

Kidney disease in hospitalised HIV positive children in Ibadan, South West Nigeria

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Abstract

Background: There is a paucity of data on the clinicopathologic pattern of kidney disease in Human Immunodeficiency Virus (HIV) seropositive children from sub-Saharan Africa and non from South West Nigeria.

Objective: To determine the clinical pattern and outcome of kidney disease among HIV positive children hospitalised at a tertiary hospital South West Nigeria

Methodology: A retrospective study of all HIV positive children who were hospitalised and managed for kidney diseases over a period of 78 months at the University College Hospital Ibadan, South West Nigeria was reviewed. Patients were followed up over the duration of hospital admission.

Results: Ten children (six males and four females) aged 4 -15(10.4±3.2) years were identified. Four presented in acute kidney injury, (AKI) three with nephrotic syndrome (NS) and two in chronic kidney failure (CKF). One patient had left renal artery stenosis. Renal biopsy performed in three children showed focal segmental glomerulosclerosis in two patients and membranous nephropathy in the third. Management included antiretroviral therapy, Angiotensin Converting Enzyme Inhibitors and acute haemodialysis. Mortality was 40%.

Conclusion: AKI, NS and CKF were the predominant clinical patterns of kidney disease in hospitalised HIV positive children and the mortality is high.

Keywords: HIV, Children, Acute Kidney Injury, Chronic kidney Failure, Nephrotic Syndrome, Nigeria

Résumé

Contexte: Il ya un manque de données sur le modèle anatomo-clinique de la maladie rénale chez les enfants séropositifs en Afrique sub-saharienne ce qui n'est pas le cas au Sud-ouest du Nigeria.

Objectif: Déterminer le profil clinique et l'issue de la maladie rénale chez les enfants séropositifs hospitalisés dans les centres hospitaliers publics au Sud-ouest du Nigeria.

Méthodologie: Une étude rétrospective sur tous les enfants séropositifs qui ont été hospitalisés et qui suivaient des traitements relatifs aux maladies rénales pendant une période de 78 mois au Centre hospitalier universitaire d'Ibadan au Sud-ouest du Nigeria a été faite. Les patients ont été suivis pendant toute la durée d'hospitalisation.

Résultats: dix enfants (six garçons et quatre filles) dont l'âge varie entre 4 et 15 ans (10,4 ± 3,2) ont été identifiés. Parmi eux, il y avait quatre cas de lésions rénales aiguës, (LRA) trois cas de syndrome néphrotique (SN) et deux cas d'insuffisances rénales chroniques (IRC). Un patient a été guéri de la sténose artérielle rénale. La biopsie rénale effectuée sur trois enfants a montré une glomérulosclérose segmentaire et focale chez deux patients et une néphropathie membraneuse chez le troisième. Le traitement incluait la thérapie antirétrovirale, les inhibiteurs de l'ECA et l'hémodialyse aiguë. La mortalité était de 40%.

Conclusion: Les LRA, les SN et les IRC étaient les principaux modes cliniques de la maladie rénale chez les enfants séropositifs hospitalisés et la mortalité était élevée.

Introduction

Kidney disease is an important cause of morbidity and mortality in HIV seropositive patients. The pattern of clinical presentation is wide and includes proteinuria, fluid and electrolyte abnormalities, tubular disorders, nephrotic syndrome (NS), acute kidney injury (AKI), chronic kidney failure (CKF) and end stage renal disease (ESRD) [1-3]. A clinically distinct entity is HIV-1 associated nephropathy (HIVAN), which is the most common cause of chronic kidney disease in HIV positive patients, with the majority of cases occurring in blacks [4-8].

HIVAN may be suspected on the basis of clinical criteria, but definitive diagnosis requires renal biopsy. Its pathogenesis involves a complicated interplay of direct viral infection of renal epithelial cells, genetic predisposition, and immune activation [9]. The disease manifests with proteinuria which may range from mild to nephrotic range, usually in

the absence of hypertension or oedema. Renal biopsy in HIV-associated nephropathy shows focal segmental glomerulosclerosis (FSGS) and/or mesangial hyperplasia [10]. Other kidney pathologies, apart from HIVAN, have also been described in HIV infection (2, 11-14).

