REVIEW ARTICLE

HIV-related nephropathy: new aspects of an old paradigm

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SUMMARY

The scenario of infection by the human immunodeficiency virus (HIV) has been undergoing changes in recent years, both in relation to the understanding of HIV infection and regarding the treatments available. As a result, the disease, which before was associated with high morbidity and mortality, is now seen as a chronic disease that can be controlled, regarding both transmission and symptoms. However, even when the virus replication is well controlled, the infected patient remains at high risk of developing renal involvement, either by acute kidney injury not associated with HIV, nephrotoxicity due to antiretroviral drugs, chronic diseases associated with increased survival, or glomerular disease associated to HIV. This review will cover the main aspects of kidney failure associated with HIV.

KEYWORDS: *HIV. Renal insufficiency, chronic. AIDS-associated nephropathy.*

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) was recognized in 1981 in the United States. The human immunodeficiency virus (HIV) was isolated in patients with AIDS in 1983, initially as HIV 1 and, in 1986, HIV 2 was identified[1]. HIV is a retrovirus with an RNA genome that belongs to the Retroviridae family. It is through the reverse transcriptase enzyme that the virus is able to transcribe viral RNA into DNA and, then, integrate the host[1].

According to data from UNAIDS, approximately 37 million people worldwide were living with HIV in 2017, and 940,000 people died of AIDS-related causes[2]. National data show that, in Brasil, over 42,000 new cases of HIV infection were diagnosed in 2017. However, what is observed over the years is a reduction in the detection rate of new AIDS cases, which is attributed to the recommendation of "treatment for all" implemented in 2013[3].

HIV infection is associated with various forms of renal involvement; this spectrum includes an involvement directly associated with the viral infection or immune response and also to the treatment against the virus[3,4]. Renal involvement associated with HIV was first described in 1984 and was characterized by kidney failure and proteinuria. Since then, different forms of nephropathy have been described, both as a result of the direct effects of the virus on the kidney and of the medications, which involve acute kidney injury, chronic kidney disease, and renal toxicity[5,6].

The pathogenesis of kidney disease associated with HIV is still poorly understood. The mechanisms proposed include direct injury of the parenchymal cells caused by viruses or indirect injury caused by the release of cytokines. However, we still have not been able to identify how the virus enters the cell[7]. In patients infected by HIV, kidney disease has become

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an important cause of mortality[7,8]. The development of combination antiretroviral therapy prolonged patient survival and changed the spectrum of kidney diseases in HIV-infected patients, decreasing the prevalence of glomerular diseases and increasing the prevalence of nephrotoxicity and comorbidities[8].

ACUTE KIDNEY INJURY IN HIV INFECTION

Acute kidney injury (AKI) is defined by the guidelines of the Kidney Disease Improving Global Outcomes (KDIGO 2012) as the presence of one of the following criteria: increased level of serum creatinine at 0.3 mg/dl or more at 48h, increased serum creatinine level at 1.5 times or more the basal level in 7 days, or urinary debt lower than 0.5 ml/kg/h for 6 hours[9]. It is known that AKI is more frequent among individuals infected by HIV than in those not infected, and its incidence varies considerably between studies since most are heterogeneous retrospective analyses in relation to the characteristics of the patients and follow-up time[8,10]. However, the lowest incidence rate of AKI is reported in outpatients, ranging from 5.7 to 9.4%, reaching up to 66% in more severe patients[8].

The identification of risk factors is fundamental to develop prevention and early diagnosis strategies. The presence of previous kidney disease is one of the most important risk factors for AKI, as well as the severity of the disease. However, the incidence of AKI seems to have decreased with the use of antiretroviral therapy, with reports of 10-fold reduction after 3 months of the start of the treatment[8,10].

