Presentation of HIV-associated nephropathy and outcome in HAART-treated patients

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Abstract

Background. Among the numerous renal diseases observed in human immunodeficiency virus (HIV) patients, HIV-associated nephropathy (HIVAN) is a major cause of end-stage renal disease (ESRD). The purpose of our study was to describe the presentation and outcome of HIVAN in the era of highly active antiretroviral therapy (HAART).

Methods. We analysed clinical features and outcome of 57 patients with histologically proven HIVAN diagnosed between 2000 and 2009 in four teaching hospitals in Paris, France.

Results. This series was characterized by median age of 41 years (18–58), frequent African origin (87%), severe renal dysfunction [estimated glomerular filtration rate (eGFR) 20 mL/min/1.73m² (1–68)], high-grade proteinuria [4.1 g/day (0.6–16.8)], high proportion of sclerotic glomeruli [31.5% (0–95)], high HIV load [4.5 log copies/mL (0–6.7)] and low CD4+ count [127/mm³ (3–713)]. Nevertheless, a non-negligible proportion of patients did not present with these typical features. Follow-up data were available for 51 patients. ESRD occurred in 30 patients (58.8%). Median renal survival was 40 months. Baseline characteristics significantly associated with ESRD were as follows: severity of renal dysfunction, percentage of sclerotic glomeruli, time from HIV infection to HIVAN diagnosis longer than 1 year and prior exposure to antiretroviral drugs. There was an insignificant trend towards better renal outcome being associated with viral suppression during follow-up. Use of renin-angiotensin system (RAS) blockers was associated with higher renal survival (P < 0.05).

Conclusion. Despite HAART, HIVAN led to ESRD in more than half of the cases. Early recognition of the disease is crucial to start HAART and RAS blockers before irreversible renal injury.

Keywords: antiretroviral; end-stage renal disease; HIV-associated nephropathy; prognostic factors

Introduction

The diagnosis of renal disease in human immunodeficiency virus (HIV)-infected patients is challenging because of a variety of causes, including HIV infection itself, drugs and opportunistic infections. A major cause of renal disease is HIV-associated nephropathy (HIVAN), a severe glomerular disease directly linked to infection of epithelial cells by HIV [1, 2]. Almost all patients developing HIVAN are of African ancestry, which was recently found to be related to polymorphisms in the APOL1 gene, rather than in the MYH9 gene as previously thought [3]. HIVAN is a major concern, as its incidence among African-American HIV-infected patients was estimated to be between 3.5% in clinical studies [4] and 12% in autopsy studies [5]. HIV represents the third cause of end-stage renal disease (ESRD) among 20- to 64-year-old African-Americans [6] and HIVAN remains the leading cause of ESRD.
among HIV-infected patients in both the USA [6, 7] and France [8, 9]. In the French cohort study DIVA (Dialysis in HIV/AIDS), HIVAN accounted for 39% of the HIV-infected haemodialysis patients [8, 9].

The link between HIV infection status and HIVAN has been well established. HIVAN mainly occurs in uncontrolled HIV infection characterized by low CD4+ count and high viral load [10]. Several reports highlighted that low CD4+ count [10–12], failure to achieve complete viral suppression [13] and concomitant infection by hepatitis C virus (HCV) [12] were closely associated with poor renal outcome and evolution to ESRD. There is hope that controlling HIV replication with highly active antiretroviral therapy (HAART) could be an efficient strategy to treat HIVAN. This hypothesis was supported by epidemiological studies showing how the introduction of HAART in 1996 resulted in a lower incidence of HIVAN [14, 15].

However, only two studies focused on the outcome of HIVAN after the introduction of HAART in 1996 [12, 16]. They failed to demonstrate a significant association between HIVAN evolution and the control of HIV infection. We aimed at describing the clinical presentation and outcome of HIVAN in a large retrospective multicentric cohort of patients with biopsy-proven diagnosis, managed in the era of HAART.

