# The Utilization of Diagnostic Ultrasound in the Evaluation of the Kidneys in HIV-Associated Nephropathy

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# **ABSTRACT**

Aim: To evaluate the renal sizes and echogenicity pattern in patients with human immunodeficiency virus (HIV)-associated nephropathy and to correlate renal echogenicity with serum creatinine levels and proteinuria. Materials and Methods: A cross-sectional study of 100 consecutively confirmed HIV- seropositive patients aged between 19 and 65 years (Mean ± SD: 35 ± 10.79) comprising 32 males and 68 females with clinical and laboratory features of HIV-associated nephropathy (HIVAN) was conducted at the Infectious Diseases Clinic of the University of Maiduguri Teaching Hospital, between April 2011 and September 2012. The subjects were evaluated with renal ultrasound scan and the observed abnormalities were recorded. Serum creatinine levels and CD4 + lymphocyte counts were also obtained for all the patients. Proteinuria was established by dipstick method. Results: Of the 100 cases studied, ultrasound showed enlarged kidneys in 28 patients (28%) and abnormal echogenicity was present in 192 kidneys (96%). 100 kidneys (50%) were globular, 160 kidneys (80%) had decreased corticomedullary definition, 90 kidneys (45%) had decreased renal sinus fat and 80 kidneys (40%) had heterogenous renal parenchymal patterns. A high serum creatinine level, increased degree of proteinuria, lower CD4 counts, reproductive age group and black race were associated with HIVAN. Conclusion: The severity of HIVAN as indicated by raised serum creatinine level and proteinuria correlated positively with the degree of renal echogenicity.

Key words: Human immunodeficiency virus-associated nephropathy; kidneys; ultrasound

# Introduction

Human immunodeficiency virus (HIV) infection has a broad spectrum of renal manifestations, and these disorders are commonly encountered in patients at all stages of HIV infection. The HIV-related renal impairment can present an acute or chronic renal disease; it can be caused directly or indirectly by HIV and/or drug-related effects that are directly nephrotoxic or lead to changes in renal function by inducing metabolic vasculopathy and renal damage. [1-3] The most common cause of renal failure in HIV patients is the syndrome of HIV-associated nephropathy (HIVAN),

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necessitates increased surveillance and adaptation of dosages of HIV drugs.  $^{[4,5]}$ 

The striking feature of HIVAN is its predominance in black patients. [6-8] Most patients with HIVAN are of African descent, [8] presenting late in the course of their HIV-1 infection. [5] Once diagnosed, rapid progression to renal failure and end-stage renal disease (ESRD) necessitating dialysis was the norm in the pre-antiretroviral therapy era. [7] Death is usually due to other HIV-related problems. [4,8]

Because HIVAN typically occurs late in the course of HIV-1 infection, risk factors for its development include a low CD4 cell count (<200 cells/mm³) and a high viral burden. <sup>[5]</sup> The biochemical feature of HIVAN is rising serum creatinine and proteinuria (>3 g/24 hours). <sup>[9,10]</sup> The prognosis worsens with higher proteinuria and serum creatinine. <sup>[10]</sup>

Renal ultrasound is the commonest and simplest imaging modality to demonstrate the increasing renal echogenicity in HIVAN. It is also affordable, non-invasive, and readily available and does not involve the use of ionizing radiation. Computerized tomography (CT) can also be used; however, it is expensive and delivers high radiation to the patient. Magnetic resonance imaging (MRI) does not involve use of ionizing radiation and has better soft tissue definition than CT, but it is much more expensive and not readily available in our locality.

The aim of this study was to evaluate the renal sizes and echogenicity pattern in patients with HIV-associated nephropathy and to correlate renal echogenicity with serum creatinine levels and proteinuria.

# **Materials and Methods**

This study was carried out prospectively at the University of Maiduguri Teaching Hospital, Maiduguri, north-eastern Nigeria between April 2011 and September 2012.

A total of 100 patients, positive for HIV antibodies as detected by enzyme-linked immunosorbent assay (ELISA) and confirmed by ImmunoComb II (Waltham, MA, USA) with clinical features of HIVAN, referred from HIV dedicated clinics to the radiology department and have fulfilled the inclusion criteria, were recruited for this study after obtaining an informed written consent.

# Data selection

### Inclusion criteria

Adult patients with confirmed HIV infection who may have one or more of;

- Proteinuria of  $2^+$  or >3 g of protein in 24-hour urine sample
- Presence of constitutional symptoms like fatigue, malaise, anorexia and pruritus
- Raised serum creatinine level
- Patients who had commenced highly active antiretroviral therapy (HAART), presenting with above features.

