HIV-associated kidney glomerular diseases: changes with time and HAART

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Abstract

Background. Treatment and co-morbidities of human immunodeficiency virus (HIV)-infected individuals have changed dramatically in the last 20 years with a potential impact on renal complications. Our objective was to assess the change in distribution of the glomerular diseases in HIV patients.

Methods. We retrospectively analysed demographic, clinical, laboratory and renal histopathological data of 88 HIV-infected patients presenting with a biopsy-proven glomerular disease between 1995 and 2007.

Results. In our study including 66% Black patients, HIV-associated nephropathy (HIVAN) was observed in 26
cases, classic focal segmental glomerulosclerosis (FSGS) in 23 cases, immune complex glomerulonephritis in 20 cases and other glomerulopathies in 19 patients. HIVAN decreased over time, while FSGS emerged as the most common cause of glomerular diseases (46.9%) in HIV-infected individuals undergoing kidney biopsy in the last 2004–07 period. Patients with HIVAN were usually Black (97%), with CD4 <200/mL (P = 0.01) and glomerular filtration rate <30 mL/min/1.73m² (P < 0.01). Compared to HIVAN, patients with classic FSGS were less often Black (P < 0.01), have been infected for longer (P = 0.03), were more often co-infected with hepatitis C virus (P = 0.05), showed more often cardiovascular (CV) risk factors (P < 0.01), had less often CD4 <200/mL (P = 0.01), lower HIV viral load (P = 0.01) and tended to be older (P = 0.06).

Conclusions. Classic FSGS associated with metabolic and CV risk factors has overcome HIVAN in HIV-infected patients. Compared with other glomerulopathies, HIVAN remains strongly associated with severe renal failure, Black origin and CD4 lower than 200/mL at presentation.

Key words: FSGS; glomerular diseases; HAART; HIV; HIVAN

Introduction

During the first 25 years of the acquired immunodeficiency syndrome (AIDS) epidemic, human immunodeficiency virus-1-associated nephropathy (HIVAN) surpassed any other causes of kidney diseases responsible for end-stage renal diseases (ESRD) in HIV-1-infected patients (USRDS 2007 Annual Data Report, [1]). HIVAN usually occurred in Blacks with advanced HIV-1 disease and was characterized by high-grade proteinuria, rapid progression to ESRD and typical pathological features with collapsing focal segmental glomerulosclerosis (FSGS) associated with tubular microcystic formations and various degrees of interstitial infiltration and fibrosis [2]. Over the past 15 years, significant advances have been made in the pathogenesis of HIVAN, including the demonstration of a direct role of HIV-1 infection in the development of the renal lesions and more recently, the identification of a genetic susceptibility locus for the development of HIVAN in African Americans (MYH9/APOL1) [3–6]. The decline of incidence of HIVAN-related ESRD after the introduction of highly active antiretroviral therapy (HAART) suggested a beneficial role for antiretroviral (ARV) therapy in the development of HIVAN, which was further supported by reports of clinical and histological improvement after initiation of HAART and by retrospective cohort studies [6–8]. During the same period, emergence of the nephrotoxicity of the new ARV agents was observed, including nephrolithiasis, proximal tubular toxicity and acute renal failure. In addition, HAART was associated with the development of metabolic alterations that included lipid abnormalities, dysregulation of glucose homeostasis and lipodystrophy. HIV infection and highly prevalent traditional risk factors, such as ageing, male sex, smoking, diabetes and hypertension, contribute not only to the increased risk of cardiovascular disease (CVD) in the HIV-infected patients but also to a higher rate of chronic kidney disease (CKD) [9].

The aim of the present study was to retrospectively analyse the change in the prevalence of glomerular diseases following the introduction of HAART in HIV-infected patients undergoing a renal biopsy in our nephrology department where they were referred to by two French infectious disease units.

Materials and methods

Study design

We retrospectively analysed clinical, biological and histological data of HIV-infected patients with a biopsy-proven diagnosis of glomerular disease.