Materials and methods

Data collection

We retrospectively reviewed all cases of biopsy-proven HIVAN identified in four teaching hospitals in Paris, France, (Bichat, Necker-Enfants Malades, Pitié-Salpêtrière and Saint-Louis Hospitals) between January 2000 and July 2009. Patients were identified through computerized records of the pathology laboratories. In the four hospitals, diagnoses of HIVAN were always made by well-trained pathologists experienced in the field of renal pathology. The diagnosis was based on the presence of the three following typical features on renal biopsy in an HIV-infected patient: (i) focal segmental glomerulosclerosis in its collapsing variant, (ii) absence of immune deposit by immunofluorescence and (iii) tubules with microcystic changes and proteinaceous casts in the lumen [17] (Figure 1A).

Clinical and biological data were collected through full review of medical charts. Baseline parameters were collected at time of renal biopsy. Longitudinal data regarding renal function, viral load and CD4+ count were also recorded. Renal function was estimated using MDRD (Modification of Diet in Renal Disease Study) formula [18]. ESRD was defined as an estimated glomerular filtration rate (eGFR) permanently <15 mL/min/1.73m². Microhaematuria was defined as a red blood cell count higher than 10/mm³ on urine cytology analysis. Reversible acute renal failure requiring transient extrarenal epuration was not taken into account for the definition of ESRD. HAART was defined as the use of a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor or abacavir, in a regimen including three or more antiretroviral agents. Hepatitis B virus (HBV) infection was defined as the presence of HBs antigen in blood.

Statistical analysis

Quantitative parameters are presented as median and range, and qualitative parameters are presented as number and percentage of patients. Data were recorded from diagnosis to last follow-up (death, ESRD or lost to follow-up).

In order to identify factors associated with early occurrence of ESRD, i.e. <3 months after HIVAN diagnosis, clinical, biological and pathological data at diagnosis were compared between patients with ESRD <3 months and other patients. Comparisons were made using Mann–Whitney test (quantitative parameters) or Fisher’s exact test (qualitative parameters).

Factors associated with occurrence of ESRD during follow-up were determined in a univariate analysis using a Cox proportional hazard model. When the proportional hazards assumption was not verified, the Gehan–Breslow–Wilcoxon test was performed. Longitudinal measurements of viral load and CD4+ count were taken into account as time-dependent covariates in a Cox model to analyse the impact of antiretroviral therapy on renal outcome. Patients in whom ESRD occurred within the 3 months following the diagnosis of HIVAN were excluded from these analyses because we considered that treatment was unlikely to lead to renal function recovery. Multivariate analysis was not feasible because of the small number of patients.

All statistical analyses and graphs were performed using GraphPad Prism software and R software (http://cran.r-project.org).

Results

Characteristics of HIVAN at diagnosis

Fifty-seven patients with HIVAN were included in the study. Clinical features at diagnosis of HIVAN are summarized in Table 1. Geographic origin was available for 53 patients (93%). Noteworthy, 46 (87%) patients were of Sub-Saharan African ancestry, 5 (9%) were North-Africans and 2 (4%) were Caucasians of European descent.

Median time between discovery of HIV infection and diagnosis of HIVAN was 40 months (0–204). Mode of HIV infection was sexual intercourse in 50 patients (88%) and intravenous drug use in 7 patients (12%). Fifty-three patients (93%) were infected with HIV-1, three patients (5%) with HIV-2 alone and one patient (2%) with both HIV-1 and HIV-2. HIV-2 viral load was detected and quantified by a specific technique. Twenty-seven patients

Fig. 1. Light microscopy of renal biopsy. (A) HIVAN manifests as a focal segmental glomerulosclerosis with collapsing variant, with collapse of the glomerular tuft (*) and overlying of the visceral epithelial cells with prominent protein reabsorption droplets. Tubulointerstitial injury is prominent, including epithelial necrosis and cystic dilation of renal tubules (arrow). Light green trichrome ×100. (B) The number of sclerotic glomeruli on diagnostic renal biopsies was frequently high and associated with interstitial fibrosis and tubular atrophy. Light green trichrome ×20.
HIVAN (Figure 1A), with a high proportion of sclerotic glomeruli in most cases (Figure 1B). In 17 patients (29.8%), biopsy sample involved at least 50% sclerotic glomeruli. Thrombosis of arteriolar lumen suggesting thrombotic microangiopathy associated with HIVAN was observed in four patients (7%). Of note, no immune deposits suggesting other types of glomerulonephritis were observed.