Most data on kidney disease in childhood HIV infection have emerged from the United States of America. In the absence of antiretroviral therapy (ART), approximately 40% of all HIV-infected children experience renal complications leading to poor growth, accelerated progression of acquired immune deficiency syndrome (AIDS), and/or premature death [10,11]. Strauss et al [15] and others [11,16] reported a prevalence of childhood HIVAN based on clinical or pathologic criteria of approximately 10-15% in the USA in populations with over 95% being African American children. With the widespread establishment of ART, the clinical outcome of HIV-infected children improved dramatically [10,15,17-19], and the pool of HIV-infected children surviving and requiring dialysis or transplantation increased [10,19-21]. There are however few reports on the pattern of kidney disease in HIV infection from sub-Saharan Africa, the epicenter of the HIV pandemic, with poor socioeconomic conditions and limited access to renal replacement therapy. The epidemiology of kidney disease among HIV seropositive children in sub-Saharan Africa is likely to be different from that of the United States of America.

At the end of 2009, about 33.3 million people were infected worldwide with HIV, 2.5 million of which were children under the age of 15 years. Seventy two percent of all infected children live in sub-Saharan Africa [22]. Nigeria with a population of 150 million is the most populous country in Sub-Saharan Africa and has an estimated 360,000 children aged 1-14 years living with HIV infection making her the country with the largest number of HIV infected children in the world [22]. Studies on the clinico-pathologic pattern of kidney disease in HIV infected children from sub-Saharan Africa are few with none coming from South West Nigeria. The knowledge of the pattern and outcome of kidney disease among HIV positive children is important for designing control and treatment strategies and evaluating the effect of interventions such as use of ART in the sub region. This study highlights the clinical pattern, laboratory and pathologic findings, management and outcome of kidney disease among HIV positive children who were hospitalised in a tertiary hospital in South West Nigeria.

Patients and methods:

The University College Hospital (UCH), Ibadan is a tertiary hospital located in Oyo State, South West Nigeria. It is an 800 bedded hospital with a 120 bed Paediatric Department. The hospital serves an immediate state population of about 5 million people (including about 2 million children less than 15 years of age) and also receives patients from other parts of Nigeria.

The hospital runs a Paediatric Infectious Diseases Unit (IDU) where HIV seropositive children are routinely managed. Over the study period, a total of 491 HIV seropositive children were managed by the IDU, and a total of 125 HIV positive children were hospitalised. HIV seropositive patients with kidney disease are co-managed with the Paediatric Nephrology unit.

A retrospective study was carried out of the case records of admitted HIV seropositive children who were managed by the Paediatric Nephrology unit of the University College Hospital Ibadan, South West Nigeria from January 2004 to June 2010 (78 months).

Ten children met the inclusion criteria. Information extracted from the case records included demographic data, clinical presentation, route of HIV infection and serum urea and creatinine levels. Data on urinalysis, CD4+ cell count, renal biopsy, as well as treatment, and outcomes were also extracted from the records. Hypertension was defined as systolic and/or diastolic blood pressure \geq 95th centile for age, gender and height [23]. Proteinuria was regarded as dipstick urinalysis of \geq 1+ (30mg/dL). Nephrotic range proteinuria was \geq 3+ (300mg/dL) on dipstick urinalysis. CD4 count of \leq 350/mm³ was regarded as severe immunosuppression [24]. Normal kidney size on ultrasound scan was assessed based on kidney length for patient's age or height [25-27]. Outcomes were analyzed in terms of resolution of kidney disease and mortality. Follow up was over the period of hospital admission. Descriptive statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 17

Results

A total of 10 HIV positive children were admitted and managed for kidney disease over the study period and 6 (60%) of them were males. Their ages ranged from 4 to 15 years with a mean of 10.4 (\pm 3.2) years. Nine (90.0%) patients were aged 8 years and above. In 6 patients (60%) with kidney disease, there was a previous diagnosis of HIV infection while in 4 patients, kidney disease was the presenting feature of HIV infection. The route of HIV infection was

vertical in all patients. In HIV seropositive children who presented with kidney disease, the diagnosis of HIV infection was made 6 -22 (mean 15.0 ± 6.6) days after the onset of features of kidney disease.