Study population

We included all consecutive HIV-infected adult patients who underwent a renal biopsy from April 1995 to November 2007 at the Tenon University Hospital (Paris, France) and in whom the histopathological diagnosis of glomerular disease was retained. Patients with non-glomerular lesions or non-contributive biopsy were excluded, as well as those whose clinical or biological data were incomplete or unavailable. Patients were referred from two infectious disease units (Tenon Hospital and Saint Antoine Hospital, Paris, France, 6000 HIV-infected patients followed). Demographic, clinical, biological and renal data were obtained from the infectious diseases unit database and completed by chart review.

Collected data on demographics and co-morbid conditions included age, sex, ethnic origin, hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg), diabetes, dyslipidaemia (total cholesterol >5.2 mmol/L and/or triglycerides >2.20 mmol/L), history of cardiovascular (CV) events (myocardial infarction, angina, congestive heart disease, stroke, peripheral arterial disease) and history of intravenous drug use. Clinical data on HIV infection were collected as follows: time since HIV diagnosis, CDC staging, history of opportunistic infections, co-infections with hepatitis B (defined as a positive HBs antigen) and hepatitis C (defined as the presence of anti-hepatitis C virus antibodies), HIV antiretroviral therapy (ART, i.e. at least one ARV drug) with HAART being defined as triple drug therapy, exposure to HAART (>6 months) or ART (history) before kidney biopsy and status of HAART or ART (current) at the time of biopsy. Renal data included treatment with angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers or nephrotoxic drugs. Laboratory measurements at the time of the biopsy included serum creatinine, urinary protein and creatinine excretion, CD4 cell count and plasma HIV RNA (with a lower detection limit of 10 000 copies/mL until September 1996, 500 copies/mL from October 1996 to November 1998, 50 copies/mL from December 1998 to November 2007). Proteinuria and nephrotic range proteinuria were defined by protein-creatinine ratio >50 and >300 mg/mmol of creatinine, respectively. Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease equation [10]. CKD was defined by eGFR <60 mL/min/1.73m² for ≥3 months.

Histological procedures

Renal biopsy specimens were analysed by a renal pathologist according to a standardized protocol, without a standardized blinded review. HIVAN was defined as collapsing glomerulopathy (collapse of at least one glomerular capillary tuft with prominence of visceral epithelial cells, with associated microcystic tubular dilatation and interstitial inflammation). Classic FSGS was defined by the presence of at least one segmental capillary wall collapse and/or segmental sclerosing lesion without podocyte hyperplasia or glomerular collapse [11]. Histopathological features other than HIVAN and FSGS were classified according to established diagnostic criteria.

Statistical analyses

Qualitative or category variables were presented in effective and per cent, continuous variables in median and interquartile range (IQR). Clinical, biological and histological data were reported and compared between three periods according to ARV generation: 1995–2000 (Period 1), 2001–03 (Period 2) and 2004–07 (Period 3). Comparative analysis was also performed between patients with classical FSGS and patients with HIVAN.

For comparative analyses, we used Fisher’s exact test or χ² test for categorical variables according to using conditions, the Student’s t-test or
HIV-associated kidney glomerular diseases

the Wilcoxon rank-sum test (or Mann–Whitney test if necessary) for continuous variables according to using conditions.

For multivariate analysis, we performed an ascending Wald logistic regression. Variables found associated to HIVAN with a P-value < 0.2 in univariate analysis were included in the model.

Results

Description of the study population

During the study period, the diagnosis of glomerular disease was established in 98 of the 142 renal biopsy specimens obtained in HIV-infected patients. As clinical and/or biological data were incomplete for 10 patients, 88 were included for the analysis.

Detailed characteristics of the 88 patients at the time of renal biopsy are shown in Table 1. Median age was 43 years (IQR, 34–50), the male-to-female ratio was 3.6/1 and 53 (63.1%) patients were Black. The median time between HIV diagnosis and the biopsy was 84 months (IQR, 36–156). Median CD4 cell count and median HIV viral load were 217/µL (IQR, 69–373) and 3071 copies/mL (IQR < 40 to 1 15 000), respectively, with undetectable viral load in 28.2% of patients. Fifty per cent of patients received HAART, with 51% of patients having a past history of opportunistic infection and 67.9% being in Stage C of HIV infection. Hepatitis B and hepatitis C co-infections were reported in 8.9 and 26.2% of patients, respectively.