Treatments before and after HIVAN diagnosis

Data regarding treatments were analysed in 51 patients with data on follow-up available (Table 2).

At time of HIVAN diagnosis, 26 of the 51 patients (51%) had already received antiretroviral therapy. Among them, four (8%) had disrupted the treatment on their own before HIVAN diagnosis, while the treatment was still ongoing in others. Twenty-three patients (45%) were naive of treatment at time of diagnosis. The status concerning antiretroviral therapy prior to HIVAN diagnosis was unknown in four patients. After HIVAN diagnosis, all patients were prescribed HAART which was started <1 month after diagnosis in all but three of them. At diagnosis of HIVAN, only two patients were receiving tenofovir and all were switched to a non-nephrotoxic drug <1 month after HIVAN diagnosis. No other nephrotoxic antiviral drug was prescribed before or after the diagnosis of HIVAN.

Thirty-seven patients (72%) were prescribed a renin–angiotensin system (RAS) inhibitor (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker) during follow-up. Seven patients (14%) received steroids (Table 2).

Evolution after diagnosis of HIVAN

Follow-up. Six patients were lost to follow-up right after the diagnosis of HIVAN and therefore could not be included in the analysis of outcome. Median follow-up was 26 months (3–94) in the 51 other patients.

Global and renal survival. Six patients (12%) died from opportunistic infections within a median time of 132 months (81–201) and 24.5 months (11–97) after diagnoses of HIV and HIVAN, respectively. Five of them died after having reached ESRD.

ESRD occurred within 3 months after HIVAN diagnosis in 10 (19.6%) patients. Twenty patients (39.2%) evolved to
ESRD 3 months after HIVAN diagnosis. Median renal survival was 40 months after the diagnosis of HIVAN (Figure 3A). In all, HIVAN caused ESRD in 30 (59%) patients.

Three patients (6%) underwent renal transplantation. One died 1 month after transplantation from urinary sepsis and the two others were still alive at last follow-up, 1 year after transplantation.

Factors associated with renal survival

Factors associated with early ESRD. In order to identify factors associated with early occurrence of ESRD, i.e. <3 months after HIVAN diagnosis, clinical, biological and pathological data at diagnosis were compared between patients with ESRD <3 months and other patients.

Coinfection with HCV (P = 0.027) and HBV (P = 0.0092) were the only factors significantly associated with early ESRD. Median proteinuria and median percentage of sclerotic glomeruli tended to be higher in patients with early ESRD although the difference did not reach significance. HIV viral load and CD4+ count were not significantly different between early ESRD patients and the others (Table 3).

Baseline factors associated with occurrence of ESRD >3 months after HIVAN diagnosis. Clinical, immunological and viral parameters at diagnosis were analysed to determine

<table>
<thead>
<tr>
<th>Table 2. Treatments administered over follow-up</th>
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<tr>
<td>Number of patients</td>
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<tr>
<td>HAART</td>
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<td>Prior to HIVAN diagnosis</td>
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<td>Ongoing at diagnosis</td>
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<td>Disrupted at diagnosis</td>
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<tr>
<td>Only after HIVAN diagnosis</td>
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<td>Steroids</td>
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<td>During follow-up</td>
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<tr>
<td>RAS blocker</td>
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<td>During follow-up</td>
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<tr>
<th>Table 3. Factors associated with early occurrence of ESRD (&lt;3 months after diagnosis)</th>
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<tr>
<td>Non-ESRD and ESRD &gt;3 months</td>
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<tr>
<td>Number of patients</td>
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<tr>
<td>Demographic features</td>
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<tr>
<td>Age (year)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Presentation of renal disease</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<tr>
<td>Proteinuria (g/day)</td>
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<tr>
<td>Percentage of sclerotic glomeruli</td>
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<tr>
<td>Immunological and viral features</td>
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<tr>
<td>Hepatitis C</td>
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<tr>
<td>Hepatitis B (positive HBs antigen)</td>
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<tr>
<td>Time from HIV to HIVAN diagnosis (months)</td>
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<tr>
<td>HIV viral load (log10 copies/mL)</td>
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<td>CD4+ count (/mm3)</td>
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<td>CDC stage</td>
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<td>A</td>
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<td>B</td>
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<td>C</td>
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<td>HAART before HIVAN diagnosis</td>
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Factors significantly associated with early occurrence of ESRD are provided in bold.

