

## Renal Manifestations in HIV-infected Jamaican Children

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### ABSTRACT

**Background:** Documentation regarding the renal complications of paediatric HIV infection from developing countries is scarce. In the era prior to highly active antiretroviral therapy (HAART), HIV-infected children in Jamaica who developed HIV-associated nephropathy (HIVAN) progressed to end stage renal disease (ESRD) and death within a few months of diagnosis. With increased public access to antiretroviral therapy since 2002 and subsequent survival, renal complications are increasingly recognized among the surviving cohort of infected children.

**Methods:** A cohort of 196 HIV-infected children was followed in four multicentre ambulatory clinics from September 1, 2002 to August 31, 2005 as part of the Kingston Paediatric and Perinatal HIV/AIDS Programme, Jamaica. We describe the clinical presentations and natural history of those patients who developed renal complications.

**Results:** Urinary tract infections were the most common diagnosis, occurring in 16.8% of patients, with a high recurrence rate and the most common organism was *Escherichia coli*. Four of seven patients who started indinavir developed complications of nephrolithiasis and tubulointerstitial nephropathy. Six patients (3%) fulfilled the criteria for HIVAN, five of whom were male. Median age at diagnosis was five years; all presented with advanced HIV disease, nephrotic syndrome or nephrotic range proteinuria and three with chronic renal failure. Patients received standard medical management and were initiated on angiotensin-converting enzyme (ACE) inhibitors and HAART. While the mortality ratio was 50%, only one death was associated with HIVAN and the median survival time was 3.1 years.

**Conclusions:** HIV-infected children present with a variety of renal complications. With improved survival since the introduction of HAART, the incidence of HIVAN is expected to increase among this maturing paediatric cohort. Early detection and treatment will optimize the outcomes for these children.

## Manifestaciones Renales en Niños Jamaicanos Infeccionados por el VIH

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### RESUMEN

**Antecedentes.** La documentación en relación con las complicaciones renales de la infección pediátrica por VIH en países en vías de desarrollo, es escasa. En la era de la terapia antiretroviral pre-altamente activa (TARAA), los niños infectados por VIH en Jamaica que desarrollaron nefropatía asociada con VIH evolucionaron hacia la enfermedad renal en fase terminal (ERFT) y la muerte dentro de pocos meses de hecho el diagnóstico. Con el aumento del acceso público a la terapia antiretroviral a partir de 2002 y la subsiguiente supervivencia, cada vez más las complicaciones renales se observan entre la cohorte sobreviviente de niños infectados.

**Métodos:** A una cohorte de 196 niños infectados con VIH, se le practicó un seguimiento en cuatro clínicas ambulatorios multicentros, desde septiembre 1 de 2002 hasta agosto 31 de 2005, como parte

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*del Programa VIH/SIDA Prenatal y Pediátrico de Kingston, Jamaica. El trabajo describe las presentaciones clínicas y la historia natural de los pacientes que desarrollaron complicaciones renales.*

**Resultados:** *Las infecciones de las vías urinarias fueron el diagnóstico más común en 16.8% de los pacientes, acompañadas de una alta tasa de recurrencia, y el organismo más común fue el Escherichia coli. Cuatro de siete pacientes que comenzaron tratamiento con indinair, desarrollaron complicaciones de nefrolitiasis y nefropatía tubulointerstial. Seis pacientes (3%), cinco de ellos varones, satisfacían los criterios de NAVIH. La edad promedio al momento del diagnóstico fue de cinco años. Todos representaron con la enfermedad de VIH avanzada, síndrome nefrótico o proteinuria de rango nefrótico, y tres con fallo renal crónico. Los pacientes recibieron tratamiento médico estándar y se iniciaron en el uso de inhibidores de enzimas convertidoras de angiotensina (IECAs) y el TARAA. Si bien la proporción de la mortalidad fue 50%, sólo una muerte estuvo asociada con NAVIH y el tiempo medio de supervivencia fue 3.1 años.*

**Conclusiones:** *Los niños infectados con VIH se presentaron con una variedad de complicaciones renales. Con el mejoramiento de la supervivencia a partir de la introducción del TARAA, se espera que la incidencia de NAVIH aumente entre la cohorte pediátrica en maduración. La detección precoz y el tratamiento temprano optimizarán los resultados obtenidos con estos niños.*

## INTRODUCTION

In the Caribbean, many of the countries have developed and expanded their response to the AIDS epidemic and increased access to antiretroviral treatment. Despite this progress, the Caribbean remains the second-most affected region in the world (1).