Clinical presentation and co-morbidities

Oedema was present in 6 patients (60.0%). Table 1 shows the distribution of the clinical presentation and co-morbidities in the patients. Seven (70%) patients including one with renal artery stenosis (see Fig 1) had hypertension. Six (60%) patients were in renal failure, four (40%) had AKI, while two (20%) were in CKF. Three patients had NS.

Acute kidney injury was secondary to acute tubular necrosis in our patients and causes were septicaemia in three patients; and intravascular haemolysis in the fourth. The co-morbidities in one of the patients with NS were Kaposi sarcoma, acute osteomyelitis of the right femur and urethritis with urethral discharge. This patient subsequently developed anterior urethral strictures.

Laboratory investigations

Table 2 demonstrates the results of laboratory investigations performed in the children. Urine dipstick examination showed varying degrees of proteinuria in 9 patients (90%) with 4 (40.0%) having levels of ≥ 300 mg/dL. Serum urea and creatinine levels among the 6 patients in renal failure ranged from 135-405 (247 ± 122) mg/dL and 1.9-10.0 (5.9 ± 3.7) mg/dl respectively. The CD4 count, available for 8 patients, all of whom were aged 8 years and above, was 8 - 479 (168 ± 138) cells/ml, (median 136 cells/ml), while the RNA viral load measured in 4 patients (patients 3, 4, 5 & 8) ranged from <200-779803.0 copies/ml, (median, 9821 viral copies/ml). Abdominal ultrasound scan showed enlarged kidneys for age and/or height in four patients (40%) and normal kidney sizes for the others. Sonography of the kidneys also demonstrated increased parenchymal echogenicity in all the children. The five patients whose HBsAg screening records were available had negative results. Renal biopsy performed in three patients

showed collapsing FSGS in patient 4, membranous nephropathy in patient 5, and collapsing FSGS with microcystic tubular dilatation in patient 7 (Fig 2).

Treatment and outcome

Seven patients received ART. Three started ART before onset of kidney disease with the duration of ART varying from 18 - 485 days before the diagnosis of kidney disease. Two of these patients showed immunologic failure with CD4 counts of 349 and 29 / ml respectively.

First line ART consisted of oral Zidovudine, with oral Lamivudine, and oral Nevirapine or Efavirenz, while second line drugs for patients who had clinical or immunologic failure were oral lamivudine, didanosine and lopinavir/retonovir. Of the patients who received ART, one died while three patients who did not receive ART died.

Four patients received the Angiotensin Converting Enzyme Inhibitor, oral Lisinopril, but mortality was recorded in one of the four patients. The mortality was in a patient who was in ESRD, and died from complications of renal failure. Steroids were not utilized in the treatment of any patient. Haemodialysis was performed in three patients, one in AKI, and two in CKF and ESRD. One of the patients in CKF and ESRD who had very low residual kidney function and required chronic dialysis died from fluid overload and pulmonary oedema. The two other patients survived till discharge from the hospital.

Blood pressure in the patient with left renal artery stenosis was controlled with oral nifedipine, methyldopa and atenolol. Anterior urethral stricture (in patient 4) was managed surgically. The duration of hospital stay for the children ranged from 2-147 (median 37.5) days. The patient who spent a total of 147 days on admission was admitted on three different occasions for 79, 35 and 33 days respectively.

Overall mortality was 40.0%. All the AKI survivors had recovered renal function by the time of discharge from the hospital while one of the patients with NS (patient 4) achieved remission by the time of discharge.