Other co-morbid conditions such as hypertension, diabetes mellitus and dyslipidaemia were recorded in 33, 12.6 and 24.1%, respectively. Twenty-seven (30.7%) patients presented with more than one CV risk factor.

Median serum creatinine was 163 µmol/L (IQR, 113–484) and median glomerular filtration rate (GFR) 40 mL/min/1.73m² (IQR 12–63). Median proteinuria level was 218 mg/mmol of creatinine (IQR 114–508), with 54% of patients presenting with nephrotic range proteinuria.

The indications for renal biopsy were as follows (several indication criteria could exist for one patient): proteinuria (65%), chronic renal failure (28%), acute kidney injury (23%), renal failure of undetermined duration (22%), haematuria (15%) and thrombotic microangiopathy (5%).

Renal biopsy findings

Table 2 shows the histological patterns. The two predominant glomerular diseases were HIVAN (29.5%) and classic FSGS (26.1%). In the classic FSGS group, no other glomerular lesions were observed. Immune complex disease was identified in 20 (22.7%) patients, comprising mesangio-proliferative glomerulonephritis, membranous nephropathy, IgA nephropathy, lupus-like nephritis, membranoproliferative glomerulonephritis and post-infectious glomerulonephritis. Undetermined glomerulonephritis was concluded for 9.1% of biopsy specimens. Other histological diagnoses are detailed in Table 2. Histopathological diagnoses of the 10 excluded patients included for the first period, two HIVAN, one classic FSGS, two glomerular thrombotic microangiopathy, two undetermined glomerulonephritis, and for the third period, one classic FSGS and one mesangial proliferative glomerulonephritis.

Comparison of the clinical characteristics and pathological findings by period

Comparison of the clinical characteristics over three consecutive periods (1995–2000, 2001–03 and 2004–07) shows that patients were comparable for overall immune status (CD4 cells count, CDC staging, history of opportunistic infections) and co-morbid conditions (Table 1). Nevertheless, the proportion of Blacks decreased (84, 66.7 and 46.9%) and the duration between HIV diagnosis and renal biopsy lengthened (48, 108 and 114 months) over the three periods. The proportion of patients receiving HAART and tenofovir, abacavir, atazanavir and lopinavir increased during the study period, while the use of d4T, ddI and ddC decreased.

Patients in Period 3 tended to have less advanced kidney disease than in Periods 1 and 2 (GFR: 20, 27 and 55 mL/min/1.73m² in Period 1, 2 and 3, respectively) (P = 0.05). Analysis of the respective distribution of the various types of glomerulopathies shows significant changes between the three periods. The prevalence of both HIVAN and classic FSGS increased from 44.4% (1995–2000) to 55.2% (2001–03) and 65.6% (2004–07). However, within this group of FSGS, HIVAN, which represented the main pathological diagnosis in the 1995–2000 period with 75% of FSGS cases, decreased to 29% in Period 3 (P = 0.01), while classic FSGS became the prominent entity, accounting for 46.9% of all glomerulopathies in the more recent period (Figure 1).

Comparison between HIVAN and classic FSGS

We separately analysed clinical and biological characteristics of the patients presenting with HIVAN or classic FSGS (Table 3). Compared to the classic FSGS group, patients presenting with HIVAN had been infected for a shorter period of time (42 versus 108 months, P = 0.03), were more often Black [96.2 versus 60.9%, odds ratio (OR) = 16.1 (1.84–140), P < 0.01], have more severe immunodeficiency (median CD4 cells count 74/mL versus 367/mL, P < 0.01), higher HIV viral load (P = 0.01) and they were less often co-infected with HCV [8.7 versus 31.8%, OR = 0.2 (0.04–1.12), P = 0.06]. They had a lower GFR (mean 10 versus 52 mL/min/1.73m², P < 0.01) with 92.3% of patients in the HIVAN group presenting with a severe CKD (GFR <30 mL/min/1.73m²) compared to only 17.4% in the classic FSGS group. Patients with classic FSGS tended to be older (46 years median age versus 40 years, P = 0.06), were more likely to receive HAART (P < 0.06), and they showed more often CV risk factors (P < 0.01). No significant difference in the level of proteinuria was observed between both groups (Table 3). Histologically, patients with classic FSGS had less severe tubular lesions, but more severe interstitial fibrosis as compared to those with HIVAN [21 versus 67% of diffuse atrophy (P = 0.005) and 64 versus 53% of interstitial fibrosis (P = 0.03), respectively].

