients was marked by rapid progression to severe uremia. The existence of AIDS nephropathy was not readily accepted due to the low incidence of the disease in certain geographic, predominantly white, areas severely affected by the AIDS epidemic. Renal biopsy specimens in seven living patients, and three at time of autopsy, showed FSGS with IgM and C3 deposition, with the 11th patient having IgG and C3 deposition, leading the authors to conclude that there is an entity of AIDS-associated FSGS, leading to rapid deterioration in renal function, now termed HIVAN. From a pathophysiologic standpoint, HIVAN is a form of podocytopathy manifested by the presence of collapsing glomerulopathy with active tubulointerstitial inflammation. At least one glomerulus with collapse of glomerular basement membranes should be present accompanied by hypertrophy and hyperplasia of the overlying glomerular epithelial cells specifically. Active tubule-interstitial nephritis manifested by microcytic tubular dilatation, interstitial inflammation, and tubular injury. HIVAN is manifested clinically with a rapid rise in serum creatinine (sCr) and proteinuria. (13, 14)

2. Epidemiology

The incidence of HIVAN peaked in the mid-1990s and has remained stable after an initial decline, attributed to the introduction of cART in 1996.(15, 16) As an almost exclusive disorder of individuals of African descent, the prevalence of HIVAN in this population has ranged anywhere from 3% to 12%. One autopsy study reported HIVAN prevalence of 12% (25 of 209 autopsies) in those of African descent.(17) The predilection of HIVAN for black race has also been reported in Europe. This striking racial predilection for African

Americans is independent of any comorbid condition or intravenous drug use. In a retrospective study of 88 HIV-positive patients with biopsy-proven glomerular lesions in France, 26 patients were found to have HIVAN.(18) The vast majority of these patients (97%) were of African ancestry, with >90% having a CD4 count <200/mL.

More recent studies have shown that even in the current era, those with HIVAN progressing to ESRD, compared to those with ESRD from other etiologies, were more likely to be male, African American, uninsured, and unemployed.(19) Razzak and colleagues looked at United States Renal Data System (USRDS) data with HIVAN listed as the primary cause of ESRD by ICD-9 codes to determine the number of patients progressing to ESRD requiring dialysis; notably these patients were not chosen based on biopsy-proven HIVAN. At present, the mortality rate for those with HIVAN-ESRD remains 2.5–3 times higher than ESRD patient without HIVAN.(19). While there have been a dearth of recent epidemiologic studies regarding HIVAN in the U.S., overall, there has been a decrease in the proportion of biopsy proven HIVAN relative to other HIV-associated kidney diseases since the advent of cART. (16, 20)

3. Pathogenesis

3.1. Viral Specific Expression

Medapalli and colleagues eloquently described the pathogenesis of HIVAN, broken up into a number of viral-specific and host-mediated factors.(21) First, HIV-1 expression must be present in the kidney for development of HIVAN, as demonstrated by early murine models. For example, in an HIV-1 transgenic mouse line with a phenotype similar to that of HIVAN, activation of transgene expression by ultraviolet light lead to the typical appearance on histology of HIVAN. {198 Bruggeman, L.A. 1997} } Even after fetal kidney explants from the transgenic murine line were transplanted into control mice, exposure to UV light to induced transgene expression lead to the development of HIVAN in these normal hosts. Further, it was also demonstrated the importance of persistence of HIV pro-viral DNA in renal tubular epithelial (RTE) cells.(22) HIV replication was shown to occur in RTE cells, where HIV-1 pro-viral DNA can remain detectable even with undetectable serum viral loads. While RTE's do not contain CD4 receptors, it has been postulated that tissue mononuclear cells infected with HIV-1 virus gain access the RTE's on the basolateral surface, after which the virus can cause direct injury. *In vitro*, this has then led to RTE cell growth inhibition and degenerative changes.(23)