An estimated 2.3 million children less than 15 years of age worldwide are living with HIV and in 2006, an estimated 380 000 children died of AIDS-related causes (1). In Jamaica, the first case of paediatric HIV infection was diagnosed in 1986 (2) and since then the incidence has been increasing accounting for 7.4% (children under 15 years) of the cumulative total HIV/AIDS cases reported between 1986 to December 2006 (3).

Renal manifestations can result from HIV infection itself, illnesses associated with HIV and adverse effects of therapeutics. Renal disease in HIV-infected children may manifest as HIV-associated nephropathy (HIVAN) but also as electrolyte abnormalities, urinary tract infections, renal tubular acidosis, acute renal failure, treatment-related nephrotoxicity, infiltrative diseases of the kidney, haemolytic uremic syndrome and IgA nephropathy (4).

HIVAN is rare in children (5, 6) and reports from the developing world are scarce (7). HIVAN affects primarily those of African descent (5, 6, 8, 9), the predominant ethnicity in Jamaica. Patients progress rapidly to end stage renal disease [ESRD] (8, 9) and survival is poor (6, 10) especially in the pre-HAART era. HIVAN usually develops in patients with severe immunosuppression and advanced HIV disease and the cause of death is often unrelated to renal disease (6, 8, 11, 12).

Prior to access to antiretroviral therapy in Jamaica, HIV-infected children who developed renal complications associated with HIV (renal failure, nephrotic syndrome; n = 3) progressed to ESRD and death within months of diagnosis.

In 2002, the Kingston Paediatric and Perinatal HIV/AIDS Programme (KPAIDS) initiated a coordinated res-

ponse for the provision of care, treatment and support, including access to antiretroviral therapy, for HIV-infected children in Jamaica (13). This report describes the clinical presentations and natural history of those children within the cohort who developed renal complications.

## SUBJECTS AND METHODS

A cohort of HIV-infected children was prospectively enrolled and followed in four multicentre ambulatory clinics from September 1, 2002 to August 31, 2005 as part of the KPAIDS. Standardized protocols for clinical care, laboratory monitoring and documentation were developed and implemented and an observational clinical database established for ongoing monitoring and evaluation (13–17). The infected infants and children were monitored by trained paediatricians and nurses at three-monthly intervals or less depending on the clinical need following enrolment.

At enrolment, children completed a detailed clinical assessment and comprehensive laboratory investigations as directed by standardized protocols (15), and these investigations included serum chemistries, urea and creatinine, liver function tests, complete blood count and lymphocyte subsets. Public access to viral load (plasma HIV RNA) testing only became available in 2005. Urinalysis (by dipstick) was usually performed at each ambulatory visit. Further evaluation of urinary protein was conducted if persistent proteinuria was identified on dipstick on consecutive visits. Urine bacteriological analysis was performed depending on patient symptomatology. Glomerular filtration rate (GFR) was estimated using the Schwarz formula (18). Renal impairment was defined as GFR < 80 ml/min/1.73 m<sup>2</sup>. Further evaluation for definitive urinary tract infections (UTI) included renal ultrasound for all children and, in addition, micturating cystourethrogram (MCUG) if age < 5 years or if over five years with abnormal ultrasound or symptoms suggestive of lower urinary tract pathology.

Cohort study staff prospectively identified patients with probable uro-renal complications and referred them to the Nephrology Service for collaborative management. Criteria for diagnosing probable HIVAN included (1) proteinuria in excess of 50 mg/kg/day or a urinary protein to creatinine ratio above 2.0 or presentation with nephrotic syndrome (NS); or (2) a progressive increase in serum creatinine or evidence of chronic renal impairment; or (3) presence of characteristic histopathological findings on renal biopsy; and (4) no other underlying disease likely to cause nephrotic syndrome or chronic renal failure.