Systolic and diastolic blood pressure were available for 15 (71.4%) of non-ESRD, 13 (65%) of ESRD >3 months and 9 (90%) of ESRD <3 months patients.

Proteinuria was available for 18 (90%) of non-ESRD, 20 (95%) of ESRD >3 months and 7 (70%) of ESRD <3 months patients.

Hepatitis B serology was available for 20 of the 21 (95%) non-ESRD, 18 (90%) of the 20 ESRD >3 months and all of the ESRD <3 months patients.

CDC stage was available for 17 (85%) of non-ESRD, 21 (100%) of ESRD >3 months and 9 (90%) of ESRD <3 months patients.
those associated with renal outcome as summarized in Table 4.

As expected, a lower eGFR, a higher serum creatinine and a higher proportion of sclerotic glomeruli at diagnosis were significant risk factors for developing ESRD.

A diagnosis of HIVAN made >1 year after the discovery of HIV infection was significantly associated with a worse renal outcome (P < 0.05) (Figure 3B). This probably reflected a delayed diagnosis of HIVAN in some patients. Indeed, the percentage of sclerotic glomeruli on the diagnostic renal biopsy was higher in patients with time between HIV and HIVAN diagnosis >1 year [41% (0–95)] than in the others [15% (0–45)] (P = 0.01).

Surprisingly, viral load was undetectable at HIVAN diagnosis in eight (16%) patients (all on HAART). This was associated with an increased risk of ESRD. Median renal survival was reduced to 15.5 months in them compared to 44 months in patients with detectable viral load (P < 0.05) (Figure 3C). At diagnosis, patients with undetectable viral load tended to have lower eGFR [20 (11–34) versus 37 mL/min/1.73m² (5–77), P = 0.26] and higher prevalence of HCV infection (43 versus 10%, P = 0.16). Proteinuria [3.5 (0.9–7) versus 4.1 g/day (0.6–14), P = 0.42] and prevalence of HBV infection were similar (14 versus 10%, P = 0.70).

In the same way, the risk of ESRD was higher in patients who had received antiretroviral therapy prior to HIVAN diagnosis. These patients had similar eGFR than those who never received antiretroviral therapy before HIVAN diagnosis [29 (6–77) versus 34 mL/min/1.73m² (5–61), P = 0.85]. Median renal survival was 31 months in these patients compared to 41 months in those who were naive of antiviral treatment (P < 0.05) (Figure 3D).

Impact of treatments and viral suppression on renal outcome. Seven patients (14%) were prescribed steroids and ESRD occurred in four of them.

For unclear reasons, eight patients (22%) were not prescribed RAS blockers (Table 2). This was associated with a higher risk of developing ESRD [hazard ratio = 5.23 (1.19–23.0), P = 0.028]. Median renal survival time was 45 months in patients who received RAS blockers compared to 17 months in those who did not (Figure 3E). Proteinuria, eGFR, percentage of sclerotic glomeruli, prevalence of HCV and HBV infections were not different at baseline between RAS blockers-treated and -untreated patients (data not shown).

Twenty (47.8%) patients achieved viral suppression in the peripheral blood during follow-up. This was associated with a 2-fold reduction of the risk of ESRD, although this result did not reach significance (Table 4).
HIVAN diagnosis and outcome

Eight (14%) patients had proteinuria <1.5 g/day and six (11%) had eGFR >60 ml/min/1.73m². CD4+ count was >200/mm³ in 19 patients (35%) and HIV viral load was undetectable in 9 patients (16%). Some authors proposed criteria for HIVAN diagnostic [14, 20, 21], such as proteinuria >3.5 g/day, CD4+ count <200/mm³ and viral load >5 log. We were able to evaluate these criteria in 45 patients with full data available. Interestingly, 4 patients (8.9%) in our study did not meet any of these three criteria, 13 (28.9%) met one criterion, 23 (51.1%) met two criteria and 5 (11.1%) met all three criteria. Therefore, some patients showed up with atypical clinical presentation and the diagnosis may have been missed by such criteria.