The etiology is multifactorial, but pre-renal causes and acute tubular necrosis remain as significant causes of AKI. The main etiologies are sepsis, volume depletion, and nephrotoxicity, corresponding to approximately 40% of the cases[8,10,11]. Nephrotoxicity evolves with varied presentations of AKI, such as acute tubular necrosis, interstitial nephritis, mainly associated with antiviral drugs or drugs such as sulfamethoxazole/trimethoprim, acyclovir and amphotericin B, crystalluria/obstruction, renal tubular disorders, and pre-renal disorder[8]. AKI of post-renal etiology is unusual in patients infected by HIV; crystalluria is induced by medication, causing deposition of insoluble crystals and obstruction, one of its main causes[8].

CHRONIC KIDNEY DISEASE IN HIV INFECTION

The prevalence of HIV-associated chronic kidney disease varies geographically and depends on the definition used[12]. In addition to having a higher risk of kidney disease, individuals infected by the virus also present greater speed of progression of renal dysfunction compared to non-infected individuals[13].

The introduction of antiretroviral therapy has increased the survival of individuals infected by HIV. However, this decrease in mortality rates has been accompanied by an increase in other related diseases, such as chronic kidney disease, which has become increasingly common in HIV-infected patients and can occur at any stage of HIV infection, even before seroconversion[13,14]. These patients have a combination of traditional risk factors, such as advanced age, black ethnicity, diabetes and arterial hypertension, in addition to the factors related to HIV, such as low CD4 lymphocyte count, high viral load, co-infection by the hepatitis C virus, use of injectable drugs, and exposure to antiretroviral therapy[11].

Since the treatment for HIV nephropathy may postpone the decline of renal function, it is recommended to screen for the disease regularly by measuring the arterial pressure, evaluating the renal function (creatinine and estimated glomerular filtration rate) and through urine examination to investigate the proteinuria, which is a common manifestation of the disease[7,14].

As a general rule, it is recommended to use antiretroviral drugs with caution in patients with chronic renal disease, avoiding nephrotoxic drugs, and adjusting the dose, with a reduction or extension of the administration period [15]. Some antiretroviral drugs, such as tenofovir, are associated with an increased risk of both the development and progression of chronic kidney disease[12]. The guidelines recommend avoiding the use of tenofovir if the glomerular filtration rate is less than 60 ml/min/1.73m^2. For patients in use of tenofovir who evolve with a decline greater than 25% in glomerular filtration rate in relation to the baseline renal function, it is recommended to replace the antiretroviral treatment by another one[12]. There is no evidence that demonstrates the best dialysis modality for HIV-positive patients. Survival in dialysis patients is similar to that of non-infected patients. There is no recommendation for isolation, nor for the exclusive use of machines in hemodialysis sessions[12].

Based on data from retrospective studies, it is known that renal transplantation is highly viable in recipients infected by HIV. One of the major challenges

is to achieve therapeutic and non-toxic levels immunosuppressants due to their interaction with antiretroviral drugs. It is recommended to avoid antiretroviral agents that act on the cytochrome P450 pathway so that it is possible to achieve a better therapeutic level of calcineurin inhibitors and decrease the incidence of renal graft rejection; integrase inhibitors are some options in this context. Induction therapy with antithymocyte immunoglobulin should be restricted to patients at a high immune risk of rejection[16].

Despite the higher rates of acute rejection in recipients infected by HIV in relation to those not infected, kidney transplant seems to be a viable renal replacement therapy in HIV patients, but some strategies need to be improved to minimize rejection and manage drug interactions[16].

EVALUATION OF KIDNEY FUNCTION

An accurate assessment of the kidney function in patients infected by HIV is essential since antiretroviral drugs are eliminated by the kidney and require dose adjustments according to the renal function, in addition to their associated effects, such as nephrotoxicity[17]. Therefore, it is recommended to screen for renal disease at the time of diagnosis and start or modification of the antiretroviral therapy[18].

Serum creatinine is the biomarker of choice for estimating the glomerular filtration rate in clinical practice, and cystatin C should be considered in cases of patients who received medications that alter the tubular secretion of creatinine, such as ritonavir or sulfamethoxazole-trimethoprim, in addition to providing a better prediction of long-term mortality[18.19].