All children with suspected HIVAN were screened for secondary nephropathy by measuring serum antistreptolysin O titre, antinuclear factor, Venereal Disease Research Laboratory (VDRL) test, Hepatitis B surface antigen (HBsAg) and complement protein (C3). Standardized therapy was initiated including HAART and ACE inhibitors. A trial of steroids (prednisone) was offered for those patients with nephrotic syndrome in consultation with the Paediatric Nephrology service.

#### Data Handling and Statistical Methods

Demographic, clinical and laboratory data were extracted from the Kingston Paediatric and Perinatal HIV/AIDS Programme database and utilized to determine frequency, incidence and outcomes of children within the cohort who presented with renal complications. The Kaplan-Meier method was used to estimate survival of children with HIVAN.

## RESULTS

One hundred and ninety-six HIV-infected children were followed prospectively in multicentre clinics, in the Kingston Paediatric and Perinatal HIV/AIDS Programme, Jamaica, between September 1, 2002 and August 31, 2005.

#### Urinary Tract Infections

Fifty-seven cases of urinary tract infections were documented in 33 HIV-infected children (16.8% of the cohort), with an incidence of 29.1% or 2908 per 10 000 HIV-infected children. The most common aetiological organism identified was multi-resistant *Escherichia coli* (36.8%) followed by *Streptococcus Group D* (19.3%) and *Klebsiella pneumoniae* (10.5%) as shown in Table 1. All patients who presented with urinary tract infection at < 5 years of age or with recurrent infections were investigated with abdominal ultrasound and micturating cystourethrogram but no underlying structural abnormalities were detected.

#### Adverse Effects of Therapeutics

Seven HIV-infected children (3.6% of the cohort) were commenced on indinavir and four of them developed renal complications. Three presented with recurrent flank pain, renal colic and haematuria (two of these had haemophilia A) and plain abdominal radiographs were normal. Both patients with

Table 1: Epidemiologic profile of episodes of urinary tract infections (n = 33)

| Organism                   | Organism  |                     | % of UTIs |
|----------------------------|-----------|---------------------|-----------|
|                            | Frequency | Incidence (per 100) |           |
| <i>Escherichia coli</i>    | 21        | 10.7                | 36.8      |
| <i>Streptococcus GpD</i>   | 11        | 5.6                 | 19.3      |
| <i>Klebsiella sp</i>       | 6         | 3.1                 | 10.5      |
| <i>Enterobacter sp</i>     | 5         | 2.6                 | 8.8       |
| <i>Proteus sp</i>          | 2         | 1.0                 | 3.5       |
| <i>Salmonella sp</i>       | 2         | 1.0                 | 3.5       |
| <i>Pseudomonas sp</i>      | 1         | 0.5                 | 1.8       |
| <i>Enterococcus sp</i>     | 1         | 0.5                 | 1.8       |
| <i>Pantoea agglomerans</i> | 1         | 0.5                 | 1.8       |
| Unknown/unidentified       | 7         | 3.6                 | 12.2      |

haemophilia A also experienced increased spontaneous haemarthrosis of the knees post-indinavir initiation. One patient (with pre-existing HIVAN) developed worsening renal failure after commencing indinavir due to possible tubulointerstitial nephropathy.

#### HIV-associated Nephropathy

The demographic and clinicopathologic characteristics of the six HIV-infected children with HIVAN (3% of the cohort) are presented in Tables 2 and 3. Five were male, median age at diagnosis was five years; all were of African descent and had moderate to severe HIV disease. All presented with nephrotic syndrome or nephrotic range proteinuria and three with established chronic renal impairment. None of the children was hypertensive at initial presentation and HIVAN was one of the major presenting features in only Case # 4; however, this case presented in an advanced stage of disease. No other secondary cause of nephropathy was identified. Abdominal ultrasound (4/6) revealed kidney sizes that were small or normal. The two with small kidneys had co-existing chronic renal failure. Renal biopsy was accessible for just one patient and this demonstrated focal segmental glomerulosclerosis (FSGS).

All patients received standard medical management in consultation with the Paediatric Nephrology service and were commenced on angiotensin-converting enzyme (ACE) inhibitors and antiretroviral therapy. Three of the four patients with nephrotic syndrome received a trial of steroid therapy but there was no improvement in clinical status.