Comparison between HIVAN and other glomerular diseases

In a multivariate analysis comparing HIVAN with all glomerular diseases and that included the age, ethnic group, hypertension, chronic hepatitis C, CD4 < 200/mL and GFR < 30 mL/min/1.73m² (Table 4), HIVAN occurred 16.8-fold
Median age, years (IQR) | 43 (34–50) | 38 (32–47) | 44 (34–53) | 46 (41–51) | <0.01
Men, n (%) | 69 (78.4) | 18 (66.7) | 21 (72.4) | 30 (93.8) | 0.03
Weight, kg (IQR) | 65 (58–72) | 63 (56–70] | 60 (53–67) | 72 (65–77) | <0.01
Black, n (%) | 53 (63.1) | 20 (80.4) | 18 (66.7) | 15 (46.9) | 0.03
Time since HIV diagnostic, months (IQR) | 84 (36–156) | 48 (24–114) | 108 (36–162) | 114 (36–171) | 0.04
CD4 count, cells/µL (IQR) | 217 (69–373) | 180 (15–354) | 211 (80–294) | 234 (143–449) | 0.18
HIV viral load, copies/mL (IQR) | 3071 (<40 to >10⁶) | 2372 (<40 to >10⁶) | 32 067 (931 to >10⁶) | 42 (<40 to >10⁶) | 0.05
Undetectable HIV viral load, n (%) | 24 (28.2) | 3 (11.5) | 7 (25.0) | 10 (50.0) | <0.01
CVD classification
Stage A, n (%) | 20 (23.8) | 3 (11.5) | 7 (25.0) | 10 (50.0) | <0.01
Stage B, n (%) | 7 (8.3) | 5 (19.2) | 1 (3.6) | 1 (3.3) | <0.01
Stage C, n (%) | 57 (67.9) | 18 (69.2) | 20 (71.4) | 19 (63.3) | <0.01
History of opportunistic infections, n (%) | 45 (51.1) | 17 (63.0) | 15 (51.7) | 13 (40.6) | 0.23
ART history, n (%) | 64 (72.7) | 18 (66.7) | 19 (65.5) | 27 (84.4) | 0.17
ART current, n (%) | 55 (62.5) | 15 (55.6) | 17 (58.6) | 23 (71.9) | 0.38
HAART current, n (%) | 44 (50) | 4 (14.8) | 17 (58.6) | 23 (71.9) | <0.01
HAART current ≥6 months, n (%) | 29 (33) | 0 | 13 (44.8) | 16 (50) | <0.01
ART with potential nephrotoxicity, n (%) | Indinavir | 19 (22.4) | 3 (12.0) | 8 (27.6) | 8 (25.8) | 0.33
Atazanavir | 6 (7.1) | 0 | 0 | 6 (19.4) | 0.00
Lopinavir | 11 (13.9) | 0 | 4 (14.3) | 7 (28.0) | 0.01
AZT | 19 (24.1) | 6 (23.1) | 8 (28.6) | 5 (20.0) | 0.75
d4T | 11 (13.8) | 6 (23.1) | 5 (17.2) | 0 | 0.04
ddi | 13 (16.5) | 6 (23.1) | 4 (14.3) | 3 (12.0) | 0.53
dDC | 1 (1.3) | 1 (3.8) | 0 | 0 | 0.35
Abacavir | 18 (22.8) | 1 (3.8) | 6 (21.4) | 11 (44.0) | <0.01
Tenofevir | 15 (17.6) | 0 | 6 (20.7) | 9 (29.0) | 0.02
Hepatitis B, n (%) | 7 (8.9) | 1 (4.2) | 4 (14.3) | 2 (6.9) | 0.17
Hepatitis C, n (%) | 22 (26.2) | 7 (29.2) | 4 (14.3) | 11 (34.4) | 0.15
Hypertension, n (%) | 29 (33.0) | 8 (29.6) | 11 (37.9) | 10 (31.3) | 0.79
Diabetes mellitus, n (%) | 11 (12.6) | 4 (14.8) | 4 (13.8) | 3 (9.7) | 0.82
Dyslipidaemia n (%) | 21 (24.1) | 4 (14.8) | 6 (21.4) | 11 (34.4) | 0.12
Cholesterol (IQR) | 5.1 (3.8–6.6) | 5.9 (4.6–6.9) | 4.6 (3.3–5.6) | 5.30 (3.7–6.6) | 0.13
Triglycerides (IQR) | 2.4 (1.4–4.6) | 2.5 (1.8–5.1) | 2.5 (1.6–3.5) | 2.0 (1.3–5.4) | 0.09
Lipodystrophy, n (%) | 6 (7.5%) | 0 | 3 (11.1%) | 3 (9.7%) | 0.28
History of CV events, n (%) | 6 (6.8) | 2 (7.4) | 2 (6.9) | 2 (6.3) | 0.98
More than one CV risk factor, n (%) | 27 (30.7) | 7 (25.9) | 7 (24.1) | 13 (40.6) | 0.3
ACE-I therapy n (%) | 14 (16.5) | 4 (16.0) | 3 (10.7) | 7 (21.9) | 0.51
ARB therapy n (%) | 5 (6.0) | 0 | 2 (7.4) | 3 (9.4) | 0.31
IDU n (%) | Current | 4 (7.5) | 1 (11.1) | 0 | 3 (15.0) | 0.16
Past | 9 (17.0) | 2 (22.2) | 3 (12.5) | 4 (20.0) | 0.72
Substitution | 4 (7.7) | 1 (11.1) | 2 (8.3) | 1 (5.3) | 0.85
Serum creatinine, µmol/L (IQR) | 163 (113–484) | 322 (101–580) | 198 (125–512) | 140 (96–182) | 0.20
GFR, mL/min/1.73m² (IQR) | 40 (12–63) | 20 (9–71) | 27 (11–52) | 55 (38–74) | 0.05
Proteinuria, mg/mmol (IQR) | 218 (114–508) | 406 (217–709) | 170 (108–400) | 160 (70–390) | 0.65