Several equations have been used to estimate the glomerular filtration rate; CKD-EPI is currently the most noteworthy of them, having been evaluated and considered the most accurate for various populations and recommended as the first method of choice to evaluate renal function by the Guidelines of the European AIDS Clinical Society (EACS)[17]. Urine analysis should be performed in all HIV-infected patients to detect the onset or worsening of proteinuria or hematuria, and, if possible, it is recommended to measure the proteinuria (albumin/creatinine or protein/creatinine ratio).

HIV-ASSOCIATED NEPHROPATHY (HIVAN)

HIV-associated nephropathy (HIVAN) was the renal involvement initially described in HIV-infected individuals and is one of the most important causes of end-stage renal disease in this population[5.7]. In recent years, its incidence has decreased sharply. The reported prevalence is approximately 20% of HIV-infected patients, corresponding to the third main cause of end-stage renal disease among African-Americans aged between 20 and 64 years[11,20,21]. It is often found in populations with no access to antiretroviral therapy, which is the case in some regions of Africa, where the decline is less pronounced, probably due to the lower availability of antiretroviral medication[5.20].

Other factors associated with a greater incidence of

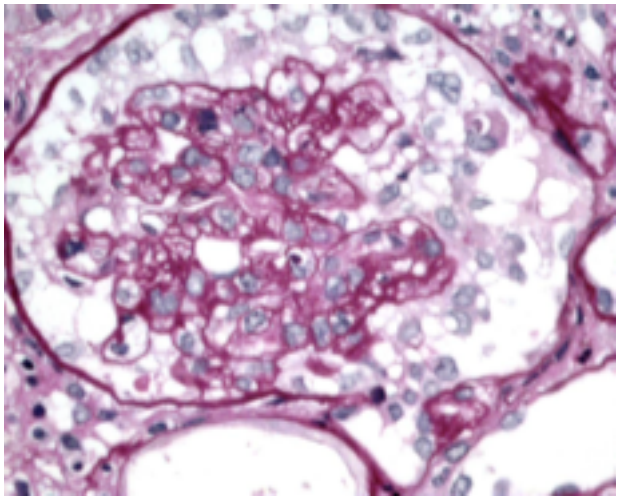

FIGURE 1. GLOBAL COLLAPSE OF THE CAPILLARY LOOPS, SURROUNDED BY HYPERTROPHIC PODOCYTES, WITH DEGENERATIVE CHANGES. (SBP - 400X). IMAGE KINDLY PROVIDED BY PROF. DR. LUIZ A. MOURA.

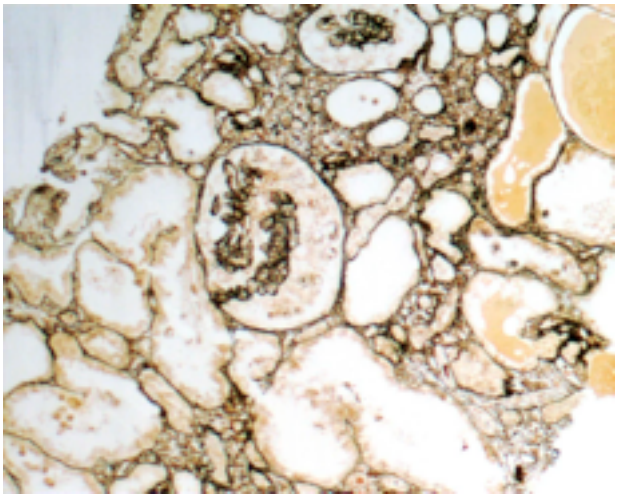

FIGURE 2. A GLOMERULUS WITH COLLAPSED CAPILLARY LOOPS AND DILATED TUBULES, WITH HYALINE CYLINDERS (INDICATED BY THE BLUE ARROW). (JONES' SILVER - 100X). IMAGE KINDLY PROVIDED BY PROF. DR. LUIZ A. MOURA.