### Exclusion criteria

- Patients who refused to consent
- Patients on immunosuppressive drug therapy
- Patients with hypertension, diabetes mellitus, nephrotic syndrome, widespread malignancies or on heroin use
- Children (16 years and below).

On entering the study after satisfying the inclusion criteria, a questionnaire was administered to each patient and details regarding demographic data (age, sex, marital status and occupation), serum creatinine level and grade of the ultrasonic renal echogenicity were documented. Proteinuria was established by dipstick method.

Blood specimen for serum creatinine level was collected and sent to the chemical pathology laboratory of the University

of Maiduguri Teaching Hospital for all the patients in the study.

Renal ultrasound was carried out on all the patients who satisfied the inclusion criteria using Aloka SSD-3500 model US scanner machine with a broadband phased array transducer (3.5-15MHZ). The right kidney was examined with the patient in the supine position or turned 45° left oblique. The left kidney was also examined with the patient supine or 45° right oblique. Examination of either kidney was facilitated by requesting the patient to hold on to deep arrested inspiratory efforts. This displaced the kidney caudally, moving it away from overlying ribs. Measurements of renal sizes in longitudinal scans (bipolar length), renal sinus fat and checking the renal configuration for any changes in shape like globular shape was done for both kidneys. Kidney size of more than 13 cm was defined as large. Evidence of parenchymal heterogeneity with or without echogenic striations was also checked for, bilaterally.

# Grading of renal echogenicity

- Grade 0 Normal; when the renal cortex is slightly less echogenic than the liver.
- Grade I When the renal cortex is of the same echogenicity with the liver.
- Grade II When the renal cortex is mildly to moderately more echogenic than the liver, with some loss of corticomedullary distinction.
- Grade III When the renal cortex is severely echogenic, with complete loss of corticomedullary distinction.

# Statistical analysis

The data obtained were recorded on a data sheet and analyzed using computer-based program statistical package for social sciences (SPSS for windows, Version 16). The results were presented in the form of graphs, tables and charts for illustration where appropriate.

### Outcome measures

- Renal ultrasound scan patterns
- Serum creatinine levels
- Proteinuria.

# Ethical consideration

Approval to carry out the study was obtained from the ethical and research committee of the University of Maiduguri Teaching Hospital. The data collected from the participants was kept with utmost confidentiality and patients had the choice to deny consent or opt out of the study at any stage.

# Results

One hundred HIV-infected patients with clinical and laboratory features of HIV-nephropathy were enrolled for the

prospective cross sectional study. Sixty eight (68%) patients were females and 32 (32%) were males. Their ages ranged between 19 and 65 years (Mean = 35; ±10.79).

Table 1 shows the frequency of HIVAN in the different age groups and sexes. The disease was most frequently seen in females aged between 20 and 29 years.

Figure 1 shows the frequency of HIVAN in the different marital status groups. We have more married men and women in our study representing 80%.

Figure 2 shows the distribution of occupation of the patients. Most of the patients in the study were either fulltime housewives or civil servants, each representing 44%.

Table 2 shows the renal sizes of the patients studied. The kidney size was determined on each image. On the basis of length, 56 kidneys (28%) were considered large while 144 kidneys (72%) were considered as normal.

Figure 3 shows the distribution of the renal echogenicity. It revealed grade I echogenicity in 4 patients (4%), grade II echogenicity in 36 patients (36%) and grade III echogenicity in 56 patients (56%). Four patients (4%) had normal renal echogenicity. Majority of the patients had grade III renal echogenicity. Homogenous echogenic parenchymal pattern (diffuse) was seen in 80% of patients while 20% had heterogeneous echogenic renal parenchymal (patchy) patterns. One hundred kidneys (50%) of the patients in this study were also noted to have a globular appearance.

The loss of corticomedullary definition (CMD) was observed in 80 patients (80%) while it was preserved in 20 patients (20%). Among the 80 patients with loss of CMD, 45 (56%) had decreased clarity of the renal pyramids while the pyramids were invisible in 35 (44%). Those patients with preserved CMD had either normal or slightly prominent pyramids.

Renal sinus fat was normal in 45 patients (45%), decreased clarity in 35 patients (35%) and the renal sinus fat was invisible in 20 patients (20%).