Table 2. Histologic glomerular lesions

<table>
<thead>
<tr>
<th>Total, N = 88</th>
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<tbody>
<tr>
<td>HIVAN, n (%)</td>
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<tr>
<td>Classic FSGS, n (%)</td>
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<tr>
<td>Immune complex disease</td>
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<tr>
<td>Mesangial prolifative glomerulonephritis, n (%)</td>
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<tr>
<td>Membranous nephropathy, n (%)</td>
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<tr>
<td>IgA nephropathy, n (%)</td>
</tr>
<tr>
<td>Lupus-like nephritis, n (%)</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis, n (%)</td>
</tr>
<tr>
<td>Post-infectious glomerulonephritis, n (%)</td>
</tr>
<tr>
<td>Minimal-change disease, n (%)</td>
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<tr>
<td>Diabetic nephropathy, n (%)</td>
</tr>
<tr>
<td>Glomerular amyloid microangiopathy, n (%)</td>
</tr>
<tr>
<td>Crescentic glomerulonephritis, n (%)</td>
</tr>
<tr>
<td>Undetermined glomerulonephritis, n (%)</td>
</tr>
</tbody>
</table>

*ARBs: angiotensin receptor blockers; IDU: injection drug use.

more often in Black (P = 0.02), 6.4-fold more often if patients had a severe immunodeficiency (CD4 <200/ mm³) (P = 0.01) and 21.4-fold more often if patients had a severe renal failure (GFR <30 mL/min/1.73m²) (P < 0.01). HAART and HIV viral load variables were co-linear with level of immunity (CD4 more or less 200/mL). There was no difference in level of proteinuria.

**Discussion**

This 12-year retrospective study of consecutive biopsy-proven glomerular diseases in HIV-infected patients shows a change in the prevalence of glomerular lesions with a decreased proportion of HIVAN concomitantly to the
emergence of classic FSGS, which represents the leading cause of glomerular diseases in the last 4 years of the present study. We analysed our data comparing three periods (1995–2000, 2001–03 and 2004–07) to take into account the impact of different therapeutic strategies.

