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Original Article

Glomerular diseases related to HIV in Colombian population: Better outcomes with highly active antiretroviral therapy?

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Abstract

Introduction: End-stage renal disease (ESRD) related to HIV is becoming a leading cause of renal replacement therapy requirement is some areas of the world. Our study aims to describe the incidence and renal outcomes of HIV-associated nephropathy (HIVAN), and immune-mediated kidney disease related to HIV (HIVICK) in Colombia.

Methodology: A retrospective cohort study was performed, including all HIVAN or HIVICK incident cases assessed by the infectious diseases division in a high complexity institution in Colombia, between 2004 and 2018. A longitudinal data model under the Generalized Estimating Equations (GEE) method was used to determine changes on the glomerular filtration rate (GFR) over time.

Results: Within a cohort composed by 1509 HIV-infected patients, we identified 22 with HIV-associated glomerular disease. Cumulative incidence was 1.45%. At diagnosis, GFR was above 30 mL/min in 90.8% of patients, and 77.2% displayed sub-nephrotic proteinuria. Factors associated with GFR at diagnosis were: level of CD4 (Coefficient 0.113, CI 95 %: 0.046, 0.179, $p < 0.01$), and the inverse of the CD4/CD8 ratio. The GEE model did not demonstrate significant changes in the GFR over a 3-year period. Findings were similar when comparing GFR at diagnosis with GFR at 12 (-3.9 mL/min/1.73m^2, CI 95% -7.3, 0.4, $p = 0.98$), 24 (-2.47 mL/min/1.73m^2, CI 95% -7.0, 2.1, p=0.85), and 36 months (0.39 mL/min/1.73m^2, CI 95% -4.4, 5.2, $p = 0.43$) of follow-up.

Conclusions: Patients with glomerular disease associated with HIV have stable GFR over a 3-year period, and low rates of progression towards dialysis requirement. Differences with previous reports could be related with early diagnosis and treatment with highly active antiretroviral therapy.

Key words: HIV; HIV-associated nephropathy; glomerular diseases; highly active antiretroviral therapy.

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Introduction

Kidney disease is among the major causes of morbidity and mortality in patients with human immunodeficiency virus (HIV)-1 [1]. The percentage of dialysis patients with HIV is increasing worldwide, being an especially serious issue in sub-Saharan Africa, where end-stage renal disease (ESRD) related to HIV is the third leading cause of renal replacement therapy requirement in black patients 60 years of age or younger [2,3].

Two groups of glomerular diseases are related to HIV: podocytopathies and immune complex-mediated [4]. HIV-associated nephropathy [HIVAN] is the most frequent podocytopathy and is the most important cause of ESRD in this population [5]. It is mediated by direct infection of renal epithelial cells by HIV, intrarenal viral gene expression, and dysregulation of host genes governing cell differentiation and the cell cycle [6]. HIV immune complex disease of the kidney [HIVICK] involves a different immunological mechanism with antibody deposits within glomerular structures. Both entities lead to proteinuria and progressive decline of glomerular filtration rates [1,5].

Classic descriptions reported rapid progression to ESRD in patients with HIVAN [7], with some factors associated with worse prognosis such as African American ancestry, *APOL1* polymorphisms, high viral load, low CD4 count, presence of comorbidities such as hypertension or diabetes, advanced kidney disease and nephrotic range proteinuria at the moment of the diagnosis [5]. However, some studies have reported a decrease in both the incidence and mortality of patients with HIVAN associated with the increasing availability of highly active antiretroviral therapy [8].

The incidence and prognosis of HIVAN and HIVICK among HIV patients in Colombia and in Latin America is unknown. It could be different to the prognosis described in other countries as the *APOL1* polymorphism in the region is very low compared with populations in Europe, North America and Africa [9,10].

This longitudinal study seeks to describe the incidence of HIVAN and HIVICK in this population, as well as the main renal outcomes, including requirement of renal replacement therapy, transplantation, proteinuria and decreased glomerular filtration rate [GFR]. Also, we aim to establish which factors are associated with progression to ESRD in a cohort of Colombian patients with glomerular disease associated with HIV as compared to previous reports in literature.