Table 3 shows the serum creatinine level of the patients studied. The minimum and maximum serum creatinine levels were 24 mmol/l and 1048 mmol/l respectively while the average serum creatinine level was 399 mmol/l ( $\sim$ 4.0 mg/dl).

Table 4 is the summary of the CD4 counts of the patients studied. Most of the patients (96%) had a CD4 count of less than 200 while only 4 patients (4%) had a CD4 of > 200. The range of CD4 counts was between 42 and 252.

Table 5 shows the relationship between renal cortical echogenicity and serum creatinine level. There was a statistical significant correlation between the serum creatinine and the

degree of renal echogenicity (r = 0.9). Patients with grade III renal cortical echogenicity (56%) had much higher values of raised creatinine levels (348-1048 mmol/l) as compared to lower value of raised creatinine (245 mmol/l) in those patients with grade I renal cortical echogenicity (4%).

Table 1: Age and sex distribution of the patients studied

Age (years)	Female	Male	Total (%)
≤19	4	0	4
20-29	36	0	36
30-39	28	4	32
40-49	0	20	20
50-59	0	4	4
60-69	0	4	4
Total	68	32	100

Table 2: Normal and enlarged renal sizes among the patients studied

	Frequency		Percentage
	Right	Left	
Normal	72	72	72
Enlarged	28	28	28
Total	100	100	100

Table 3: The frequency distribution and percentage of the serum creatinine level of the patients studied

Serum creatinine (mmol/l)	Frequency	Percentage
200-399	72	72
400-599	16	16
600-799	8	8
≥800	4	4
Total	100	100

Table 4: The frequency distribution and percentage of the CD4 count of patients studied

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CD4 count	Frequency	Percentage
0-99	28	28
100-199	68	68
200-300	4	4
Total	100	100

Table 5: Correlation of patients' serum creatinine with renal echogenicity

Serum creatinine	Renal echogenicity		
(mmol/l)	Grade I	Grade II	Grade III
200-399	4	36	32
400-599	0	0	16
600-799	0	0	8
≥800	0	0	4

Pearson's correlation coefficient, r=0.9 (significant correlation at +1 to -1)

Figure 4 shows the distribution of protein in the urine of the patients. Majority of the patients (48%) had severe proteinuria, 36% of the patients moderate while 16% had mild proteinuria.

Seventy two patients (72%) had no hematuria, while 28 patients (28%) had blood in their urine. Figures 5 to 9 shows the patterns of renal changes on ultrasound scan in patients with HIVAN.

# Discussion

The age distribution of HIVAN patients as reported by other workers is 20-64 years, [5-7] similar to the age range noted in the current study. It suggests that HIVAN is more common in people in their reproductive and sexually-active years.

The fact that patients involved in this study were predominantly black Africans who presented late in the course of their HIV-1 infection is in keeping with the findings noted by Freedman *et al.*, [6] Mockrzycki *et al.*, [7] Bourgoignie *et al.* [8] and Schoenfeld *et al.* [12] reported that

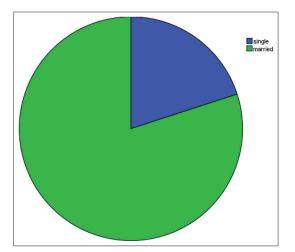


Figure 1: The frequency of HIVAN in the different marital status groups

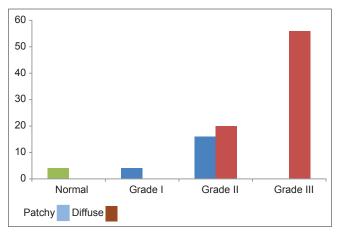


Figure 3: Frequency distribution of renal echogenicity in the patients studied

there is high incidence of HIVAN and the resultant ESRD in patients of African descent; and this is attributed to a genetic predisposition to the disease. This association is supported by the work of other researchers.<sup>[5-7]</sup>

The male:female ratio reported by authors in other parts of the world  $^{[13,14]}$  and Nigeria  $^{[15]}$  found a male preponderance, while Mockrzycki *et al.*  $^{[7]}$  found an even sex distribution. The more females involved in our study may be a reflection of the polygamous tradition in our environment as well as the better heath seeking behaviour amongst women.