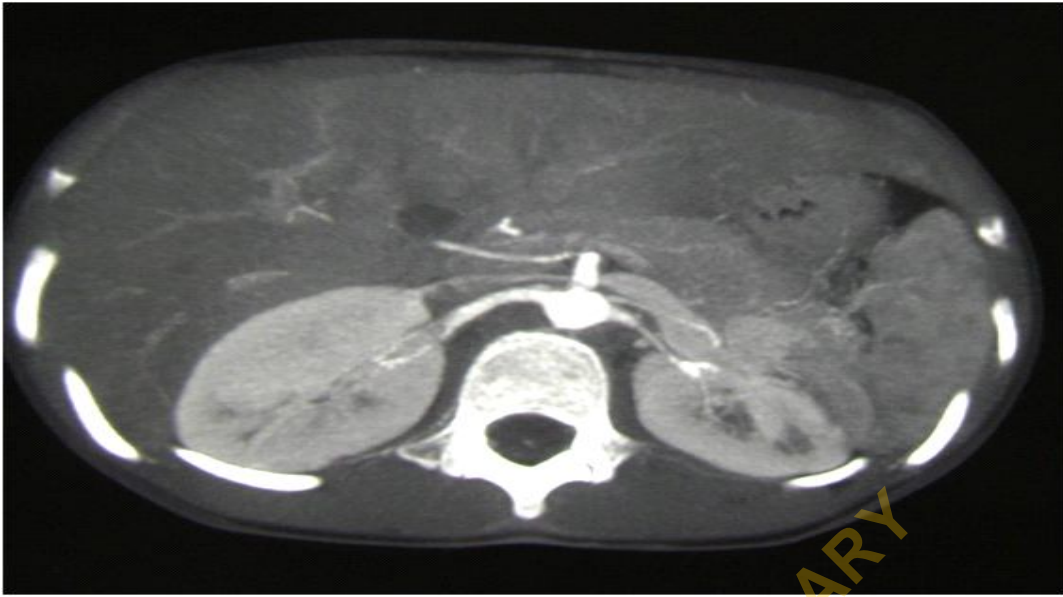


Fig 1: Contrast enhanced CT scan showing left renal artery stenosis (arrow) and compensatory right renal enlargement in an 11 year old HIV seropositive girl with hypertension.

Table 1: Demography, clinical presentation and co-morbidities in admitted HIV seropositive children with kidney disease

Patient No.	Age(Years)	Gender	Clinical Presentation	Co-morbidities
1	4	M	NS	Septicaemia
2	8	M	AKI	Septicaemia
3	10	M	NS, HTN	
4	10	M	NS	Kaposi sarcoma, urethritis, Acute osteomyelitis left femur, anterior urethral strictures
5	13	F	CKF/ESRD, HTN	
6	11	F	AKI, HTN	AIHA, septicaemia
7	15	F	AKI, HTN	Septicaemia, vaginal discharge, Genital ulcers, mouth ulcers
8	11	F	Lt RAS, HTN	
9	14	M	CRF, ESRD, HTN	
10	8	M	AKI, HTN	Meningitis, Pneumonia, Septicaemia

AIHA: Autoimmune Hemolytic Anaemia; AKI: Acute kidney injury; CKF: Chronic kidney failure; ESRD; End stage renal disease; HTN: Hypertension; Lt RAS: Left renal artery stenosis; NS: Nephrotic Syndrome

Table 2: Laboratory profile in HIV seropositive children with kidney disease

Patient no	PCV	Serum urea	Serum Cr	Serum Alb.	CD4 count (%)	HIV Viral load (copies/ml)	Dipstick Urinalysis	kidney size (USS)	Renal biopsy
1	10	29	0.7	1.8	-	-	NRP, H	Enlarged	-
2	12	322	6.0	-	-	-	P, H	N	-
3	28	59	0.7	1.4	479 (20.1)	121679	NRP, H	Enlarged	-
4	30	25	0.2	2.0	29(5)	779803	NRP	N	FSGS
5	22	339	10	3.5	349	76,163	P, H	N	MN
6	19	405	6.5	3.0	39 (6.93)	-	P, H	Enlarged	-
7	24	148	4.0	-	10 (3.7)	-	P	N	-
8	34	19	0.8	4.2	380	<200	H	N	-
9	20	217	4.2	3.8	8	-	NRP,H	N	FSGS
10	22	137	1.9	-	124	-	P	Enlarged	-

Alb: Albumin; Cr: Creatinine; FSGS: Focal segmental glomerulosclerosis; H: Haematuria; MN: Membranous nephropathy; N: Normal; NRP: Nephrotic range proteinuria ; PCV: Packed cell volume; P: Proteinuria; USS: Ultrasound;

