

ORIGINAL ARTICLE

The Spectrum of Renal Diseases in HIV Infected Adults Presenting with Renal Insufficiency at the University Teaching Hospital, Lusaka, Zambia

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ABSTRACT

Background: The spectrum of renal diseases in HIV infected adults undergoing biopsy is vast. Previous studies have indicated that HIV-associated nephropathy (HIVAN) is the commonest diagnosis in HIV-infected patients presenting with renal insufficiency. More than 90% of patients with HIVAN are black. The natural history of the renal diseases associated with HIV infection has been radically changed by antiretroviral therapy. There are other diseases, however, that account for a good percentage to the spectrum of renal diseases other than HIVAN. A group of diseases known as HIV immune complex kidney diseases have gained prominence in this regard. Other diseases include acute tubular necrosis, acute and chronic interstitial nephritis, haemolytic uremic syndrome and many others.

Objective: To determine the clinical and histopathological presentation of the spectrum of renal diseases in HIV infected adult patients presenting with renal insufficiency at the University Teaching Hospital, Lusaka

Methods: This was a descriptive cross-sectional study of HIV infected adults presenting with renal insufficiency who underwent kidney biopsy. It was conducted at the University Teaching Hospital from June 2014 to November 2015. The primary outcome was proportion of major histological diagnosis of renal diseases in this patient population while secondary outcomes included proportion of other renal histological diagnoses and the patient's clinical characteristics.

Results: The commonest histological diagnoses in this study were HIV immune complex kidney disease (HIVICK) (32%) and focal segmental glomerulosclerosis (FSGS) (29%) of various histologic variants other than the collapsing type. We did not see the classic HIVAN on histopathology in our study population. All the patients presented with severe renal dysfunction with mean eGFR of 17 ml/min/173m² and massive proteinuria of 3+. Patients had advanced HIV infection with mean CD4 count of 197 cells/mm³. Majority of patients (64.5%) were not yet been initiated cART. 16% of the study patients were hypertensive.

Conclusion: HIVICK and FSGS were the commonest histological diagnoses. Classical HIVAN on histopathology was not found in this patient population at the UTH.

Recommendation: Kidney biopsy should mandatory to make definitive diagnosis in HIV with renal dysfunction.

INTRODUCTION

HIV prevalence in sub-Saharan Africa accounts for a significant proportion of the world's burden of the disease.¹ Zambia, a country in this region of the world, is not spared; with the HIV prevalence being 13% according to the 2014 Zambia Demographic Health Survey. HIV seropositive patients have an increased risk for the development of a variety of acute and chronic renal diseases.² Thus the spectrum of renal diseases in HIV infection is wide. Renal failure causes so much morbidity and mortality and the cost of managing these disease entities is huge.

Keywords: Renal insufficiency, biopsy, HIV immune complex kidney disease, HIVAN, FSGS

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Kidney dysfunction, in HIV infection, is a very common complication. It can be caused by drugs used to treat opportunistic infections in HIV, antiretroviral drugs; co-infections like Hepatitis B and C and can also be due to HIV infection of the renal cells. Genetics and race have been found to be a major contributor to certain forms of parenchymal renal diseases. The HIV has been implicated in the pathogenesis of parenchymal renal diseases like HIVAN and HIVICK. Other concurrent diseases like diabetes mellitus, hypertension and autoimmune diseases have a tendency to increase the burden of renal dysfunction in HIV patients.

Previously HIV-associated nephropathy (HIVAN) was shown to be the commonest diagnosis in HIV-infected patients presenting with renal insufficiency with more than 90% of patients with HIVAN being of African descent.³⁻⁵ The natural history of renal diseases associated with HIV infection has, however, been radically changed by antiretroviral therapy. Most investigators believe that combination antiretroviral therapy (cART) needs to be initiated in patients with renal disease in the presence of HIV infection, more so in those patients found to have HIVAN and immune mediated kidney diseases.

There are other renal parenchymal diseases seen in HIV infection that account for a good percentage of renal diseases other than HIVAN. A group of diseases known as HIV immune complex kidney diseases have gained prominence in this regard.⁶ Other diseases include acute tubular necrosis, acute and chronic interstitial nephritis, haemolytic uraemic syndrome and many others. The latter disease entities usually account for the majority of patients with acute renal failure in HIV infection.⁷ The clinical presentation of the majority of acute renal failure patients does not differ significantly from one another hence necessitating kidney biopsy.