HIVAN, besides the African-American descent (which means an estimated risk 18 times greater of developing the disease), are: advanced stage of immunosuppression with high viral load and low CD4 lymphocyte count and nephrotic proteinuria, which are associated with the risk of both development and progression to end-stage chronic renal disease[7,12]. APOL1 is a gene of the chromosome 22 whose variants APOL1 G1 and G2 were strongly associated with HIVAN[12]. The association between the genetic variants of the apolipoprotein 1 (APOL1) and HIVAN has been recognized since 2010, especially among the African population[22].

The classical presentation of HIVAN is defined as collapsing glomerulopathy, with nephrotic proteinuria, tubulointerstitial involvement with dilation and formation of tubular microcysts, interstitial inflammation, and tubular injury, whose manifestations may include hematuria, rapidly progressive kidney failure, and arterial hypertension[6,11,18]. In electronic microscopy, endothelial tubuloreticular inclusions (viral footprints) are highly specific and classical characteristics of HIVAN[11,18].

It is recommend the use of angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARB) in patients with suspected or confirmed HIVAN or clinically significant albuminuria (in diabetes mellitus, DM, with over 30mg of albumin/day, and in patients without DM with over 300 mg albumin/day), combined or not with corticosteroid therapy with the purpose of reducing proteinuria and preserving renal function, although the recommendation is based on consensus and small studies[6,9,12].

Kidney disease associated with immune complex deposition

Another form of renal involvement in HIV infection is related to intraglomerular immune complex deposition (HIVICK), which includes a spectrum of renal diseases, among them membranous and membranoproliferative nephropathy, and IgA nephropathy[20,23].

Unlike HIVAN, it is predominant among European and Asian populations and rarely affects people of African descent[12,24]. It usually occurs after years of the disease, in patients undergoing treatment with antiretroviral drugs, with lower viral load and CD4 lymphocyte counts, also unlike HIVAN, which tends to occur earlier, besides presenting a lower probability of progression to end-stage kidney disease[20,23].

Its pathogenesis is associated with changes in immune regulation and increased gamma globulin, which contributes to the formation of immune complexes[25]. Renal manifestations can be varied, depending on the extent and location of the glomerular deposits; some examples are proteinuria, hematuria, decreased glomerular filtration rate, and consumption of supplement[25]. Histologically, it is characterized by deposits of immune complexes in the capillary loops and mesangium, besides mesangial expansion and tubulointerstitial inflammation[12].

The long-term progression of renal disease associated with the deposition of immune complexes is not well defined. There are few studies on the therapy; it is assumed that the HIV infection should be controlled and that conservative measures for blood pressure and proteinuria control should be implemented[14].

Kidney biopsy: when to indicate it?

Proteinuria and renal dysfunction are not findings exclusive of HIVAN, and ultrasound parameters (kidney size and changes in the echogenicity of the renal parenchyma), proteinuria in nephrotic levels and low CD4 lymphocyte counts are not able to predict renal involvement due to HIVAN.

The indication of kidney biopsy is based mainly on the clinical presentation, typical or atypical, and the possibility of alternative diagnoses, as well as to guide the prognosis and therapy, particularly when there is significant proteinuria present[12,24].

Nephrotoxicity associated with antiretroviral therapy

The introduction of ARVT has changed the natural history of HIV infection, reducing the risk of HIVAN; however, some antiretroviral drugs can be harmful due to their direct tubular toxicity, obstruction induced by crystals, or interstitial nephritis, which makes it important to monitor the renal function during the treatment[11,26].

The antiretroviral drugs most significantly involved with renal injury are the protease inhibitors (in particular the indinavir and atazanavir) and tenofovir disoproxil fumarate[5].

Atazanavir

The risk of nephrolithiasis may be greater with atazanavir than with other protease inhibitors, especially in individuals with higher plasma concentrations of the medication, with alkaline urinary pH, dehydration, and associated kidney disease[5,26,27]. The use of atazanavir can cause three types of renal involvement,

nephrolithiasis, acute interstitial nephritis, and crystal nephropathy. Nephrolithiasis is the most common adverse event associated with the use of the medication and usually occurs after two years from the start of the antiretroviral therapy, which suggests something related to the cumulative exposure to the drug. In general, kidney function is preserved, and urine examination under polarized light can reveal the birefringence of needle-shaped crystals[27].