In the clinical setting, this phenomenon of persistent HIV infection of kidney tissue despite undetectable viral load was described by Winston and colleagues.(24) Stock and colleagues offer a number of explanations for this observation of reduced graft survival in HIV positive patients receiving kidney transplantation.(25, 26) In HIV-positive patients undergoing kidney transplant, unexplained reduced graft survival was observed at 3 years suggesting persistent recipient HIV infection as a cause through various mechanisms. They hypothesize there may be increased allosensitization due to the presence of human leukocyte antigen molecules contained within the HIV virus. Further, the development of memory T cells may increase responsiveness in general of these T cells, leading to increased alloimmunity. Finally, memory T cell formation from prior infections can lead to cross-reactivity. This was

subsequently confirmed in protocol renal transplant biopsies from 19 recipients with HIV-1 who did not have detectable levels of plasma HIV-1 RNA at transplantation. (26) Out of 19 recipients, HIV was detected in 13 (68%) allograft kidneys, in either podocytes (38% of recipients) or tubular cells only (62% of recipients).

3.2. Genetics:

The genetic role in the development of HIVAN, and kidney disease in general, has been increasingly investigated in recent years. As Abbott and colleagues describe, in the pre-cART era, HIVAN had the strongest association with African American race and progression to ESRD over any other cause of renal failure with the exception of sickle cell disease.(27) While it was previously thought that a polymorphism in the MYH9 gene on chromosome 22 was central to the higher risk of CKD in those of African ancestry, two groups in 2010 concurrently described the new and more likely genetic risk gene, the *APOL1* gene (encoding apolipoprotein L1), also located on chromosome 22 close to the MYH9 locus.(28, 29) Genovese and colleagues described two variations; G1 and G2, in the *APOL1* gene that are associated with increased susceptibility to FSGS and hypertension-associated ESRD in African Americans.(28) The wild type is the G0/G0 genotype while kidney disease high-risk genotypes are G1/G1, G1/G2, and G2/G2. Approximately 12% to 14% of black Americans carry *APOL1* high-risk variants (2 risk alleles, G1 or G2).(28) The G1 allele consists of two missense mutations, rs73885319 and rs60910145, leading to the variants S342G and I384M. This kidney risk allele was found in 52% of FSGS in this study compared to 18% in geographically matched African American controls without kidney disease. The G2 allele, consisting of a 6 base-pair deletion, (rs71785313), was noted in 23% of FSGS cases compared to 15% in controls. Tzur and colleagues demonstrated that these two missense mutations S342G and I384M protect against *Trypanosoma brucei rhodesiense* transmitted by the tsetse fly and leading to African sleeping sickness.(29) The protective effect against this disease may have led to these variants being passed down to those of African ancestry via natural selection. These authors examined the lower incidence of HIVAN among HIV-positive patients of East African Ancestry carrying the wild type *APOL1* genotype (G0/G0), namely Ethiopians, compared to those from other parts of Africa. A smaller proportion of *APOL1* missense mutations was noted in those from northeastern Africa, compared to those from central, western, and southern Africa, where sleeping sickness has historically been more prevalent.(29)

Kopp and colleagues described the role of *APOL1* variants in the development of HIVAN. (30) Patients with *APOL1* high-risk alleles were found to have 17-fold higher odds of FSGS and a 29-fold higher odds of the development of HIVAN, in the HIV population. Although the majority of African-American patients with HIVAN have two *APOL1* risk variants, the minority had none despite having similar clinical and pathologic characteristics suggesting other host or environmental factors triggering this disorder.(31)

3.3. Pathology and clinical presentation

From a pathological standpoint, HIVAN is characterized by a collapsing glomerulopathy, distinct from other forms of HIV associated kidney disease (Figure 1), including minimal change disease, immune complex kidney disease in the setting of HIV, HIV-associated

thrombotic microangiopathy, etc. (13) Other, more specific features of HIVAN on biopsy include collapse of glomerular capillaries, parietal cell proliferation with extensive foot process effacement, the specific absence of immune complex deposition, mesangial hypercellularity, and microcytic tubular dilatation (Figure 1).(2, 13, 32, 33) Electron microscopy can often show tubular reticular inclusions as well. The pathological features of HIVAN are currently being updated by renal pathology experts.