In addition, other renal diseases, especially those with glomerular involvement, may have features similar to HIVAN [19]. The differential diagnosis of HIVAN includes immune complex glomerulonephritis, thrombotic microangiopathy, interstitial nephritis, infectious diseases and drug toxicity [22–26]. In the study by Atta et al. [20], HIVAN accounted for only two-thirds of renal diseases in HIV patients with CD4+ count <200/mm³. Identification of the cause of renal damage may be crucial in directing specific treatments, including steroids, immunosuppressive drugs, plasmaphaeresis or drug discontinuation [27]. We suggest that renal biopsy should be considered in all HIV-infected patients with proteinuria, whatever their renal function, CD4+ count or viral load.

With the use of ultrasound-guided renal biopsy and automatic biopsy devices, percutaneous renal biopsy became safe. Recent studies reported life-threatening complications in <0.1% of cases [28, 29]. A recent study established that percutaneous renal biopsy in HIV-infected patients was as safe as in other patients [30], which is consistent with our experience. Trans jugular renal biopsy may represent a relatively safe and reliable alternative to conventional percutaneous biopsy in patients with risk factors for bleeding such as thrombopaenia [31, 32].

In our study, ESRD occurred in more than half of the patients and median renal survival was 40 months, which is similar to the results reported by Post et al. [16]. Ten years ago, an even worse prognosis was reported in a French [11] and an American [12] study, with a median renal survival of only 16.6 months and 8.5 months, respectively. Although renal prognosis remains poor, this suggests a significant improvement in the era of HAART. We found a non-significant trend towards better renal outcome in patients who achieved viral suppression in peripheral blood after HIVAN diagnosis (Table 4). A beneficial effect of HAART is expected because HIVAN is directly caused by infection of renal epithelial cells [33] and because the introduction HAART was shown to be associated with a reduction of HIVAN incidence [14, 15]. Nevertheless, renal outcome was poor despite the fact that all patients received HAART after HIVAN diagnosis and half of them achieved viral suppression in the peripheral blood during follow-up.

One explanation may be that HAART was started too late, as many patients in our study showed low eGFR and high proportion of sclerotic glomeruli at diagnosis. Patients with time interval between HIV and HIVAN diagnoses <1 year displayed lower proportion of sclerotic glomeruli and had a

Table 4. Factors associated with evolution to ESRD during follow-up

<table>
<thead>
<tr>
<th>Renal features at diagnosis</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>3.46</td>
<td>1.14–10.48</td>
<td>0.028</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.74</td>
<td>0.23–2.46</td>
<td>0.63</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>3.29</td>
<td>1.27–8.50</td>
<td>0.014</td>
</tr>
<tr>
<td>Glomerulosclerosis</td>
<td>1.78</td>
<td>0.32–9.73</td>
<td>0.51</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1.63</td>
<td>0.54–4.96</td>
<td>0.29</td>
</tr>
<tr>
<td>Positive HBs antigen</td>
<td>1.29</td>
<td>0.21–8.09</td>
<td>0.79</td>
</tr>
<tr>
<td>RAS blockers</td>
<td>1.70</td>
<td>0.56–5.14</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Factors significantly associated with evolution to ESRD during follow-up are provided in bold. Systolic and diastolic blood pressure values were available for 15 (71%) of non-ESRD patients and 13 (65%) of ESRD patients. Serum albumin was available for 16 (76%) non-ESRD patients and 15 (75%) ESRD patients.

Discussion

HIVAN represents a major complication of HIV infection that usually occurs in uncontrolled disease and often leads to ESRD [10–12, 16]. We report the results of a retrospective study on 57 patients with HIVAN, which represents one of the most important published cohorts. We focused on cases evidenced by renal biopsy, in order to rule out alternative diagnoses.