Tenofovir

After the introduction of antiretroviral therapy, several classes of drugs emerged targeting different points of the viral cycle; among them, the reverse transcriptase enzyme inhibitors, in 2001, of which tenofovir is the most used, since it is recommended as the first-line therapy by the "Clinical Protocol and Therapeutic Guidelines for the Management of HIV Infection in Adults" (2018) by the Ministry of Health, but also by the American Academy of HIV Medicine and European AIDS Society[4,20,28].

Tenofovir is a prodrug that is filtered by the glomeruli but also secreted by the tubules, with a good safety profile and, since it has a prolonged intracellular half-life, it facilitates the dosage and adherence to treatment; however, it is one of the ARVs more frequently involved with kidney disease[4,11,29,30].

The main site of toxicity of tenofovir is the proximal tubule due to its intracellular accumulation, which leads to transport defects and mitochondrial injury, after the entry in tubular cells through the pericellular space and organic anion transporters1 and 3[4.11]. Tenofovir can cause renal dysfunction, such as acute tubular necrosis, nephrogenic diabetes insipidus due to distal tubular dysfunction, and, in more severe cases, Fanconi's syndrome, characterized by excessive urinary excretion of amino acids, glucose, phosphate, bicarbonate, and uric acid[4,14,29].

The diagnosis of tenofovir toxicity is usually clinical, and kidney biopsy is not necessary in cases of classic presentation[5]. The tenofovir dose should be reduced in patients with previous kidney failure and, if the estimated glomerular filtration rate is less than 60 ml/min, it should not be used[28.29]. If there is an alternative therapy available, the recommendation is to discontinue tenofovir[5].

The prodrug tenofovir alafenamide is associated with a lower risk of kidney toxicity compared to tenofovir disoproxil fumarate, because it is not a substrate for organic anion transporters 1 and 3 and, therefore, does not accumulate in the proximal tubular cells, in addition to resulting in lower plasma concentrations[4.5].

HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

The first case of HIV-associated thrombotic microangiopathy (TMA) was reported in 1984; however, TMA is rarely the initial manifestation of the virus infection[24]. It manifests with microangiopathic hemolytic anemia and thrombocytopenia, presence of schistocytes in peripheral blood, and decreased