Methodology

A retrospective cohort study was carried out, including all patients who developed glomerular disease associated with HIV who were assessed by the Infectious Diseases Division at the San Ignacio University Hospital in the city of Bogotá, Colombia, in the timeframe between 2004 and 2018. This cohort consists of patients 18 years of age or older, with a diagnosis of HIVAN or HIVICK defined through histology findings. Patients on which renal biopsy was not performed and those who had another cause for deterioration of the previously established GFR were excluded. The ethics committee at San Ignacio University Hospital and Pontificia Universidad Javeriana approved the study protocol.

At the Infectious Diseases Division at our institution, an infectious diseases specialist monitors patients on a monthly basis, and further blood work-up is performed every 6 months. The latter includes renal function tests and immuno-virological status assessment. Controls can even be more frequent if there are any complications or failure in therapy. Follow-up data of these patients are collected systematically and recorded in a central database. Data on clinical variables, physical examination and biochemical parameters are retrieved from each follow-up appointment, according to the institutional protocol. This population benefits from strict monitoring. Therefore, blood work-ups are conducted on a regular basis, and all tests are processed in the institutional clinical laboratory, which maintain the same measurement techniques over time. In case of complications such as decreased renal function, patients are referred to the institution's Nephrology Unit for further evaluation and if an apparent cause is not found, a kidney biopsy with basic staining, immunofluorescence and electron microscopy is performed and interpreted by expert staff.

Our cohort is composed by patients without renal involvement related to HIV or kidney failure at the baseline assessment. Then, incident cases were determined during follow-up. *KDIGO* (The kidney Disease improving Global Outcomes) classification was used to describe stages of chronic kidney disease [4]. For the evaluation of factors associated with impaired renal function, a linear regression model was initially performed to determine which factors were associated with the GFR at the time of diagnosis of HIVAN or HIVICK.

Given that multiple measurements for proteinuria, CD4 count, viral load and GFR were available over the follow-up period, a longitudinal data model was planned under the Generalized Estimating Equations (GEE) method, seeking to determine which values were associated with a greater deterioration of kidney function through time. An interchangeable correlation structure was used and a sensitivity analysis was carried out assuming independent and unstructured relationship structures. The most significant model was considered to be the one with the lowest QIC (quasi-likelihood under the independence model criterion) and a value of $p < 0.05$. A STATA® 15.0 package was used for the analysis.

Results

The cohort consisted of 1,509 patients assessed by the Infectious Diseases Division at a high-complexity University Hospital in Bogota, Colombia. Of these, 22 patients had been diagnosed with HIV-associated glomerular disease; eleven corresponded to HIVAN and eleven to HIVICK by histological diagnosis. The cumulative incidence was 1.45%.

Clinical and demographic characteristics of patients according to histological characteristics on biopsy are shown in Table 1.

Table 1. Description of patients at the start of follow-up and during renal injury.