In accordance with previous reports [11, 12, 16, 19], severe renal dysfunction and high-grade proteinuria in a black patient with highly replicative infection and severe immunodeficiency were the commonest presentation of HIVAN. Nevertheless, a non-negligible proportion of patients in our study showed less typical characteristics. Although HIVAN was previously reported almost exclusively in patients of Sub-Saharan African ancestry [5, 12, 16, 19], seven patients (12.3%) were Caucasians or North Africans.
better prognosis. This emphasizes the crucial importance of early recognition of HIVAN in order to start treatment before the development of irreversible renal injury. Screening for proteinuria should therefore be systematically performed in HIV patients and a biopsy realized if necessary.

Another explanation may be that the HIV-infected renal epithelium constitutes a distinct viral compartment that would be hard to access with antiretroviral therapy. Active viral replication in the kidney was detected even in patients with undetectable viral load in the peripheral blood [1]. Using laser-capture microdissection, Marras et al. removed infected renal epithelial cells and compared kidney-derived viral sequences to sequences from peripheral blood cells. This elegant study demonstrated kidney-specific evolution of the virus [2]. Post et al. [16] found no clear correlation between the control of viral replication in blood and HIVAN outcome. These data argue strongly for localized replication of HIV in renal epithelial cells and the existence of a renal viral reservoir, as shown in the central nervous system and the genito-urinary tract [34].

The persistence or occurrence of clinical renal disease despite achieving control of viral replication in the peripheral blood may indicate a subset of patients with active viral replication in the kidney that would be particularly difficult to control. This may explain the poor renal outcome observed in patients with undetectable viral load at HIVAN diagnosis or previously treated with antiretroviral drugs (Table 4 and Figure 3C and D). However, we cannot exclude that this finding could be related to the trend towards a lower glomerular filtration rate at baseline in patients with undetectable viral load at time of HIVAN diagnosis. Anyway, it would be of great importance to develop tools allowing the monitoring of renal-specific viral replication and also to determine which antiretroviral drugs are the most efficient to control it.

HCV and HBV infection were more prevalent in patients who reached ESRD precociously. HCV infection has been pointed out as a risk factor for renal disease in HIV-infected patients [35]. However, the mechanism is unknown and the impact of HCV on the course of HIVAN remains elusive.

We observed that patients who did not receive RAS blockers had a very poor outcome. Although these findings should be interpreted carefully given the design of our study, this in accordance with clinical and experimental studies [36–38] supporting a beneficial effect of RAS blockers on the course of HIVAN. In addition to HAART, RAS blockers should be considered as an important part of HIVAN treatment.

The association between renal dysfunction at diagnosis and evolution to ESRD observed in our study may also result from inadequate dosage of antiretroviral drugs in patients with renal dysfunction. Inadequate dosage may result in renal toxicity secondary to overdosing or low efficacy related to underdosing. Tourret et al. [39] drew attention to the high frequency of antiretroviral drug dosing errors in HIV patients on dialysis in France and the necessity of dosage adjustment to renal function.

Only a few patients received steroids and they had a poor outcome. The limited number of patients treated and the absence of control group did not allow us to draw any conclusion on the impact of steroid therapy. Given the controversial effect of steroids on the course of HIVAN [40, 41] and the risk of adverse infectious events, this treatment should be selectively and cautiously applied.

Our study has several limitations. We were not able to provide data on adherence to treatment and adjustment of drug dosage to renal function, which could have a strong impact on prognosis. Patients in our study did not receive nephrotoxic antiretroviral drugs (except two patients under tenofovir at diagnosis). However, many other drugs often used in HIV patients, such as antibiotics, can potentially cause renal adverse effects, especially in patients with decreased renal dysfunction.

At last, the limited number of patients and events prevented us to do multivariate analysis of prognosis factors.

In summary, HIVAN remains a severe complication of HIV infection leading to ESRD in more than half of the patients. A high level of suspicion should be maintained in all HIV patients with proteinuria or renal dysfunction. Screening for proteinuria and broad indications for renal biopsy are of crucial importance to detect HIVAN early and start HAART and RAS blockers.

Conflict of interest statement. None declared.

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