The diminution of HIVAN frequency over time since the introduction of HAART is consistent with most of the previous reports but is more prominent in the last period in the present study. Our clinical–pathological study identified three classical risk factors for HIVAN compared with other glomerular diseases including black race, CD4 <200/mL and GFR <30 mL/min/1.73m², whereas nephrotic range proteinuria (>300 mg/mmol) did not represent a discriminating marker, as previously underlined [13].

Immune complex glomerulonephritis was identified in 22.7% of biopsy specimens, with various histological presentations. The racial distribution of patients with these pathological findings was in accordance with previous series, with 80% being of Caucasian origin. Deposition of immune complexes containing HIV antigens has been occasionally demonstrated in renal tissue from patients with immune mediated glomerulonephritis suggesting a direct viral effect [14]. In addition, specific implication of co-infection with hepatitis B and C virus has also been suggested, mostly for mesangio proliferative and membranoproliferative glomerulonephritis [15]. However, despite the inclusion of 26% of patients with hepatitis C co-infection, none of them presented with immune complex glomerulonephritis.

The most striking feature is the identification of classic FSGS as the leading cause of glomerular lesions in the last period, the prevalence of this pathological finding being increased by almost 3-fold (46.9%) compared to the 2001–03 period (17.2%) and by almost 5-fold compared to the 1995–2000 period (11.1%). Most of the previous clinical–pathological studies were conducted between 1995 and 2004 and usually involved 80–100% of Black patients [9, 16–19]. The prevalence of classic FSGS in those studies varied from <5 to 27% of the glomerular diagnoses, while HIVAN usually was the most frequent aetiology. In a recent autopsy series of a cohort of ARV-experienced AIDS patients unselected for the presence of overt kidney disease, glomerular lesions were observed in 32% of the subjects, mostly related to HIVAN and membranoproliferative glomerulonephritis [19]. No classic FSGS was identified in this study including 48% of Black patients. Epidemiological and genetic studies have established that African Americans were at higher risk for kidney diseases. Genetic variation at a locus in or near the MYH9 gene on Chromosome 22 has been associated with the increased susceptibility to HIVAN, FSGS and hypertension-associated ESRD (HA-ESRD) in African Americans [5, 6]. Recently, a stronger association of FSGS and HA-ESRD