Variable	TOTAL n = 22	HIVAN n = 11	HIVICK n = 11
Age (years), Mean (SD)	42.9 (10.2)	44.3 (9.3)	41.4 (10.3)
Male gender, n (%)	20 (90.9)	11 (100)	9 (81.8)
CD4 count at the start of the follow-up, n (%)			
0 – 49	2 (9.0)	1 (9.0)	1 (9.0)
50 - 99	5 (22.7)	2 (18.1)	3 (27.2)
100 - 149	2 (9.0)	2 (18.1)	0 (0)
150 - 100	2 (9.0)	1 (9.0)	1 (9.0)
≥ 200	11 (50)	5 (45.4)	6 (54.5)
HIV viral load at the start of follow-up, n (%)			
0 – 999	7 (31.8)	4 (36.4)	3 (27.3)
1,000-4,999	3 (13.6)	2 (18.2)	1 (9.1)
≥ 5,000	12 (54.6)	5 (45.5)	7 (63.6)
CD4 count at the time of kidney injury, n (%)			
0 – 50	3 (13.6)	1 (9.0)	2 (18.1)
50 - 100	4 (18.1)	3 (27.2)	1 (9.0)
100 - 150	1 (4.5)	1 (9.0)	0 (0)
150 - 200	2 (9.0)	1 (9.0)	1 (9.0)
Greater than 200	12 (54.5)	5 (45.4)	7 (63.6)
HIV viral load at the time of kidney injury, n (%)			
0 – 999	10 (45.5)	5 (45.5)	5 (45.5)
1,000-4,999	3 (13.6)	2 (18.1)	1 (9.1)
≥ 5,000	9 (40.1)	4 (36.4)	5(45.5)
CD4 / CD8 ratio at the time of kidney injury			
Less than 0.1	2 (11.7)	1 (9.0)	1 (9.0)
0.1 – 0.5	14 (82.3)	6 (54.5)	8 (72.7)
0.5 – 1	1 (5.8)	0 (0)	1 (9.0)
Not quantified	5(22.7)	4 (36.3)	1 (9.0)
Intercurrent infections, n (%)	5 (22.7)	1 (9.0)	4 (36.3)
HBV, n (%)	1 (4.5)	0 (0)	1 (9.0)
HCV, n (%)	0 (0)	0 (0)	0 (0)
CMV, n (%)	1 (4.5)	0 (0)	1 (9.0)
Associated drugs at the time of renal injury			
ACEi / ARB	6 (27.2)	4 (36.3)	2 (18.1)
NSAID	1 (4.5)	0 (0)	1 (9.0)
TMP/SMX	10 (45.4)	5 (45.4)	5 (45.4)
Without associated medications	5 (22.9)	2 (18.1)	3 (27.2)
Comorbidities			
Diabetes Mellitus 2	3 (13.6)	2 (18.1)	1 (9.0)
Dyslipidemia	14 (63.6)	6 (54.5)	8 (72.7)
Hypertensión	5 (22.7)	3 (27.2)	2 (18.1)
History of opportunists	6 (27.2)	5 (45.4)	1 (9.0)
Proteinuria in gr /24 hours at the time of kidney damage			
Less than 3.4	17 (77.2)	10 (90.9)	7 (63.6)
Greater than 3.5	3 (13.6)	1 (9.0)	2 (18.1)
No data	2 (9.0)	0 (0)	2 (18.1)
Glomerular filtration rate at the time of renal injury (ml / min / 1.73m2)			
0 - 14.9	0 (0)	0 (0)	0 (0)
15 - 29.9	2 (9.09)	2 (18.1)	0 (0)
30 - 59.9	10 (45.4)	6 (54.5)	4 (36.3)
Greater than 60	10 (45.4)	3 (27.2)	7 (63.6)
Pharmacological intervention			
ACEi / ARB	15(68.1)	8 (72.7)	7 (63.6)
Statins	7 (31.8)	4 (36.3)	3 (27.2)
ACE / ARB / Statins	6 (27.2)	3 (27.2)	3 (27.2)
Weight (Kg), Mean (SD)	67.9 (8.9)	70.7 (8.8)	64.9 (7.6)
Height (cm), Mean (SD)	169 (6.9)	171 (3.3)	167 (8.5)

The majority were men (90.9%), and the mean age was 42.9 ± 10.2 years. 59.1% had an HIV viral load below 5,000 copies at the time of kidney injury. Intercurrent infections were found in five patients during the period where renal lesions were detected (22.7%): latent tuberculosis was found in three patients and two cases of genital herpes were found. One patient was co-infected with Hepatitis B.

At the time of renal deterioration, GFR estimated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) was above 30 ml/min/m2 in 90.8% of patients. 77.2% of patients presented proteinuria in the sub nephrotic range.

Changes in data derived from blood work-ups during the follow-up period are shown in Table 2. Most patients had proteinuria in the sub nephrotic range at 12, 24 and 36 months of follow-up, and the CD4 count was above 200 cells/ml in the majority of patients.

According to biopsy descriptions, 11 patients had focal segmental glomerulosclerosis findings, compatible with HIVAN (50%). Histological patterns compatible with HIVICK were displayed by 11 patients (50%). The most frequent histological patterns are shown in Table 3.