HIVAN often presents with severe proteinuria and acute to sub-acute decline in renal function, attributed to interstitial inflammation and glomerular injury, in the setting of uncontrolled HIV infection. We and others have previously examined the utility of non-invasive measures including ultrasonography, proteinuria, CD4 count, viral load, and APOL1 risk variants in predicting HIVAN in HIV-positive patients.(8, 9, 11, 34–37) Based on these data, none was deemed sufficient to preclude the need for kidney biopsy in patients suspected of having HIVAN.

4. Therapy

In 2013 Yahaya and colleagues published a Cochrane review summarizing observational studies to date regarding the management of HIVAN, noting that no randomized controlled trial data exist regarding medical therapy and effects in HIVAN.(38) Their findings noted 11 observational studies that investigated the response of HIV positive patients with biopsy-proven HIVAN over various follow up periods. Their summarized findings, as well data from additional retrospective trials, are listed in Table 2. In general, management of HIVAN can be broken down into medical therapy, including inhibition of the RAAS pathway, as well as cART, with progression to renal replacement therapy (RRT) and transplantation as patients progress to ESRD (Figure 2).

4.1. cART

In the pre-cART era, when HIV was universally fatal, the progression to ESRD was inevitable, if they lived to reach ESRD. However, the rates of HIVAN, and HIV-related ESRD has declined significantly since cART was introduced.(16, 19, 39) This continues to be the mainstay of treatment at the time of diagnosis, regardless of CD4 count, though there remains a significant risk to progression to requiring renal replacement therapy and/or renal transplantation.

Bige and colleagues conducted a study of patients with HIVAN and their outcomes after the introduction of cART.(39) Patients in this study were most predominantly of African origin (87%), and with severe proteinuria ranging from 0.6–16.8g/24 hours (average of 4.1g). The median CD4 count in this study was also notably low, at 127 copies/ μ L. In this and other studies, the rate of progression of renal disease is notable. The median renal survival time in this study was 40 months, and overall 60% of patients progressed to ESRD. In this study, co-infection with HCV and HBV were associated with progression to early ESRD.

Following the introduction of cART, the proportion of patients with HIVAN has steadily declined. One study showed that in the United States, the rate of HIVAN has decreased from 75% of all HIV-related kidney disease to 29% in a cohort of 88 HIV-1 positive individuals

spanning 1995 through 2007(18, 40) One study demonstrated the use of cART reduced the mortality in patients with HIVAN by 57%, compared to those not on cART.(41) We have previously published the Johns Hopkins experience regarding use of ART in HIVAN, from a cohort of 263 consecutive HIV positive patients at the Johns Hopkins Nephrology clinic from 1995–2004.(42) Out of this cohort, 152 patients underwent kidney biopsy, of whom 53 received a diagnosis of HIVAN. Among these patients, 36 met inclusion criteria, and 26 received cART while 10 did not. Renal survival was significantly improved among the patients receiving ART compared to those who did not, with an adjusted hazard ratio of 0.30 (95% CI 0.09–0.98; $P < 0.05$).

The HIV Medicine Association of the Infectious Disease Society of America (IDSA) released clinical practice guidelines regarding the care of HIV positive patients with chronic kidney disease in 2014. These authors place a strong recommendation to initiate cART at the time of biopsy-proven, or clinically suspected HIVAN to reduce the risk of progression to ESRD.(43)

4.2. Steroid therapy

Smith and colleagues published two studies prior to the cART era, in 1994 and 1996, investigating the role of corticosteroid therapy in the management of patients with HIVAN(44, 45) In their first study, the authors enrolled four patients with HIV and a CD4 count of $<200/\mu\text{L}$, biopsy-proven HIVAN, a serum creatinine $>2 \text{ mg/dL}$ and at least 2 grams of proteinuria on a 24 hour collection. These patients were given 60 mg prednisone daily for 2–6 weeks. At the end of therapy, serum creatinine levels decreased from an average of $9.1 \pm 5.7 \text{ mg/dL}$ to $3.3 \pm 1.8 \text{ mg/dL}$ ($P < 0.05$) though 24-hour urinary protein excretion was unchanged overall.