#### Outcomes

The mortality rate was fifty (50%) per cent and median survival time at the end of the study period was 3.1 years (Fig. 1).

#### Progress of survivors

Case 1 was asymptomatic and demonstrated resolution of nephrotic syndrome within eight months of HAART initiation. Case 3 had similar resolution of oedema coincident

Table 2: Demographic and clinical presentation at diagnosis of presumed HIVAN

| Case | Sex | Age (years) | CDC Category | HAART   | Comorbidity   | Presentation  | Outcome   |
|------|-----|-------------|--------------|---|---|---|---|
| 1    | M   | 0.7         | C            | Nil   | Recurrent UTI, hepatitis, encephalopathy, FTT                   | Nephrotic syndrome (NS)   | Resolution of NS  |
| 2    | M   | 8.0         | C            | zidovudine (AZT), lamivudine (3TC), indinavir (IDV) | FTT (stunting)  | Chronic renal failure (CRF), nephrotic range proteinuria, low albumin but no oedema | Reduction in proteinuria; further deterioration of renal function |
| 3    | M   | 6.0         | C *          | Nil   | FTT   | NS, renal impairment  | Resolution of NS; stabilisation of renal function                 |
| 4    | M   | 8.0         | C            | Nil   | Tuberculosis, recurrent sepsis, UTI, focal neurological defects | CRF, hypertensive, acidotic, nephrotic range proteinuria but no oedema              | Died (9.0 years)  |
| 5    | M   | 4.0         | C            | Nil   | FTT   | NS, hypertensive  | Died (8.0 years)  |
| 6    | F   | 11.0        | B            | AZT, 3TC, nevirapine (NVP)                          | Nil   | NS, hypertensive  | Died (13.0 years)   |

\* CD4 count and percentage at presentation were 297 cells/ $\mu$ L and 9% respectively, but not available for other cases  
FTT = Failure to thrive

Table 3: Laboratory and investigation outcomes in children with HIVAN

| Case                              | 1           | 2            | 3            | 4             | 5            | 6           |
|-----------------------------------|-------------|--------------|--------------|---------------|--------------|-------------|
| Haemoglobin (g/dl)*               | 7.5 – 12.5  | 3.7 – 9.7    | 8.4 – 13.4   | 5.2 – 10.2    | 3.4 – 10.5   | 7.2 – 9.8   |
| Urea (mmol/l)*                    | < 1.0 – 8.3 | 5.1 – 39.6   | 3.7 – 10.8   | 8.2 – 36.3    | 1.0 – 21.7   | 1.0 – 5.7   |
| Creatinine ( $\mu$ mol/l)*        | 14.0 – 67.0 | 76.0 – 992.0 | 84.3 – 141.1 | 166.0 – 492.0 | 44.0 – 580.0 | 20.0 – 61.4 |
| GFR (ml/min/1.73m <sup>2</sup> )* | n           | 5.6 – 54.0   | 36.0 – 60.0  | 10.2 – 60.5   | 9.0 – 123.0  | N           |
| Albumin (g/dl)*                   | 11.0 – 48.0 | 16.0 – 38.0  | 24.0 – 43.0  | 21.0 – 34.0   | 15.0 – 42.0  | 9.0 – 26.0  |
| Urine protein:creatinine ratio*   | 0.1 – 47.3  | 5.7 – 12.6   | 14.0 – 17.0  | 14.8 – 21.8   | 14.9 – 21.8  | 5.5 – 10.0  |
| Triglyceride/Cholesterol          | n           | increased    | increased    | –             | n            | –           |
| Kidney size                       | n           | small        | –            | small         | –            | n           |
| Renal biopsy                      | –           | –            | –            | –             | –            | FSGS        |

\*Values represent lowest to highest recorded parameters; n = normal

with significant reduction of proteinuria and stabilization of renal function. Case 2 showed an initial dramatic improvement after HAART initiation but this was reversed after 18 months due to antiretroviral treatment failure characterized by clinical deterioration, significant immunosuppression and progressive worsening in renal function. Subsequent change to second line HAART resulted in reduction of proteinuria but renal function continued to deteriorate up until the end of the study period.