Most studies done on HIVAN have shown that the kidneys appear enlarged and echogenic on ultrasound. [9,11,15] Rao and co-workers [16] first described renal abnormalities associated with HIV in 1984. These researchers described associated sonographic findings of enlarged kidneys and increased echogenicity. The work of Hamper *et al.*, [11] in 1988 described the kidneys of patients with HIVAN as enlarged and echogenic, measuring greater than 13 cm in their bipolar length. Saidu *et al.* [15] at Sokoto Nigeria in 2005, reported enlarged kidneys in HIV/AIDS patients with renal disease suggestive of HIVAN. Glassock *et al.*, [17] in 1990 postulated the renal enlargement in HIVAN to be the result of insufficient time for global sclerosis and fibrosis, given the rapid progression of renal disease; marked dilatation of

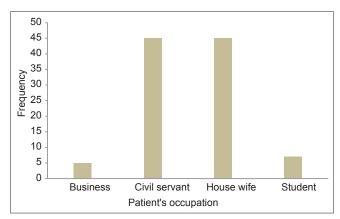


Figure 2: Distribution of occupation among the patients studied

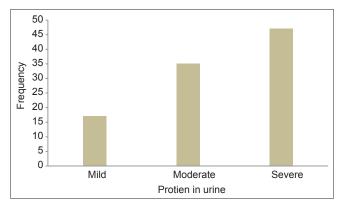


Figure 4: Distribution of protein in the urine of patients studied

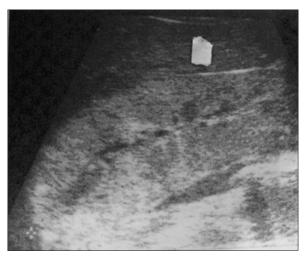


Figure 5: A 28-year-old woman with HIV nephropathy, the longitudinal sonogram of right kidney shows increased echogenicity, loss of renal sinus fat and renal enlargement

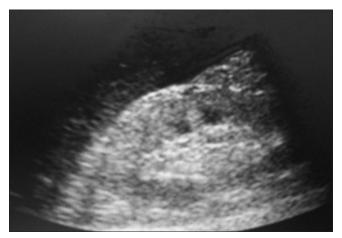


Figure 7: Longitudinal sonogram of the right kidney showing grade II renal echogenicity in a patient with HIVAN

the tubules with numerous microcysts, in contrast to the tubular collapse frequently seen in other forms of chronic renal injury; and interstitial edema. The finding in this study is in agreement with the observations of the above workers and the reasons for the renal enlargement are probably the same as those postulated by Glassock *et al.*<sup>[17]</sup>

N'zi et al. [14] applied or conducted abdominal ultrasound on 146 grade IV AIDS patients in Cote d'Ivoire and detected hyperechoic kidneys suggestive of HIVAN in 13.7%. Obajimi et al., [18] in 2008 conducted abdominal ultrasound on 391 HIV/AIDS patients in Ibadan, and demonstrated increased renal cortical/medullary echotexture in 8.4% of that series. The increase in renal echogenicity is in conformity with the finding in this study. The percentage is however higher in this study, presumably because renal ultrasound was carried out involving patients with clinical features of HIVAN most of whom presented late in the course of the disease.

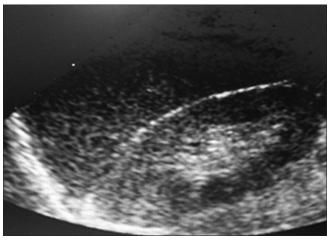


Figure 6: Longitudinal sonogram of the right kidney showing grade I renal echogenicity in a patient with HIVAN

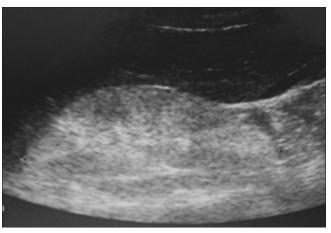


Figure 8: Longitudinal sonogram of the right kidney showing grade III renal echogenicity in a patient with HIVA

The work of Wachsberg et al.,<sup>[19]</sup> described the increase in renal echogenicity on ultrasound in HIVAN patients which may manifest as patchy or spotty echogenicity. He added that advanced stages typically demonstrate a diffuse increase in renal echogenicity and pelvi-calyceal thickening. According to a study by Di Fiori et al.,<sup>[9]</sup> advanced stages of HIVAN may also show decreased corticomedullary definition, decreased renal sinus fat, parenchymal heterogeneity with or without echogenic striations, and globular renal configuration. The findings in this study are similar to those of the above workers. The findings were found mainly in patients with much advanced HIV infection.

In a study by Hamper *et al.*,<sup>[11]</sup> a standard grading system was employed to evaluate the sonographic renal cortical echogenicity. The degree of increasing echogenicity was found to be directly proportional to the severity of the disease. They postulated that the main factors for the increased echogenicity in AIDS nephropathy are the striking tubular abnormalities seen in these patients.