In a follow-up study published two years later, the investigators enrolled a total of 20 HIV-positive patients with a similar biochemical profile though with either biopsy-proven (17) or clinically suspected (3) HIVAN.(45) These patients were treated with prednisone 60 mg daily for a range of 2 to 11 weeks with a taper over the following 2 to 26 weeks and then with close follow-up ranging from 8–107 weeks. Over an average of 44 weeks of follow-up, 8 out of the 20 patients eventually required initiation of dialysis, 11 patients died and 7 had not progressed to ESRD. Notably, 6 patients reportedly developed a serious infection while on steroid therapy. Notably, there was a significant reduction in the average serum creatinine from $8.1 \pm 1.2 \text{ mg/dL}$ to $3.0 \pm 0.4 \text{ mg/dL}$ ($P < 0.001$) though 5 patients relapsed after steroid therapy was stopped; however, for these patients, serum creatinine again declined after re-initiation of prednisone. 13 patients were followed for 24-hour protein excretion, and 12 out of 13 showed a marked reduction in proteinuria from $9.1 \pm 1.8 \text{ g/day}$ to $3.2 \pm 0.6 \text{ g/day}$ ($P < 0.005$).

Esutace and colleagues later conducted a retrospective cohort study investigating the effectiveness and safety of prednisone therapy in HIVAN.(46) Out of 21 patients with biopsy-proven HIVAN and serum creatinine $>2 \text{ mg/dL}$, 13 patients received prednisone therapy, with an average serum creatinine at baseline of 6.2 mg/dL , compared to 8 who did not, with an average serum creatinine of 6.8 mg/dL . Patients in the prednisone group received a regimen of 60 mg daily for one month, followed by a gradual taper over several

months (range of 2.3 to 9.4 months total course). On long-term follow-up, the relative risk of progressive CKD, defined in this study as a rise from baseline serum creatinine at time of biopsy when measured three months later, was 0.20 (95% CI: 0.05, 0.76, $P<0.05$) in the prednisone group compared to the non-prednisone treated group. The mean 24-hour urinary protein excretion also decreased by an average of 5.5 g in 24 hours ($P=0.01$) in this population. Similar to prior studies, these authors found that the vast majority (7/8) patients not treated with prednisone required dialysis, compared to 5 out of the 13 who received prednisone. Given these and other findings, the IDSA recommendations from 2014 (though with a designation of a weak recommendation based on low-quality evidence) note that steroids should be considered as an adjunct to cART and RAAS blockade in those with biopsy-proven HIVAN.(43). Important to note with the use of steroids, in the studies presented and as reflected in the IDSA guidelines, patients were required to have evidence of kidney injury, usually with sCr >2.0 mg/dL and or proteinuria of 2g/day or greater, along with biopsy proven HIVAN. Also, patients were excluded in the trials of steroid therapy if they had any evidence of active infection, often required to be abstinent of active IV drug use. Further, corticosteroid use comes with risk of avascular necrosis in patients with HIV, as well as the potential to increase risk of other infections.(43)

4.3. RAAS Blockade

The role of RAAS blockade has been studied extensively both in the clinical setting as well in murine models of HIVAN. Bird and colleagues published a study demonstrating the effects of captopril in a transgenic mouse model phenotypically resembling HIVAN.(47) These authors treated wild type and transgenic T26 mice with captopril between the ages of 7 and 100 days. In the transgenic line, those treated with either low (30 mg/kg) or high-dose (100 mg/kg) captopril had a lower mortality, reduced urine protein/Cr, lower BUN than transgenic mice treated with placebo. More recently, Shimizu and colleagues have shown a similar result with ARB use in a murine model, demonstrating ARB treatment attenuated podocyte injury and glomerular scarring when given losartan (30 mg/kg) compared to placebo.(48)