In this study, we defined renal insufficiency as raised serum creatinine level above 146 $\mu\text{mol/L}$ and/or persistent proteinuria of 1+ and above. This definition was adopted from the Kidney Disease Improving Global Outcomes (KDIGO) technical working group of 2012. Persistent proteinuria in the study was defined as proteinuria that remained positive for two weeks after the initial urine dipstick test.

At present there are no serologic markers that exist to make a diagnosis of the spectrum of renal diseases in HIV, and the differential diagnosis for renal failure in HIV patients renal is broad. This therefore necessitates the

need for renal biopsy.⁸ Viral infection of renal cells, and genetic factors, however, are assumed to play a central role in the pathogenesis of some of the diseases seen in HIV.⁹

The University Teaching Hospital in Lusaka has a high burden of patients with HIV who present with renal insufficiency [9%].¹⁰ Thus this study was conducted with the aim of identifying the spectrum of various histologically proven HIV related renal diseases and the clinical characteristics that these patients.

METHODS

This was a descriptive cross sectional study conducted at the University Teaching Hospital in Lusaka from June 2014 to November 2015. A total number of 31 adult HIV infected patients, aged 21 to 58 years, with renal dysfunction underwent kidney biopsy. An independent pathologist evaluated the specimens and generated a histopathology report.

The primary outcome was the major histopathological diagnoses found on the biopsy specimens and secondary outcomes included the clinical characteristics of these patients and comparison of these clinical characteristics in the major histopathological diagnoses.

Patients were screened and recruited on a daily basis in Adult Medical Emergency Unit, Adult Infectious Disease Centre and Medical Admission Ward based on the inclusion/exclusion criteria. Patients' demographic characteristics were obtained from the clinical files and documented.

Careful selection of patients was conducted so as to minimize the complications of a renal biopsy. A detailed history was obtained at the screening points and included patient demographics, presenting complaints, past medical and drug history. Urinalysis was conducted by a single research assistant and findings recorded.

Investigations that were conducted included serum creatinine, urea and electrolytes, full blood count, hepatitis B surface antigen, clotting profile, random blood sugar, liver function tests, CD4 cell counts. For safety reasons, abdominal ultrasound scans were done by an experienced radiographer and the researcher and the findings were documented.

Percutaneous kidney biopsy, with the patient in the prone position was performed under local anaesthesia, 1%

lignocaine, in the radiology department, of the UTH, under ultrasound guidance.

Patients with kidney failure in danger of uraemic coagulopathy were put on haemodialysis prior to biopsy. Strict control of blood pressure was done to reduce bleeding risk in patients that had hypertension. Post-biopsy care and supervision was done by monitoring any signs of bleeding. Post-procedure monitoring included monitoring for blood in urine, monitoring patients' vital signs which included blood pressure, pulse rate and quality of pulse. In our study no patient experienced worsening renal function or post biopsy complications. Paracetamol and tramadol were given for pain relief after the procedure.

Continuous variables such as: age, CD4 cell counts, level of haemoglobin, creatinine levels were expressed as means and/or medians, and percentages. Categorical variables like sex, histological diagnoses and level of proteinuria were expressed as percentages or proportions.

Fisher's exact test was used to quantify correlations between dichotomous variables (e.g. the main histological diagnosis and patient characteristics). A p -value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using the Epi Infor software version 7.

Ethics approval

Ethical approval was granted by ERES Converge IRB and permission to carry out the study at the University Teaching Hospital was granted by the office of the senior medical superintendent. The study had IRB No. 00005948.

RESULTS

Two hundred and thirty-four patients were screened during the period of the study, July 2014-December 2015. Of these patients, we performed 31 percutaneous kidney biopsies. Figure 1 shows the recruitment and enrolment flow of the study.

The reasons for non-eligibility into the study included the following:

1. Moribund and severe co-morbid conditions (54 patients)
2. Refused consent to enter into the study (45 patients)
3. Resolved renal dysfunction during hospital stay (these were mainly patients who presented with

severe sepsis and kidney dysfunction) (37 patients)

4. Small kidneys on abdominal ultrasound scan (22 patients)
5. Refusal to sign consent to the study procedure (kidney biopsy) (15 patients)

Among the 31 patients that underwent renal biopsy, none had the classical HIVAN diagnosis on histopathological description. The most common histological diagnoses were HIV immune complex kidney disease (HIVICK) and focal segmental glomerulosclerosis (FSGS). This is shown in Figure 2.