#### Mortality

The incidence of death from onset of HIV nephropathy was 25/100 person years. These deaths represented 23% of the deaths that occurred within the cohort during the study period

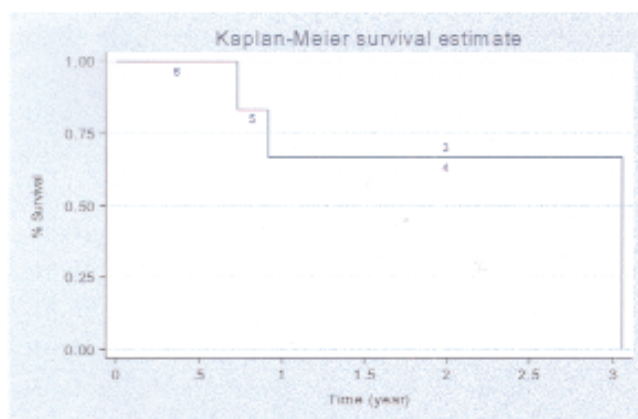


Fig. 1: Survival among children with HIVAN.



(3 of 13 deaths) with 7.7% being directly related to HIVAN. The three children (Cases 4–6) who died all had advanced HIV disease at the time of diagnosis (Fig. 2) and the final

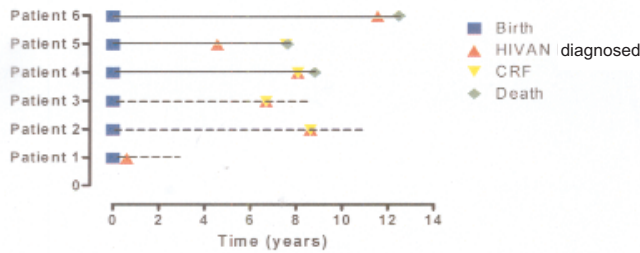


Fig. 2: Timeline of outcomes among children with HIVAN.

causes of death were cardiomyopathy, pulmonary complications of HIV associated with anasarca secondary to nephrotic syndrome/HIVAN and neurological complications of AIDS respectively. The caregiver of Case 6 opted for palliative care and he died at home.

## DISCUSSION

There was a relatively high incidence of primarily infectious renal complications of HIV disease in this cohort. Significant urological and nephrotoxic complications associated with indinavir use were also documented. The incidence of HIVAN was 3% with a mortality rate of 50% but with only one death (7.7% of the deaths in the KPAIDS cohort) being attributable to HIVAN. These findings are similar to those reported in other studies internationally (4–6, 8, 19, 20).

Urinary tract infections are a relatively common presentation in HIV-infected children (21–23) and as, with our cohort, *Escherichia coli* is the most common aetiological organism (21–26). Urinary tract infections in HIV-infected children have clinical presentations similar to the uninfected population (25) although there is the tendency to recurrence, infection with multiple organisms and resistant isolates (26), all of which increase the possibility of renal dysfunction.

The spectrum of renal and urinary tract complications including nephrolithiasis, renal colic, pain without stone formation and dysuria have been documented with indinavir use in children, similarly in adults (27–29). Tubulointerstitial nephritis and acute renal impairment have also been observed in association with indinavir (30, 31). In a previous study (31), children treated with indinavir had a high incidence of sterile leukocyturia and frequently had an increase in serum creatinine greater than 50% above normal.

HIV-infected patients with low body mass index and body surface area (32, 33) and those receiving trimethoprim-sulfamethoxazole (32) have increased risk of indinavir-related nephrotoxicity. These were characteristic of most children within our cohort. One could infer from this that children would be more at risk for indinavir toxicity, given the poor bioavailability of the currently available paediatric formulations and the need to use the adult preparations (27).

Brodie *et al* (34) also showed that the overall incidence of indinavir-associated nephrolithiasis was significantly greater in haemophiliacs than in non-haemophiliacs (50% vs 17%) and the median duration of indinavir therapy prior to the development of nephrolithiasis was significantly shorter among haemophiliacs.