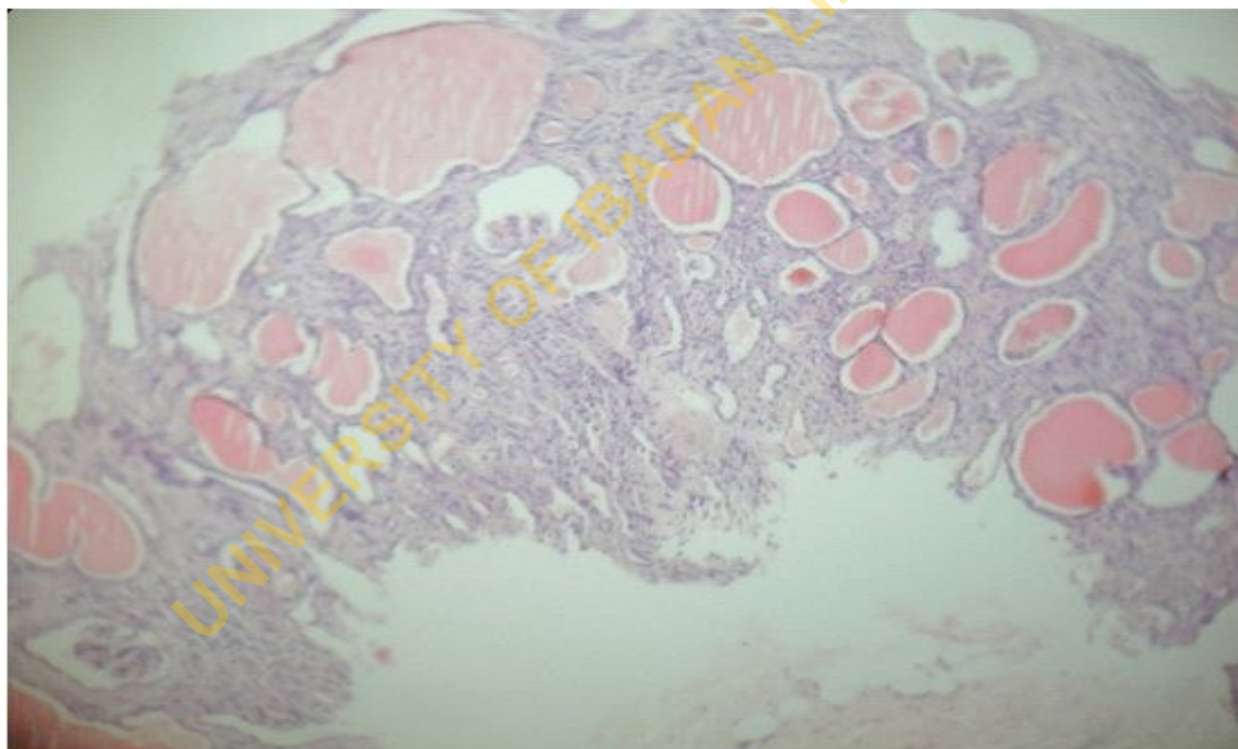


Fig 2: Photomicrograph of renal biopsy showing collapsing FSGS and microcystic tubular dilatation in patient 7 (H& E x160)

Table 3: Treatment and outcome in HIV positive children with kidney disease

Patient No.	ART	ACEIs	RRT	Outcome
1	-	-	-	Died
2	-	-	-	Died
3	AZT, 3TC, EFV	-	-	Alive
4	d4T, 3TC, NVP; 3TC, ddI, LPV/RTV	Lisinopril	-	Alive
5	AZT, 3TC, EFV; 3TC, ddI, LPV/RTV	Lisinopril	HD	died
6	AZT, d4T, NVP	-	HD	Alive,
7	3TC, NVP, d4T	Lisinopril	-	Alive
8	3TC, AZT, NVP	-	-	Alive
9	d4T, 3TC, NVP	Lisinopril	HD	Alive
10	-	-	-	Died

Discussion

There is limited published data on the pattern of kidney disease on HIV seropositive children in many parts of sub-Saharan Africa, the sub region most affected by the disease. There are no reports on the clinical spectrum of kidney disease among HIV positive children in South West Nigeria, our study documents the pattern of kidney disease among HIV positive children in South West Nigeria.