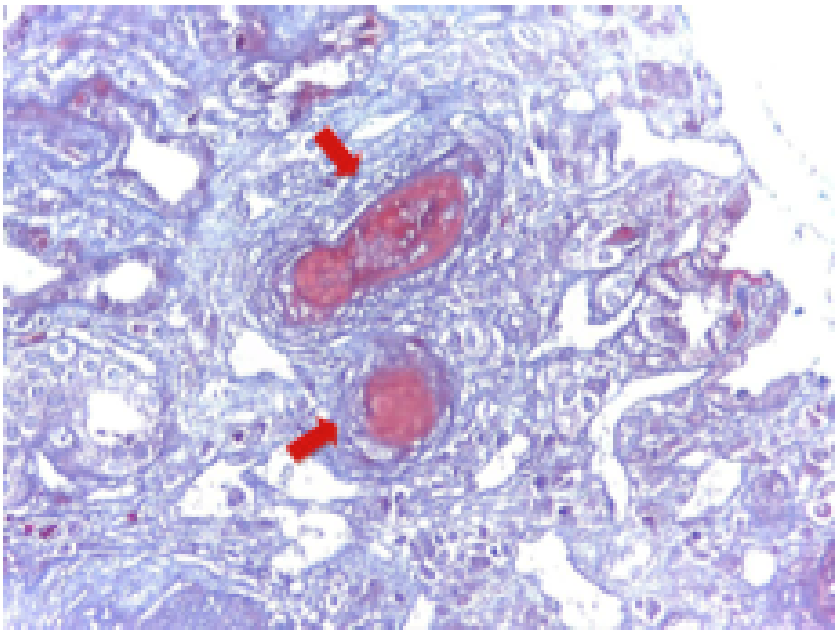

FIGURE 3. INTERLOBULAR ARTERY BRANCHES WITH DISSOCIATED WALL AND LUMEN OCCLUDED BY FIBRINOID MATERIAL (INDICATED BY THE RED ARROWS). (MASSON'S TRICHROME - 400X). IMAGE KINDLY PROVIDED BY PROF. DR. LUIZ A. MOURA.

haptoglobin levels. Clinically, HIV-associated TMA presents acute onset with rapid progression of kidney failure, hematuria, and proteinuria[19].

Its mechanism of pathogenesis can be associated with the direct cytopathic effects of the viruses that cause endothelial injury, leading to TMA, as well as to a systemic inflammatory response triggered by HIV or an opportunistic infection[4,19]. Some conditions, such as opportunistic infections and antiretroviral therapy, may be involved in the pathogenesis; a high viral load and decreased CD4 count may also be involved in the development of TMA, which, therefore, generally occurs in more advanced stages of the disease[4,19].

The treatment decision can often be a challenge due to the difficulty in making differential diagnoses (thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome). After the introduction of antiretroviral therapy, there was a substantial decline of HIV-associated TMA; therefore, for this condition, antiretroviral therapy is strongly recommended, as well as the treatment of opportunistic infections[19]. In addition, good results have been reported with the use of immunosuppressants, corticosteroids, infusion of fresh frozen plasma, plasmapheresis, and eculizumab[19].

CONCLUSION

The spectrum of kidney diseases associated with HIV has changed with the introduction of antiretroviral therapy. Currently, HIVAN is understood as a secondary effect to medications, despite the recognized interaction between the virus and the host. It is also noted an increase in renal injury associated with comorbidities that are not exclusively related to the virus, such as diabetes mellitus and hypertension.

The management of HIV-associated nephropathy is based on the suppression of viral replication and minimizing kidney injury in the long term, with emphasis on the importance of antiretroviral therapy. The screening and early detection of kidney failure in strongly recommended for the start of the treatment so that the outcomes of patients infected with HIV can be increasingly improved.

The proposed goal is that, by 2020, 90% of all people living with HIV know that they have the virus, with 90% of the people diagnosed receiving antiretroviral therapy and, then, 90% of all individuals receiving antiretroviral therapy will have viral suppression; it is known and recognizable that an undetectable viral load means that the virus is not transmissible.

Regarding the kidney disease scenario, the change was significant over the last 20 years with the effectiveness of HIV treatment. The understanding of the pathogenesis of interactions associated with kidney injury and the monitoring of current development can provide a better service for these individuals.

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Contribution of the authors

Érica Lofrano Reghine, drafting of the text; Renato Demarchi Foresto, drafting and revision of the text; Gianna Mastroianni Kirsztajn; drafting and revision of the text.

RESUMO

O panorama da infecção pelo vírus da imunodeficiência humana (HIV) vem sofrendo alterações nos últimos anos, tanto em relação ao entendimento da infecção pelo HIV quanto aos tratamentos disponíveis. Como resultado, a doença, que antes estava associada a alta morbimortalidade, é agora considerada uma doença crônica que pode ser controlada, tanto em relação à transmissão quanto aos sintomas. No entanto, mesmo quando a replicação viral é bem controlada, o paciente infectado tem um alto risco de desenvolver complicações renais, seja através de lesão renal aguda não relacionada ao HIV, por nefrotoxicidade causada por drogas antirretrovirais, por doenças crônicas associadas com o aumento da sobrevida ou por doença glomerular associada ao HIV. Esta revisão abordará os principais aspectos da insuficiência renal associada ao HIV.

PALAVRAS-CHAVE: *HIV. Insuficiência renal crônica. Nefropatia associada a AIDS.*

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