From a clinical standpoint, a number of case reports and small studies have investigated the role of angiotensin-converting enzyme (ACE) inhibition in HIVAN.(49, 50) Kimmel *et al.* published a matched cohort study of 18 patients with biopsy proven HIVAN, 9 of whom received captopril and 9 without ACE inhibitor (ACEi) therapy.(51) Renal survival, defined as time from biopsy with or without initiation ACEi therapy to time on dialysis, was significantly longer for patients receiving captopril (156 days vs. 37 days; $P<0.002$). Following a case report of successful ACEi use in a patient with HIVAN, Burns and colleagues published a retrospective study of ACEi therapy in 20 patients with HIVAN in 1997.(52, 53) Out of 11 patients with nonnephrotic proteinuria, 7 received fosinopril 10 mg daily, while 4 did not. At 24-week follow-up, those who received ACEi had a lower serum creatinine and 24-hour protein excretion compared to those without treatment ($P=0.06$ and 0.02 respectively). Out of the other 9 patients who did have nephrotic range proteinuria, 5 patients received fosinopril therapy. In this population, those who received ACEi therapy had a lower 24-hour protein excretion at 12-week follow-up ($P=0.02$). More recently, Wei and colleagues conducted a prospective cohort study of 44 patients with biopsy-proven HIVAN,

enrolled prior to severe kidney injury with an enrollment criterion being a serum creatinine level <2.0 mg/dL.(54) Over the course of more than 5 years, 28 patients were treated with fosinopril 10 mg daily while 16 were given placebo. Again, renal survival, or time to ESRD, was significantly longer in those patients treated with ACEi (479.5 days vs 146.5 days; $P<0.0001$).

4.4. Progression to End-Stage Renal Disease

Renal replacement with dialysis in any of its available forms should be offered to HIVAN patients who progressed to ESRD. In contrast to those with chronic hepatitis B infection, isolation of HIV positive patients in the dialysis center is not required. In view of the overall decline HIVAN incidence, progression to ESRD has predictably decreased in cohort data. For example, Chaudhary and colleagues outlined the trends in incidence of patients with HIVAN progressing to ESRD between 1989 and 2011.(19) The author here demonstrated a persistent rise in the rates of HIVAN-ESRD through 2006, with a steady decline since that time through 2011. As described previously, it is important to note that the authors analyzed USRDS data for HIVAN as a diagnosis for ESRD requiring dialysis, though these patients did not necessarily all have biopsy-proven HIVAN. While there still exists a significant burden of morbidity and mortality in patients requiring RRT, there was a significant decline in mortality between those who started HD in 1999/2000 compared to those started between 1989 and 1992 (40%). When compared to those patients who started dialysis between 2009–2011, the difference in mortality was even greater (64%). In keeping with other epidemiologic studies for HIVAN in general, the HIVAN-ESRD cohort was predominantly of African ancestry (>90%) with 70% being male. In a resource-limited urban area, among HIV positive African Americans with ESRD of any cause and are undergoing RRT, older age, lower serum albumin level, lower CD4 cell count, and the lack of cART were demonstrated as independent predictors of poor survival.(55) In another study, Sexton and colleagues investigated the number of patients starting maintenance RRT between the years 2001–2010(56). Compared to 2001–02, when 1,669 new patients were started on RRT for HIVAN as a primary diagnosis (based on the ESRD Medical Evidence Report), the incidence of new RRT start continued to rise through 2005–06, when 1709 patients were initiated. The trend has since been downward, with 1573 new patients started on RRT between 2007–08, down to 1359 patients in 2009–10. In this study, only 2.1% of patients went on to renal transplantation. Further research focused on longitudinal data in those with biopsy proven HIVAN is required to determine a more refined information on trends of ESRD progression in this population.