A factor associated with glomerular filtration rate at the time glomerular disease was diagnosed was the level of CD4 (Coefficient 0.113, CI 95 %: 0.046, 0.179, $p < 0.01$). Also, we documented an inverse association with the CD4/CD8 ratio at the time of renal injury (Coefficient - 64.370; CI 95% - 97.544, - 31.197, $p < 0.01$). We did not find an association with the HIV viral load at the time of kidney injury ($p = 0.150$).

During the 36-month follow-up period, two patients (9%) developed stage 5 chronic kidney disease requiring renal replacement therapy; one of them had a histological diagnosis of HIVAN and the other patient had findings compatible with HIVICK. Both were men and had low GFR at the time (< 30 mL/min), glomerular deterioration was diagnosed and their admission to dialysis was scheduled. None of the patients underwent renal transplantations. There were no deceases during the 3-year follow-up period.

Table 3. Histological characteristics of patients with HIVAN or HIVICK.

Histological description	n (%)
Focal and segmental glomerulosclerosis, n (%)	11 (50)
IgA nephropathy, n (%)	6 (27.2)
Minimal change disease, n (%)	2 (9.0)
C3 nephropathy	1 (4.5)
Focal membranoproliferative, n (%)	1 (4.5)
Membranous nephropathy, n (%)	1 (4.5)
Total	**22**

The longitudinal data model under the generalized estimation equation (GEE) methodology did not demonstrate significant changes in the glomerular filtration rate during the 3 years of patient follow-up. Similar findings were found when comparing GFR at the time of diagnosis with GFR at months 12 (Mean difference -3.9 mL/min, IC 95% -7.3, 0.4, $p = 0.98$), 24 (Mean difference -2.47 mL/min, IC 95% -7.0, 2.1, $p = 0.85$), and 36 (Mean difference 0.39 mL/min, IC 95% -4.4, 5.2, $p = 0.43$) of follow up using a paired t-test.

Discussion

This is the first study that evaluates the main renal outcomes of patients with glomerular involvement due to HIV in Latin America. We found a low incidence of HIVAN and HIVICK, and a relatively good prognosis

Table 2. Laboratory testing evolution during follow-up.

	At the time of diagnosis	12 month	24 month	36 month
GFR*, Mean (SD)	59.2 (27.1)	63.1(23.3)	61.7(26.4)	58.8(28.2)
Less than 14.9	0 (0)	0 (0)	2 (9)	2 (9)
15 – 29.9	2 (9.09)	2 (9)	1 (4.5)	1 (4.5)
30 – 59.9	10 (45.4)	8 (36.3)	6 (27.2)	7 (31.8)
Greater than 60	10 (45.4)	12 (54.5)	13 (59)	12 (54.5)
Proteinuria (gr/24h), Median (IQR)	1.19 (0.7-3.1)	1.08 (0.4-1.9)	1.44 (0.4-3.9)	0.39 (0.3-1.15
< 3.49	17 (85)	9 (90)	6(75)	4 (100)
≥ 3.5	3(15)	1 (10)	2(25)	0 (0)
NDA	2	12	14	20
CD4 count (cel/ml)				
Less than 50	3 (13.6)	0 (0)	0 (0)	0 (0)
50 – 100	4 (18.1)	2 (10)	0 (0)	0 (0)
100 – 150	1 (4.5)	5 (25)	4 (22.2)	3 (18.7)
150 – 200	2 (9)	1 (5)	0	2 (12.5)
Greater than 200	12 (54.5)	12 (60)	14 (77.7)	11 (68.7)
NDA		2	4	6

*GFR measured in (ml/min/1.73m^2); NDA: Not data available; SD: Standard deviation; IQR: Interquartile Range.

compared with data previously reported in the literature.

Our cumulative incidence was 1.4%, which is lower than expected, considering that initial studies reported that approximately 10% of patients with HIV infection developed HIVAN [11,12]. The latter could be associated with the increasing availability of highly active antiretroviral therapy in the last fifteen years, as was suggested by Chaudhary, who additionally reported a declining trend in the incidence of end-stage renal disease from HIV-associated nephropathy between 1989 and 2011 using data from the United States Renal Data System [8].