All patients who were diagnosed with HIVAN in the present study presented typically with clinical manifestation of proteinuria. This is one of the earliest and most classical clinical presentations of HIVAN and can range from minimal to nephrotic range proteinuria with associated oedema (5, 6, 8, 11, 19). None of the cases was hypertensive on presentation, unlike a recent study of HIV-infected children in Nigeria that reported 50% of the cases presenting with hypertension (35). Three (50%) patients also presented with chronic renal impairment or failure. Rapid progression to ESRD has been observed among patients with HIVAN, especially in the pre-HAART era (8, 10). Just one of the three patients with chronic renal impairment/failure was on HAART at the time of diagnosis and all had advanced HIV disease.

The ultrasonographic finding of small to normal size kidneys in the children with HIVAN is in contrast to findings described in other studies where echogenic kidneys, large for age and height are virtually pathognomonic for HIVAN (5,6,12,19). Both patients with small kidneys presented with chronic renal failure and against the background of recurrent urinary tract infections, it maybe possible that an early insult may have led to scarring with resultant reduced renal size. A review of infected children from Washington DC suggests that the finding of enlarged echogenic kidneys, proteinuria and urine microcysts occur in the early stages of HIVAN in children (6). The one attainable renal biopsy showed FSGS, a commonly demonstrated histological finding in paediatric HIVAN (5, 8, 11, 19). Other reported histological findings include, mesangial hyperplasia, minimal change and focal necrotizing glomerulonephritis (5, 8, 11, 19). Children generally have a less aggressive clinical course than adults, except for those with FSGS (5, 11, 19).

All children with HIVAN received HAART and ACE inhibitors which is the standard therapeutic management (4, 5). Three of the four patients who presented with nephrotic syndrome were given a trial of prednisone but showed no improvement of clinical status. A similar response was seen in prior studies and prednisone is not indicated in the treatment of HIVAN in the paediatric population (4, 5, 8, 19).

The mortality ratio was 50% and the median survival time 3.1 years as compared to 100% and a few months respectively in the pre-HAART era. The three children who were alive at the end of the study period all showed clinical improvement with HAART and ACE inhibitor therapy.

Several studies in adults have shown beneficial effect of HAART and ACE inhibitor on reducing proteinuria and slowing the progression of renal disease in HIV-infected cohorts (36–40). Studies in children are limited but few case

reports have substantiated the resolution of HIVAN in paediatric HIV-infected patients receiving HAART (41, 42). Evidence suggests a direct role of HIV infection in the pathogenesis of HIVAN (43, 44), hence effective control of viral replication should result in slow progression of renal disease.

The poor survival in the affected children is reminiscent of the natural history of HIVAN documented in other studies (6, 8, 10–12). HIVAN is a late presentation of HIV infection and is usually seen in patients with advanced disease who subsequently die from other co-morbid HIV-related conditions (11, 12). With routine screening, earlier detection and the use of HAART, the prognosis will be more favourable for these children.

The study was limited by the small number of patients and the diagnostic challenge of accessing renal biopsies for histological characterization to confirm HIVAN. Despite this, these findings increase awareness of HIVAN in the population of infected children who are now surviving into adulthood.

In conclusion, HIV-infected children present with a variety of renal complications, of which HIVAN is associated with a high mortality rate. Nevertheless, survival is improved with early detection and use of HAART and ACE inhibitors. As the current cohort of children survives to adulthood, the incidence of HIVAN is expected to increase. It is thus prudent that protocols for routine screening for proteinuria and early detection of HIVAN be implemented to ensure optimal outcomes for affected children.

We therefore propose the following recommendations for management:

- \* Screening urinalysis (urinary dipstick) every three months.
- \* Complete urinalysis, serum electrolyte, blood urea nitrogen and creatinine levels (4), and blood pressure monitoring every six months.
- \* Aggressive treatment of intercurrent urinary tract infections.
- \* Avoidance of nephrotoxic drugs, where possible.
- \* Avoidance, where possible, of the use of the protease inhibitor, indinavir, in the paediatric population and contraindication in those with haemophilia.
- \* Paediatric HIVAN should be treated with HAART and ACE-inhibitor in consultation with nephrologists, where possible. Steroid use is not recommended (4).
- \* Promote and support adherence to HAART and continuing care.

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