The findings that 90% of the patients were aged 8 years and above and were infected through the vertical route indicate that kidney disease was a late manifestation of HIV infection among our patients. Many studies from developed countries also indicate that kidney disease was a late feature of HIV infection [11,28-30]. Similarly, the finding that blood transfusion was not a route of HIV infection in any of the patients agrees with reports from developed countries where blood transfusion accounted for a negligible rate of HIV transmission [11,31,32]. It however contrasts with the observation from Port Harcourt in Nigeria which showed a high rate (40%) of blood transfusion acquired HIV infection among patients with HIVAN. Vertical transmission was recorded in only 30% of patients in that study [33]. The differences in the modes of transmission may be as a result of differences in the blood transfusion practices prevailing at the times the studies were undertaken. Reduction of mother to child transmission of HIV infection will go a long way in reducing paediatric HIV infection and hence prevent related kidney disease.

The finding of oedema and hypertension in many of the HIV seropositive children with kidney disease in our series is similar to the experience in Port Harcourt, South - South Nigeria [33]. Hypertension and oedema are however not usual features of HIVAN. Persistent proteinuria, in the absence of severe hypertension and oedema remains an early feature of HIVAN [11,19,34,35].

Microalbuminuria has also been identified as a predictor of HIVAN and proteinuria [14,36]. The high rates of hypertension and oedema in our study may have been due to the late presentation in our patients, many of whom were in late stages of AKI and CKF, coupled with inadequate access to renal replacement therapy. In addition, hypertension was secondary to left renal artery stenosis in one of our patients.

The kidneys exhibited increased echogenicity on abdominal ultrasound in 80% of the patients, and 40% of our patients had enlarged kidneys. Bilateral echogenic kidneys that are often enlarged are the usual finding in HIVAN, but some studies have indicated the presence of small or normal sized echogenic kidneys [10,28,33,37]. The echogenicity and enlargement of the kidney are presumably due to prominent interstitial expansion by cellular infiltration, and markedly dilated tubules containing echogenic, proteinaceous casts. On the other hand, normal or small sized kidneys may occur as a consequence of long standing kidney disease or previous episodes of recurrent acute pyelonephritis leading to CKF [3,33]. However a typical renal ultrasound appearance has not been described in most reports of AKI in HIV seropositive patients, possibly because the aetiology of AKI in HIV seropositive individuals is heterogeneous [38].

In the studies, conducted before ART became widely available in developed countries, HIVAN was associated with evidence of severe immunosuppression such as low CD4 counts, or development of opportunistic infections within 6 months of the diagnosis of HIVAN [30]. AKI in HIV seropositive patients has also been associated with more severe immunosuppression evidenced by low CD4 counts, and high viral load [39-41]. Consequently, the low CD4 count in our patients is in keeping with previous studies and supports the observation that kidney disease is a late finding in HIV infection.

Studies in adults indicate that HIV infected patients are at increased risk of acute kidney injury compared with individuals who do not have the virus [38,42,43]. AKI occurred with an incidence rate of 5.9 per 100 patient years in a cohort of 750 ambulatory HIV infected adult patients. Among hospitalized patients about 18% of HIV seropositive patients developed AKI with nearly a 2-3 fold higher risk of AKI compared with HIV uninfected patients [39,40,44,45]. AKI including mild elevations in serum creatinine has been associated with increased long term risk of ESRD, mortality or cardiovascular disease in HIV seropositive patients [45]. In Port Harcourt, South South Nigeria, AKI was the clinical manifestation of kidney disease in 50% of HIV seropositive patients [33], which is similar to the observation in this study.

The causes of AKI in HIV seropositive patients are usually not directly related to HIV infection as also shown in this study. All the cases of AKI in our study were secondary to acute tubular necrosis, which has also been observed to be a common cause of AKI in adult HIV seropositive patients, accounting for about 20% of cases [39,46]. Although pre renal azotaemia is noted to be the commonest cause of AKI in adult HIV infected patients [41], it was not a common finding in our series probably because patients with pre renal azotaemia were not routinely referred to the nephrologist. Furthermore none of our patients had AKI secondary to thrombotic microangiopathy, as observed in South Africa [46]. This may be related to the observation that HUS is not a common cause of AKI in Nigeria [38,47,48].

Five patients (50%) presented with NS or CKF. HIVAN initially manifests with proteinuria which may range from minimal to nephrotic range with oedema; and then progresses slowly or rapidly to end stage kidney disease [10,15,37]. In black HIV seropositive patients with glomerulopathy, HIVAN is the most frequently identified lesion [10,11,15,16,37]. Other reported histological findings include mesangial hyperplasia, minimal change and focal necrotizing glomerulonephritis, lupus like glomerulonephritis, membranoproliferative glomerulonephritis and membranous nephropathy [1,14-16,37,49]. Renal biopsies performed in three of the five patients showed FSGS in two children which is consistent with a predominance of HIVAN in the patients with NS or CKF.