4.5. Kidney Transplantation

HIVAN has historically been considered a contraindication for renal transplantation, though recent studies have shown that renal transplantation is safe and effective in selected patients. (57–59) In a prospective trial of 18 kidney transplant patients with HIV published in 2008, 3-year recipient survival was 94%, with graft survival was 83%, similar to the general transplant population based on 1999–2004 transplant data.(60) Recurrent HIVAN was not commonly seen in recipients.

One theory suggests that recurrent HIVAN depends on having the *APOL1* in the donor kidney and not based on recipient's genotype, which was explored by Freedman and colleagues.(61) These authors investigated outcomes of a total of 1,153 African American deceased donor kidney transplantation (DDKT) donors with *APOL1* genotype analyzed in addition to adjustments for a number of factors including age, sex, race, HLA match, cold ischemia time, and donor age. These authors found that donor kidneys with 2 high-risk *APOL1* variant alleles had higher follow-up serum creatinine levels and decreased renal allograft survival compared to *APOL1* heterozygotes and those with no high-risk alleles at 6-year follow-up ($P=0.0003$), though overall recipient survival was similar. In a small retrospective analysis on the outcomes of renal transplantation in 11 patients with biopsy-proven HIVAN, delayed graft function was noted in 7 out of the 11 patients (64%), 6 requiring post-operative dialysis.(59). While the rate of delayed graft function was higher than in the general ESRD population, 1 and 3-year graft survival (100% and 81%, respectively) were not significantly different compared to the non-HIV positive population.

Since the initiation of renal transplantation in HIV-positive patients, there are robust data showing good graft and recipient survival in a select population.(58, 62) There are still no definitive selection criteria for HIVAN recipients; Frassetto and colleagues explored this further in their review from 2009.(58) These authors proposed criteria for renal transplantation for HIV-positive patients based on prior retrospective studies. In addition to meeting the standard criteria for all transplant recipients, HIV-positive patients should have CD4 ≥ 200 at least 16 weeks prior to transplantation, adherence to a stable cART regimen, follow-up with a dedicated HIV specialist, nephrologist with expertise in this discipline, among others. Overall, more work in this area is needed to define these criteria in a more standardized fashion. To this end, the HIV Optimized Patient Experience (HOPE) Study is an ongoing large, multi-national prospective study to evaluate the safety and efficacy of this strategy as well as tackling the issue of organ shortage for this population.

Notably, over the past several years, the practice of HIV-positive donor to HIV-positive recipient kidney transplantation has been successfully implemented, carried forth by seminal work from Dr. Muller in South Africa and Dr. Segev in the U.S. following provisions from the HOPE Act.(63, 64). In the South African experience, where roughly 30% of HIV positive patients suffer from HIVAN, potential donors must have a normal sCr and no evidence of proteinuria.(65) Short-term outcomes have demonstrated that out of 29 recipients, 5 died after transplant, 2 patients suffered allograft failure within 1 week post transplant, and a third patient had graft failure after two years. Longer-term outcomes data are required to determine the effect on the re-development of HIVAN in this population.

5. Conclusion

Patients with HIV, particularly those with *APOL1* high risk alleles and those with poorly controlled HIV as evidenced by high viral load and low CD4 count, are at increased risk for developing HIVAN. HIVAN remains a major risk factor for progression to ESRD requiring either dialysis or renal transplantation, and places patients at a much higher risk for death. While certain diagnostic tests may aid in the diagnosis of, or be suggestive of, HIVAN, including kidney ultrasound, urinary protein excretion, and uncontrolled HIV particularly in

the setting of high risk APOL1 variants, the gold standard for diagnosis remains kidney biopsy. Currently, cART remains the mainstay of treatment of HIVAN, either biopsy proven or clinically suspected. Other therapies including RAAS blockade and prednisone therapy, should be considered in the appropriate clinical context. Ultimately, for those who progress to ESRD, dialysis remains the mainstay treatment strategy, though increasing evidence has demonstrated kidney transplantation can be very effective, in the right patient population.