Figure 1: Flow Chart Of The Study

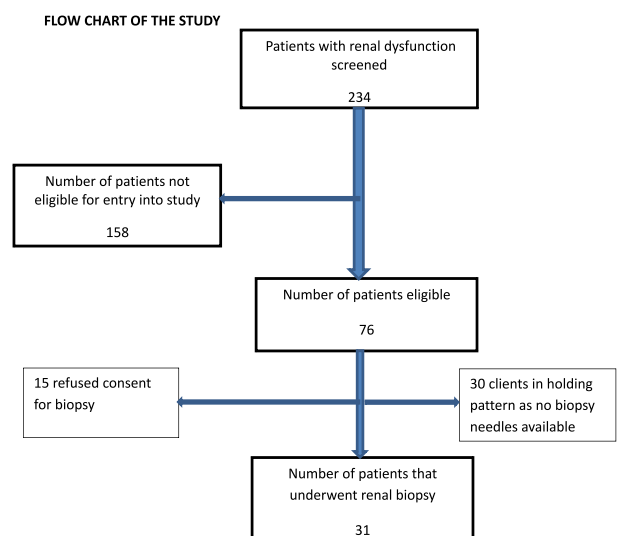
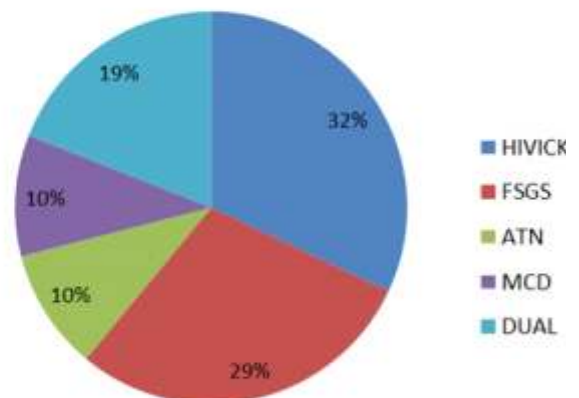


Figure 2: Histological diagnosis distribution (N=31)



HIVICK- HIV immune complex kidney disease, **FSGS**- Focal segmental glomerulosclerosis, **Dual** – dual diagnosis of HIVICK and FSGS, **MCD**- Minimal change disease and **ATN**- Acute tubular necrosis

Clinical characteristics of the patients

Most of the study participants, twenty of the 31 (64.5%), were pre HAART exposure with male to female ratio of 1:1. All the patients, mean age 41.3 years, had both severe renal dysfunction with average eGFR of 23 ml/min/m² and nephrotic range proteinuria. Table 1 shows the clinical characteristics of the study participants.

Table 1: Patients' demographics and clinical characteristics

Variable	Total number N=31	On cART N=11	PreHAART N=20	HIVICK N=10	FSGS N=9
Mean age in years (±SD)	41.3±10 (21-58)	47.9±9.7 (28-58)	37.6±8.3 (21-52)	43.1±7.1 (31-52)	42.4±13.1 (21-58)
Males N [%]	16 [51.6]	3 [27.3]	13 [65]	4 [40]	3 [33.3]
Females N [%]	15 [49.4]	8 [72.7]	7 [35]	6 [60]	6 [66.7]
Mean CD4 cell counts in cells/UL (±SD)	197±120 (21-425)	236.4±110 (98-425)	175.5±22.6 (21-423)	211.6±137.9 (21-387)	229.5±114.5 (103-425)
Mean creatinine in umol/L (±SD)	321±112.9 (154-569)	359±102.3 (243-569)	301±115.6 (154-569)	318 ±133.6 (154-569)	332±108.8 (225-569)
Mean eGFR in ml/min/1.73m ² (±SD)	24±12 (8-57)	21±13 (10-58)	23±13 (8-57)	24±12 (8-57)	23±11 (12-44)
Hypertension N [%]	5 [16.2]	3 [9.7]	2 [6.5]	3 [9.7]	0 [0]
Mean Hb in g/dL (±SD)	9.7±1.8 (6.8-13.7)	10.2±1.7 (7.9-12.8)	9.5±1.9 (6.8-13.7)	9.5±1.8 (6.8-12.4)	8.8±1.3 (6.8-11.2)