Antiretroviral therapy has changed the natural history and epidemiology of kidney disease in HIV infected patients. Several observational studies in adults indicate the beneficial effect of ART in reducing proteinuria and preserving renal function in

adults with HIVAN [50-53]. Studies in children are limited, but case reports show dramatic response of HIVAN to ART [54,55]. In ART naive patients, AKI has been reported to carry a sixfold higher risk of in-hospital mortality related to severe immunosuppression, high viremia, and late commencement of ART [46,56]. In the general HIV population emerging studies record renal benefits of ART with reduced incidence of CKD, preservation of renal function or improvement of glomerular function with regular use of ART [57]. In our study ART was given in 70% of patients with a mortality of 14% among patients who received ART compared with the overall in hospital mortality of 44.4%. Three patients commenced ART before onset of kidney disease, two of these patients had evidence of treatment failure. One patient with good immunologic and virologic control developed left renal artery stenosis. The renal artery stenosis may have been an incidental finding, a study from France, however, observed development of left renal artery stenosis in young patients with HIV and good virologic control [58]. Three patients did not receive ART either because they presented before ART became available in our country, or they presented late and died before commencement of ART was possible.

Apart from ART other drugs that have been used in the management of kidney disease in HIV seropositive patients include angiotensin converting enzyme inhibitors (ACEIs) and steroids [10,59]. Case control and cohort studies in adults have indicated ACE inhibitors are associated with delayed progression of HIVAN and long term renal survival in adult patients [35,60-62]. However, no prospective studies have been performed to determine the efficacy of ACEIs in children with HIVAN. The benefit of ACEIs may be maximal when it is commenced early in the course of HIVAN before the onset of renal failure [62]. Steroids were not used in any of the patients as evidence of the benefit of steroid therapy in childhood HIVAN is inconclusive [3,10,15].

The in-hospital mortality of 40%, caused mainly by co morbidities such as septicaemia, and complications of renal failure, highlight the high mortality associated with kidney disease in HIV seropositive children in our study. In the United States of America, HIVAN, especially before ART became widely available, was typically associated with reduced immunity, increased likelihood of death from opportunistic infection, severe bacterial infections, AIDS defining illness and progression to end stage kidney disease [3,10,11,15,16,29,32,37]. The children with HIVAN in that era frequently died from

opportunistic infections before developing ESRD, or shortly after commencing dialysis [10,15,32]. Since ART became widely available, however, a greatly increased number of children with HIVAN surviving and requiring chronic dialysis or kidney transplantation in the United States of America has been documented [10,19-21,29]. AKI in HIV adult seropositive patients has also been associated with poor prognosis with a mortality of 43-60% in the United States of America [29,42,63]. In Nigeria as in many parts of sub-Saharan Africa late diagnosis of HIV infection and HIV related kidney disease, the late commencement of ART, coupled with the absence of facilities for paediatric renal replacement therapy in many centres imply that co-morbidities such as septicaemia and complications of renal failure will be the main causes of death in HIV seropositive children with kidney disease.

Our study is limited by the small number of renal biopsies and short period of follow up. It also does not assess for sub clinical kidney dysfunction in other HIV positive children seen during the period of study, which may have contributed to the morbidity or mortality in these other children. It however highlights the morbidity, and high mortality associated with kidney disease and HIV infection in our country, and sub region. Furthermore with improvement in management of opportunistic infections in HIV seropositive children in the sub region, kidney disease may occur more frequently in the surviving cohort.

In conclusion, the spectrum of kidney disease in HIV seropositive patients is heterogeneous with AKI; NS and CKF as the predominant clinical presentation. Kidney disease in HIV seropositive children is associated with very high in-hospital mortality. Early detection of HIV infection in children, as well as kidney disease in those who are found to be seropositive, prompt use of ART and ACEIs as indicated may improve the outcomes in affected children. Facilities for paediatric renal replacement therapy should be provided in the country and prevention of mother to child transmission of HIV remains the ultimate goal.

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