We found that GFR at the time of renal injury is related to the level of CD4. The same finding has been reported in previous studies, which have found association between low CD4 counts [mainly <200 cells/mm^3] and end stage renal disease [13,14].

In accordance to our study, recent reports have suggested an association between low CD4/CD8 ratios and non-AIDS related events, which include acute kidney injury and end stage renal disease. A ratio < 0.44 was independently associated with an increased risk of non-AIDS-defining events or death. Non-AIDS-related illnesses are mainly a consequence of the increased burden of age-associated disease and likely to be driven by persistent immune activation. Outside the scope of HIV infection, a low CD4/CD8 ratio, has been proposed as a surrogate marker for defining immune-related defects defining ‘‘immunosenescence’’ a phenomenon characterized by T-cell proliferation and differentiation resulting in the generation of antigen-experienced, highly differentiated and dysfunctional T-cells. The latter seems to be correlated with all-cause mortality in the elderly [15,16].

In our cohort, during the 3-year follow-up period, only two patients [9.0%] required renal replacement therapy, and there was not a significant reduction in the GFR after three years of follow-up. These findings differ with data described by Post and Bigé, who found that more than half of patients developed chronic kidney disease with dialysis requirement during a 4-year follow-up in cohorts of patients in the United Kingdom and France [7,17]. Several differences exist between the patients included in those studies and our population: First, their patients had severe renal dysfunction (GFR < 20 ml/min) and high-grade proteinuria (> 4 gr/24 hours) at the moment of diagnosis, differing from our patients who had sub nephrotic proteinuria and GFR above 30 mL/min/m2 predominantly. In fact, the only two patients that finally required renal replacement therapy in our study were those who had GFR under 30 mL/min/m2 at the beginning of the follow-up period. Our data suggest the importance of an early diagnosis for improving renal outcomes in this population, and that this could be achieved through strict clinical control and frequent blood work-ups as done in our program.

Furthermore, the patients included in Post and Bigé cohorts were predominantly African descendants [approximately 90%], a population that has been associated to worse outcomes [18], related to the apolipoprotein L-1 (*APOL1*) gene variants [19], a polymorphism that has not been found in Latin American populations [9].

Finally, our cohort includes only patients diagnosed after 2004, a period in which highly active antiretroviral therapy has been available, suggesting a positive impact of this treatment in the prognosis of renal function. Data Collection on Adverse Events of Anti-HIV Drugs [D:A:D] antiretroviral therapy, showed similar findings. 21% improved GFR, 67% stabilized and 12% progressed. Individuals remaining on tenofovir [TDF] or atazanavir boosted with ritonavir (ATV/r) 24 months post chronic renal impairment had worse eGFR outcomes compared with those unexposed [19–21].

A strength of the study is the use of a longitudinal data model under the generalized estimation equation (GEE) methodology that allows incorporating multiple data sources derived from monitoring in the analysis, in order to determine if there are factors associated with the deterioration of the GFR. However, because of the stability of the GFR during the follow-up period, it was not possible to determine the factors associated with short-term deterioration. New studies with longer follow-ups will be required to determine if the stability of renal function is maintained over time, and which factors predict the long-term evolution of renal function.

Several limitations should be disclosed. To begin with, our sample size is low and the three-year follow-up period is relatively short to determine the probability of mortality and dialysis requirement in this population. However, data suggest that the deterioration of renal function is much slower than reported previously in scientific literature. Secondly, we did not evaluate the presence of variants of the ApoL1 and MYH9 in our population. New studies are necessary to assess whether APOL1 polymorphisms are present in our country or if they are absent as has been reported in other Latin American populations.

Conclusion

As previously mentioned, it is the first study in our country that investigates the evolution of glomerular diseases associated to HIV. The obtained results contrast with that previously reported, with stability of the GFR over time, low rates of progression towards renal disease requiring dialysis and low percentage of patients with proteinuria in nephrotic range. These differences could be associated to genetic differences in Latin American populations, and improved outcomes related with early diagnosis and treatment with highly active antiretroviral therapy.

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