N= Number, **eGFR=** estimated glomerular filtration rate, **Hb=** haemoglobin, **HIVICK=** HIV immune complex kidney disease, **FSGS=** Focal segmental glomerulosclerosis, **c ART** combined antiretroviral therapy

Most patients in this study were not on ART (64.5%). The mean CD4 cell count for those that were pre cART was 175 cells/mm³ while those on cART had a mean of 211 cells/mm³. There were more female patients on combination ART, 72.7%, compared to men at 27.3%. The patients who were on combination ART were older, with mean age at 47.9 years, than those patients who were not on ART whose mean age was 37.6 years. Patients that were on combination ART had a mean estimated GFR of 23 ml/min/m² compared to 24 ml/min/m² those patients who were not on ART. The most common ART regimens in those who were on combination ART was protease inhibitor based, with lopinavir/ritonavir combination being the commonest, and tenofovir based regimens.

Description of Histological diagnoses in study patients

The comparison of the clinical characteristics in the 19 patients with the two commonest histological diagnoses is as shown in Table 2. It can be seen that there was no

significant difference in the clinical characteristics in the two main histological diagnoses as can be seen from the p values in Table 2.

Table 2: Comparison of the main histological diagnoses variables

Variable	HIVICK	FSGS	P value
Mean age in years(±SD)	43.1±7.1 (31-52)	42.4±13.1 (21-58)	1.00
Males N [%]	4 [44.4]	3 [30]	1.00
Females N [%]	5 [55.6]	7 [70]	1.00
Mean CD4 cell counts in cells/mm ³ (±SD)	211.6±137.9 (21-387)	229.5±114.5 (103-425)	1.00
Mean creatinine in umol/L(±SD)	318.1±133.6 (154-569)	332±108.8 (225-569)	1.00
Mean eGFR in ml/min/1.73m ² (±SD)	24±12 (8-57)	23±11 (12-44)	1.00
Mean Hb in g/dL(±SD)	9.5±1.8 (6.8-12.4)	8.8±1.3 (6.8-11.2)	1.00

The histological diagnoses in the remaining 12 patients were as indicated in Figure 2; six had dual diagnosis of FSGS and HIVICK, 3 had minimal change disease and 3 were diagnosed as acute tubular necrosis. Of interest is that the 3 patients with ATN presented with sepsis. They however, had persistent proteinuria (of 3+ on urine dipstick) and the renal scan showed echogenic, normal sized kidneys. They were thus diagnosed as acute on chronic kidney disease clinically before renal biopsy was performed.

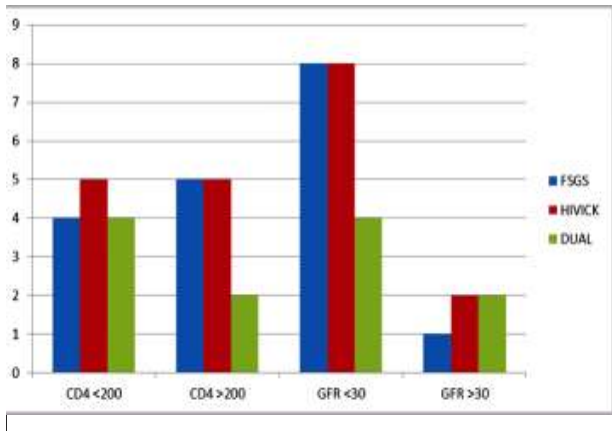
The clinical characteristics of the patients that had a dual diagnosis of FSGS/HIVICK did not differ clinically from the patients who had either FSGS or HIVICK as a single diagnosis. The severity of renal dysfunction and immunosuppression were not different in these patients. Figure 3 shows this distribution.

Of the nine patients that had the diagnosis of FSGS, the commonest histologic variant was the Tip variant accounting for 55%. One patient (12%) had the cellular variant while 33% had the perihilar variant. This description is seen in Table 3. Table 4 shows the detailed description of the patients who had HIVICK.

The patients in this study had severe immunosuppression as can be seen from the mean CD4 cell count of 197 cells/mm³. Putting, these patients in the various strata of CD4 cell counts; of the 31 study patients, 17 had CD4 cell counts of <200 per microliter. Seven of these patients had

CD4 count less than 100 cells/mm³. Most of these patients with severe immunosuppression were not on cART. Of the 17 patients with severe immunosuppression, only six were on combination antiretroviral therapy (ART). The duration of ART ranged from 6 weeks to 6 years.