6. Expert Opinion

Since the start of cART, the rates of HIVAN have declined, though this remains a significant burden especially in those untreated with cART and in terms of progression to ESRD and mortality. Furthermore, in order to appreciate the most accurate representation of the prevalence and true impact of HIVAN, precise diagnosis must be addressed. While other methods have been employed as surrogate markers for HIVAN, kidney biopsy remains the gold standard for diagnosis. Further research is needed to explore other non-invasive techniques, including imaging such as nontoxic gas-filled microbubbles sonogram and laboratory assays, to identify those with HIVAN, particularly in patients in whom kidney biopsy is contraindicated. Such methods may be even further used to determine who may be at risk for HIVAN in order to guide future HIV treatment strategies. With these tools, one can make stronger inferences on treatment strategies and specifically on trends in the development, progression, and outcomes of HIVAN.

With regard to current management options, prevention remains a priority and while medical therapies such as cART, RAAS blockade, and prednisone have all shown benefit in HIVAN and CKD progression, more research is needed to determine novel therapies such as molecular targeting to prevent or delay progression to ESRD. Kidney transplantation should be considered as a treatment option in those with ESRD and controlled HIV disease. The initiation of HIV-positive donor to HIV-positive recipient kidney transplantation, in South Africa and now available in the United States, offers great promise to patients who previously may not have survived to transplantation, though long-term outcomes remain unclear as well as the lack of data on estimated risk of recurrent disease. Successful HIV management with viral load suppression and advances in kidney transplantation can substantially improve outcomes including reduction in mortality.

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- **64. Durand CM, Segev D, Sugarman J. Realizing HOPE: The ethics of organ transplantation from HIV-positive donors. *Ann Intern Med.* 2016 7 19;165:138–42 [PubMed: 27043422]
- **65. Muller E Transplantation in resource-limited setting: Using HIV-positive donors for HIV-positive patients. *Clin Nephrol.* 2015;83:39–41 [PubMed: 25725240] - These final two papers describe the future of kidney transplantation in the setting of HIV, from HIV positive donors to HIV positive recipients

Article highlights

- HIVAN remains a significant burden for patients with HIV, leading to significant morbidity and mortality.
- Combination antiretroviral therapy remains central to proper HIVAN management and can improve patient outcomes dramatically.
- Additional medical therapies including steroids and RAAS blockade in the appropriate patient population.
- Patients with HIVAN progress to ESRD at a higher rate than the general population, and dialysis remains the mainstay of management.
- Kidney transplantation has been shown to be effective in patients with HIVAN, and new milestones in the use of HIV-positive donors to HIV-positive recipients offers promise for the future.

Figure 1: Typical renal pathological features of HIVAN

A. Collapsing glomerulopathy with characteristic epithelial proliferation in Bowman's capsule.

B. Tubular cystic dilation Characteristic of HIVAN (photos courtesy of Dr. S. Bagnasco).

Figure 2: Diagram of HIVAN Diagnosis and Management:

Table 1:**Kidney Diseases in HIV-positive Patients^{2, 4}**

HIV-associated Nephropathy (HIVAN)
Immune Complex Kidney Disease in the setting of HIV
Antiretroviral Therapy-associated Nephrotoxicity - examples:
• Tenofovir - proximal tubular dysfunction
• Protease inhibitors – crystalluria
HIV-associated Thrombotic Microangiopathy
Non-HIV Related Diseases
• Acute Interstitial Nephritis
• Amyloidosis
• Diabetic Nephropathy
• Minimal Change Disease
• Membranous Nephropathy
• Post-Infectious Glomerulonephritis

Table 2:Differential Diagnosis of HIVAN^{4,32}

Membranoproliferative glomerulonephritis (especially with concurrent HCV infection)
Non-HIV related FSGS
Minimal Change Disease
Post-infectious Glomerulonephritis
Membranous Nephropathy
Immunoglobulin A (IgA) Nephropathy
Amyloidosis
Diabetic Nephropathy
Thrombotic Microangiopathy