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**Table 3. Patients’ characteristics according to the type of FSGS (49 patients)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIVAN, N = 26 (%)</th>
<th>Classic FSGS, N = 23 (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (IQR)</td>
<td>40 (34–46)</td>
<td>46 (38–53)</td>
<td>0.9 (0.24–3.56)</td>
<td>0.06</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>20 (76.9)</td>
<td>18 (78.3)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Weight, kg (IQR)</td>
<td>64 (54–72)</td>
<td>65 (60–72)</td>
<td>16.1 (1.84–140.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>25 (96.2)</td>
<td>14 (60.9)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Time since HIV diagnosis, months (IQR)</td>
<td>42 (8–96)</td>
<td>108 (36–156)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>CD4 count, cells/mm³ (IQR)</td>
<td>74 (22–185)</td>
<td>367 (179–516)</td>
<td>13.4 (3.3–54.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CD4 &lt;200/µL, n (%)</td>
<td>21 (80.8)</td>
<td>5 (23.8)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>HIV viral load, copies/mL (IQR)</td>
<td>36 532 (956 to &gt;10⁶)</td>
<td>&lt;40 (&lt;40 to 35 000)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Undetectable HIV viral load, n (%)</td>
<td>3 (12.0)</td>
<td>12 (54.5)</td>
<td>0.11 (0.026–0.49)</td>
<td>0.06</td>
</tr>
<tr>
<td>History of opportunistic infections, n (%)</td>
<td>11 (42)</td>
<td>12 (52)</td>
<td>0.5 (0.16–1.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>HAART ≥6 months, n (%)</td>
<td>5 (19.2)</td>
<td>10 (43.5)</td>
<td>0.3 (0.08–1.1)</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>Hepatitis B, n (%)</td>
<td>1 (4.3)</td>
<td>1 (4.8)</td>
<td>0.9 (0.53–15.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hepatitis C, n (%)</td>
<td>2 (8.7)</td>
<td>7 (31.8)</td>
<td>0.2 (0.04–1.12)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3 (12)</td>
<td>11 (48)</td>
<td>0.14 (0.03–0.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (8)</td>
<td>2 (9)</td>
<td>0.83 (0.11–6.45)</td>
<td>0.86</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>3 (12)</td>
<td>9 (39)</td>
<td>4.7 (1.1–20.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>More than one CV risk factor, n (%)</td>
<td>1 (3.8)</td>
<td>12 (52.2)</td>
<td>0.037 (0.004–0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lipodystrophy, n (%)</td>
<td>0 (0)</td>
<td>3 (13.6)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, µmol/L (IQR)</td>
<td>539 (243–836)</td>
<td>137 (112–186)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>GFR, mL/min/1.73m² (IQR)</td>
<td>10 (7–26)</td>
<td>52 (36–71)</td>
<td>&lt;0.01</td>
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</tr>
<tr>
<td>GFR&lt;30 mL/min/1.73m², n (%)</td>
<td>24 (92.3)</td>
<td>4 (17.4)</td>
<td>57.0 (9.4–345.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proteinuria, mg/mmol (IQR)</td>
<td>215 (120–964)</td>
<td>138 (104–420)</td>
<td>0.07</td>
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</table>
has been demonstrated with two variants of the APOL1 gene, which is adjacent to the MYH9 locus [5]. In Black patients, classic FSGS may reflect a treated form of HIVAN, with modification of the collapsing pattern by HAART. Indeed, previous clinicopathological studies have demonstrated that the histopathological pattern of HIVAN can be observed in patients with only subclinical glomerular disease with microalbuminuria, a screening that is not usually performed in HIV patients [19]. However, 39.1% of classic FSGS were diagnosed in Caucasian patients, factors other than genetic predisposition may have contributed to the development of these renal lesions. In our classic FSGS group, patients tended to be older, with 39 and 48% presenting with dyslipidaemia and hypertension, respectively. Moreover, 52.2% of the patients presented with more than one CV risk factor compared to 3.8% in the HIVAN group (P < 0.01). The presence of more severe interstitial fibrosis in classic FSGS biopsy specimens may indicate a contribution of ageing and hypertension to the development of the glomerular lesions. We also found an unexpected high level of co-infection with hepatitis C, which is not a classic aetiological factor of FSGS. Diabetes mellitus was present in 12.5% of our cohort but was not associated with classic FSGS. We also report a low prevalence of diabetic nephropathy representing >5% of the glomerular diagnoses.

Our study presents several limitations. The histopathological study was not standardized by blinded review. We are aware that inclusion of patients during a period of evolution of therapeutic guidelines might result in heterogeneity of the population, with HAART regimen being significantly more prevalent in the last two periods. However, we found that severity of immunosuppression (CD4 <200/mL), prevalence of HBV and HCV co-infections as well as co-morbidities were comparable over the three periods. Given the disparity in the prevalence of HBV and HCV co-infections as well as co-morbidities were comparable over the three periods. However, we found that severity of immunosuppression (CD4 <200/mL), prevalence of HBV and HCV co-infections as well as co-morbidities were comparable over the three periods. Given the disparity in the severity of immunosuppression, thiopurines were stopped before biopsy, which is not a classic aetiological factor of FSGS.

In conclusion, our clinical–pathological study showed significant changes in the distribution of glomerular diseases in HIV-infected patients, mainly in the more recent 2004–07 period. The emergence of classic FSGS raises many questions regarding the potential implications of metabolic changes, CV risk factors, long-term HIV infection, HAART exposure, ageing and co-infection with hepatitis C together with racial predisposition. Only prospective control studies will allow the analysis of the impact of each of these parameters and longitudinal follow-up is required to appreciate long-term outcome of the renal function. Due to potential benefits of ACE-I as well as control of CVD risk factors to limit glomerular lesion progression, systematic screening for glomerular disease markers, which include proteinuria, albuminuria and GFR, is required for early detection of glomerular diseases in HIV-infected patients.

**Conflict of interest statement.** None declared.

**References**


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