Figure 3: Distribution of three main histological diagnoses in the study based on severity of renal dysfunction and immunosuppression (Total number 25)



There was no overall difference in the histological diagnoses of those patients with CD4 cell counts <200 cells/mm³. The distribution of the histological diagnoses in these was; four had a dual diagnosis of HIVICK and FSGS, four had FSGS, five had HIVICK, and two each for MCD and ATN.

Of the 14 patients in the study that had CD4 cell count ≥ 200 cells/mm³, five each had HIVICK and FSGS while two had a dual diagnosis of HIVICK/FSGS, and one each for MCD and ATN. The main histological diagnosis distribution based on level of immunosuppression is as shown in Figure 3.

The abdominal ultrasound report showed mostly hyperechoic, normal sized kidneys. Even the patients that were found to have ATN were found to have similar descriptions on abdominal ultrasound. There was only one patient who had bilateral enlarged kidneys on ultrasound (14×6.5×4.8 cm on the right and 15.3×6.3×4.3 cm on the left). This patient had FSGS with the perihilar variant. As indicated this patient had heavy proteinuria of 3+ on urine dipstick, severe immunosuppression and was on cART for two months at the time of kidney biopsy. This patient would have been postulated to have classical HIVAN in the absence of histology.

Table 3: Histopathological Description of FSGS

Cortico-medullary junction	Number of Glomeruli	% of glomerular sclerosis	Tubulointerstitial involvement	Histologic Variant of FSGS
Present	18	47	Multifocal chronic interstitial nephritis of moderate intensity	Tip variant
Absent	27	50	Diffuse chronic interstitial nephritis of moderate intensity	Cellular variant
Present	55	33	Diffuse chronic interstitial nephritis of marked intensity	Perihilar
Absent	12	25	Multifocal active chronic interstitial nephritis of mild intensity	Tip
Absent	18	32	Multifocal active chronic interstitial nephritis of mild to moderate intensity	Tip
Present	36	29	Diffuse chronic interstitial nephritis of moderate intensity, mild activity	Perihilar
Absent	8	24	Active chronic interstitial nephritis with mild intensity	Tip
Present	12	25	Diffuse chronic interstitial nephritis with moderate intensity	Tip
Present	10	5	Patch chronic interstitial nephritis of mild intensity	Perihilar

Table 4: HIVICK subtypes

Subtype	Number	Interstitial involvement
HIVICK with global sclerosis (NOS)	3	Patchy active chronic interstitial nephritis mild intensity involving 20 - 25% cortical volume. Tubulo - interstitial nephritis with tubule microcystic dilatation changes.
		Multifocal active chronic interstitial nephritis of moderate intensity accounting for 25 -30% of cortical volume
		Diffuse active interstitial nephritis of marked intensity accounting for 35 - 40% cortical volume
Membranous glomerulonephritis	2	Active chronic interstitial nephritis patchy in distribution and moderate intensity accounting for 10 -15% of cortical volume. There were also basement membrane holes noted.
		Active chronic interstitial nephritis patchy in distribution with mild intensity accounting for 20 -25% cortical volume
HIVICK with minimal change disease	2	Mild and patchy active chronic interstitial nephritis of mild intensity
		Moderate tubulo -interstitial nephritis composed of lymphocytes and plasma cells
HIVICK with Glomerulopathy with organised deposits and immunotactoidglomerulopathy	1	Mild and global active chronic interstitial nephritis of moderate intensity accounting for 30% of cortical volume. Also global mesangiopathic alterations
HIVICK with Immune complex mediated membranous glomerulopathy	1	Active chronic interstitial nephritis which is patchy to diffuse of moderate intensity
HIVICK with membranoproliferativeglomeronephritis	1	Mild and patchy active chronic interstitial nephritis of mild intensity

DISCUSSION

In this study, of the 31 renal biopsies performed, there was no case of classical HIVAN found based on histological description. This is in contrast to studies conducted previously in Africa (mostly in South Africa) and the United States of America where HIVAN was the commonest diagnosis in individuals of African descent.^{2,3,4,6,11} This could be due to our small sample size and fact that our study did not have follow up biopsies.