Table 3:Treatment options for HIVAN: a summary of prior observational studies³⁸

Study	Year	Study Type	# of Patient	Population/Inclusion criteria	Treatment protocol	Results
RAAS Blockade						
Kimmel{{240 Kimmel,P.L 1996}}	1996	Retrospective	18	African Americans with biopsy-confirmed HIVAN	Captopril 3 times a day vs nothing	Progression of kidney disease was significantly lower in treatment group
Burns{{225 Burns,G.C. 1997}}	1997	Retrospective	20	Biopsy-confirmed HIVAN in homosexual men, proteinuria > 0.5 g/24 hours and Scr < 2 mg/dL	Fosinopril 10 mg daily vs nothing	Scr and proteinuria were significantly lower in the Fosinopril group at 12 and 24 weeks
Wei{{235 Wei,A. 2003}}	2003	Prospective	44	HIVAN (clinically or biopsied confirmed) patients with normal BP and SCr < 2 mg/dL and	Fosinopril 10 mg daily vs nothing	Survival was higher in Fosinopril group. Progression to dialysis significantly lower in the treatment group
Szczech{{234 Szczech,L.A. 2004}}	2004	Retrospective	89	HIV patients who had kidney biopsy	11 patients with HIVAN received ART, 6 patients with HIVAN received ACEI/ARBs, 16 patients with no HIVAN took ART and 10 patients with no HIVAN received ACEI/ARBs	Progression of kidney disease was slower in patients with HIVAN who received ART therapy. Patients who received ACEI/ARBs had slower progression to dialysis compare to others
Steroid Therapy						
Smith{{233 Smith,M.C. 1996; 232 Smith,M.C. 1994}}	1994	Case series	4	HIVAN confirmed by biopsy and CD4 < 200 cells/uL with 24 h proteinuria > 2 g and kidney dysfunction	All patients received 60 mg/d of prednisolone for 3–6 weeks	Scr significantly improved in all patients with no change in proteinuria/24 h
Kalayjian{{228 Kalayjian,R.C. 1995}}	1995	Case series	14	HIVAN (clinically or biopsy-confirmed)	All patients received 60 mg prednisolone for an average of a 1	Scr significantly trended down in 12

Study	Year	Study Type	# of Patient	Population/Inclusion criteria	Treatment protocol	Results
					month followed by taper (over 5 weeks)	patients after a median of 5 weeks
Smith{ {233 Smith,M.C. 1996} }	1996	Prospective	20	HIVAN (clinically or biopsy-confirmed) with 24 h proteinuria > 2 g and Scr > 2 mg/dL	Prednisolone 60 mg/d for average 2–11 weeks followed by taper over 2–26 weeks	Scr and proteinuria/ 24 h significantly improved in treated patients
Eustace{ {227 EustaceJ.A. 2000} }	2000	Retrospective	21	Biopsy-confirmed HIVAN, Scr>2 mg/dL	60 mg of prednisolone × 1 month followed by slowly taper (over 2–4 months) vs nothing	Progression to dialysis with azotemia, Scr and proteinuria were significantly lower in treatment group
ART						
Cosgrove{ {226 Cosgrove,C.J. 2002} }	2002	Retrospective	23	African American and Hispanic patients with clinically and biopsy confirmed HIVAN	cART vs nothing	Mortality and progression to dialysis were lower in the cART therapy group
Atta{ {245 Atta,M.G. 2006} }	2006	Retrospective	53	HIV-1 patients with biopsy-proven HIVAN	ART vs nothing	Renal survival significantly higher in treatment group
Kalayjian{ {229 Kalayjian,R.C. 2008} }	2008	Prospective multicenter	1776	HIV-1 patients treated with ART	cART for HIV-1 patients	Decrease in HIV viral load to < 400 copies/mL significantly associated with increase in GFR (9.2 from baseline)
Peters{ {231 Peters,P.J. 2008} }	2008	Prospective	508	HIVAN patients diagnosed clinically and received cART therapy × 24 months	cART therapy × 24 months	Scr and CrCl were significantly improved in 24 months