Figure 9: Longitudinal sonogram of the right kidney showing grade III renal echogenicity with globular appearance in a patient with HIVAN

Majority of the previous researchers<sup>[5,9,10,16]</sup> found that most patients with HIVAN have advanced renal failure at the time of diagnosis, with high serum creatinine level. Chioma et al.[20] studied 400 HIV/AIDS patients in all using biochemical parameters (proteinuria and serum creatinine) and found elevation of serum creatinine in 38% of the patients. This agrees with the reports by of Atta et al.[21] who described serum creatinine level of 300 mmol/l or more in patients with HIVAN. These authors further explained that creatinine levels quantify the ability of the kidneys to clear the blood of waste products. As kidney function declines (for instance in HIVAN), creatinine is less effectively cleared from the blood, and the level rises. However, Burns et al.[22] reported a cohort of patients with HIVAN and mild renal insufficiency with normal creatinine level (mean serum creatinine of 114.9 mmol/l).

This study found a statistically significant correlation between the degree of increased renal echogenicity and the raised serum creatinine level (direct exponential relationship). It also correlated well with the renal parenchymal echo pattern and the diffuse parenchymal patterns were associated with higher values of raised serum creatinine whereas patchy parenchymal patterns were associated with lower values of elevated serum creatinine. Although series of studies<sup>[3,9,21]</sup> did not show a direct correlation between creatinine levels and renal echogenicity, many of them showed that there is a rapid rise in creatinine levels among patients with HIVAN, resulting in renal failure.

Di Fiori et al.<sup>[9]</sup> and Szczech et al.<sup>[10]</sup> concluded that the significantly higher creatinine levels among the patients with HIVAN compared with HIV-positive patients without HIVAN is said to play a role in the increased renal echogenicity and diffuse echo pattern seen in these patients. HIVAN seem to produce increased echogenicity along with steep increases in creatinine levels. Atta et al.<sup>[21]</sup> further

described that renal failure developed so quickly that most of the patients with HIVAN presented with renal failure, even after being seen several months earlier with normal creatinine levels.

Klotman  $et\,al.^{[4]}$  and Atta  $et\,al.^{[23]}$  observed that patients with HIVAN have nephrotic-range proteinuria (>3 g/24 hours) at presentation and many develop full-blown nephrotic syndrome.

Earlier studies <sup>[5,24]</sup> have shown that hematuria is uncommon in patients with HIVAN. Brook  $et\ al.^{[24]}$  in a cohort study of 30 children with HIVAN reported that hematuria is rare, and so when present, would suggest an alternative cause for the renal dysfunction. Atta  $et\ al.^{[23]}$  however, reported that urinalysis in these patients may reveal microhematuria, leucocytes, hyaline casts and oval fat bodies, but no cellular casts. This study reported much higher percentage of hematuria than the above workers which may necessitate further investigation.

Winston *et al.*<sup>[5]</sup> and Szczech *et al.*<sup>[10]</sup> reported that HIVAN typically occurs late in the course of HIV-1 infection and the risk factors for its development include a low CD4 cell count (<200cells/mm³) and a high viral burden. These observations are similar to those noted in the current study.

The data in this report support the idea that HIVAN exists as a separate entity as opposed to the controversy that existed in the earlier report by Rao *et al.*,<sup>[16]</sup> as to whether HIVAN is an actual entity or simply a misdiagnosed heroin nephropathy. No subject in this study had a history of heroin use. Focal segmental glomerulosclerosis is a histologic feature seen in both HIV- and heroin-associated nephropathy.

It is worth noting in this study that, sonographic findings (globular kidney appearance, decreased corticomedullary definition and renal sinus fat, and renal cortical heterogeneity) were seen in patients with advanced HIV/AIDS and renal disease on the basis of decreased CD4 count and proteinuria/uremia, respectively. These findings might have occurred because patients with HIVAN now live longer than before. The longer survival in these patients seems to be related to better overall management of HIV-infected patients.

### Conclusion

The degree of renal echogenicity was found to be positively correlated with the severity of HIVAN indicated by raised serum creatinine level and proteinuria. Prognosis also worsens with higher serum creatinine and proteinuria.

# Recommendation

Renal ultrasound scan should be carried out on all patients with suspected HIVAN because it is a good determinant of

renal parenchymal disease (echogenicity/echopattern).

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