The commonest diagnoses in our study were HIVICK (32%), focal segmental glomerulosclerosis (29%) and the dual diagnosis of FSGS/HIVICK (19%). All the patients had massive proteinuria (grade 3+ on urine dipstick) and severe renal dysfunction with mean GFR of 16 ml/min/m². One study in South Africa found a similar percentage of HIVICK in individuals of African descent.¹⁰

The severe renal dysfunction that patients with HIVICK presented with is in agreement with some studies which indicate that patients with HIVICK tend to have severe renal dysfunction.^{10,12} These patients, however, do not show the rapid decline in renal dysfunction seen in patients with HIVAN.^{12,13} Most patients with HIVICK in this study were not on HAART and had severe immunosuppression as can be seen from the mean CD4 cell count of 211 cells/mm³. Previous studies though have shown that patients with HIVICK usually have had more exposure to ARVs.¹² All the patients in this study had massive proteinuria on urine dipstick, including those patients that were diagnosed as HIVICK. This is in contrast to what was observed in a study where patients with HIVICK had proteinuria less than 1+ on urine dipstick.¹²

In this study, there were only five patients, out of 31 (16.1%) who were hypertensive and on medication for hypertension. Two of these patients had a dual diagnosis of HIVICK/FSGS and two had HIVICK. This is in agreement with what has been observed in other studies which show that HIVICK is more prevalent in patients that have comorbid conditions like hypertension and diabetes.¹² In our study however, there was none among the patients enrolled who had diabetes as a comorbid condition.

The patients with HIVICK had global sclerosis not otherwise specified (NOS) as the commonest subtype. The only patient who had hepatitis B had membranoproliferative glomerulonephritis. This patient was on tenofovir based ART regimen which was adjusted based on the creatinine clearance that was calculated. In previous studies, Hepatitis C infection has shown to be strongly associated with the development of HIVICK.^{14,}

¹⁵We did not however see a patient with Hepatitis C in our study.

Focal segmental glomerulosclerosis was the second commonest diagnosis in this study. This is in accordance with what has been found in other studies which indicate that FSGS is a very common histological finding in patients of African descent that have HIV infection.¹⁶ We however did not observe any collapsing histologic variant of FSGS. There was also no microcystic tubular dilatation, podocyte proliferation and effacement of the foot processes to confirm the diagnosis of classic HIVAN. The most common histologic variant of FSGS was the tip variant accounting for 55.5%. The second commonest variant was the perihilar variant (33.3%). Studies elsewhere have shown varying frequencies of these histologic variants of FSGS.¹⁷⁻²⁰ Most of these studies have shown that the histologic variant NOS (not otherwise specified) is the commonest.

There was major involvement of the interstitium in FSGS with most patients having chronic interstitial nephritis with moderate to marked intensity. The study from Pakistan found that there 93% interstitial involvement in the patients with FSGS.²¹ Of the nine patients with FSGS, only one had secondary FSGS. This patient had also been treated for hypothyroidism and nephrotic syndrome in the younger years (about 10 years before recruitment in the study).

The patients in this study had severe immunosuppression with mean CD4 cell count being 197 cells/mm³ overall, 175 in those patients who were not on cART and 236 in those patients on cART. The patients that had FSGS 66.6% (6 out of 9) were on cART with a mean duration of 2 years. Thirty percent of the patients with a diagnosis of HIVICK were on cART; while the majority of the patients (70%) were not yet on cART. This is contrast with literature that indicates that patients with HIVICK tend to have more exposure to drugs like HAART.¹²

In this study there were no patients with microangiopathies. Most of the patients that came in with acute kidney injury had recovery of their kidney dysfunction on conservative treatment and they thus did not undergo renal biopsy. The other reason could that most of the patients who came in very sick and had serious comorbid conditions were excluded from the study and that the patients who had severe renal dysfunction at presentation actually had chronic kidney disease.

There was no major post kidney complication that was recorded in the study. This was as a result of careful

selection of patients before performing the biopsy. This is in agreement with studies conducted in Europe which did not recorded major adverse events even in critically ill patients. This study has strengthened the fact that a percutaneous kidney biopsy is an important and necessary procedure to diagnose kidney diseases and guide therapy in the process.^{22,23}

Kidney biopsy, as has been shown in this study, is an important procedure for diagnosis and subsequent management of patients especially in this study population. Without biopsy, most of the patients in this study could have been wrongly diagnosed as HIVAN.

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