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ABSTRACT

***Background*: HIV-infected children are at higher risk of opportunistic infections that could result in hospitalisation. The outcomes of hospitalisation are variable and depend on the admission diagnosis, the patients' immune status and whether or not the patient is on anti-retroviral drugs.**

***Objective*: To describe the characteristics and causes of hospitalisation and mortality for HIV infected children admitted to Moi Teaching and Referral Hospital in Western Kenya.**

***Design*: A retrospective study of prospectively collected data.**

***Setting*: The paediatric wards of Moi Teaching and Referral Hospital (MTRH). A Kenyan National Referral Hospital.**

***Subjects*: HIV-infected children admitted the paediatric wards.**

***Interventions*: Treatment with combination anti-retroviral therapy (cART), treatment of common opportunistic infections.**

***Main outcome measures*: Demographic and clinical data, including diagnosis, immune status, and treatment with combination anti-retroviral therapy (cART), were extracted from hospital admission records of HIV-infected children registered with the USAID-Academic Model Providing Access to Healthcare (AMPATH) partnership. We conducted descriptive statistical analyses and used chi-square and fisher's exact tests to assess for associations between categorical variables and each of the independent variables.**

***Results*: Between December 2006 and May 2009, 396 HIV-infected children were admitted to MTRH. Median age at admission was 2.0 years (range 0-15); 236 (59%) were male; 36 (15%) of available 236 orphan status entries were orphaned; 198 (73%) were in CDC categories B and C and 61 (16%) of available 386 had been on ART. Among 108 patients with documented immunologic status, the mean CD4 cell percentage was 16% (SD 10.8). Among the 396 children, 104 (15%) were diagnosed with pneumonia, 92 (14%) with gastroenteritis, 36 (9%) with tuberculosis and 37 (9%) with malaria. Deaths occurred in 28(7%) of the patients. The median duration of hospitalisation was seven days (range 1- 516) for discharged patients and six days (range 0-72) for those who died. A significantly higher percentage of the children who were not previously enrolled in AMPATH died, signifying 14 (15%) mortality among this population of admitted patients, p = 0.0017. Of those who died, (17%) were diagnosed with pneumonia and 22 (79%) of them were not on cART.**

***Conclusion*: The common diagnoses at hospitalisation included pneumonia, gastroenteritis, malaria and tuberculosis. Higher mortality occurred among those**

diagnosed with pneumonia and those not previously enrolled in the HIV care programme. Aggressive treatment and prevention of the most prevalent diseases and early enrollment into HIV care are recommended for HIV-infected children. A follow-up study to investigate the pathological causes of death in this population is recommended.

INTRODUCTION

In Kenya, over 1.3 million people are HIV infected, including over 150,000 children (1). The adult prevalence has declined from a high of 15% in 1998 to a current low of 7.8 % (2). There are over 1,100,000 orphans in Kenya due to parental HIV-infection and death. In 2005 alone, over 140,000 people died from HIV infection/AIDS in the country. HIV infection is one of the top five causes of mortality in Kenya and has greatly contributed to the infant mortality rate rising from 73 per 1000 in 1998 to over 78 per 1000 in 2004 (3) and the under-five mortality rate rising from 112 per 1000 in 1998 to 120 per 1000 in 2004 (4). The number of paediatric HIV infection related hospitalisations and deaths have increased markedly in the last decade. Data from Moi Teaching and Referral Hospital (MTRH) in western Kenya, the second largest referral hospital in the country, show that HIV infection related paediatric admissions have been increasing over the last decade. The percentage of adult deaths attributable to HIV infection related causes during this same period rose from 2 to 15% (hospital annual summaries).

Although the spectrum of HIV-related disease has been reported in several African countries, few studies have evaluated the causes of HIV-related morbidity and mortality, particularly for children (5-8). While some studies have reported the causes of death in HIV infected children in Africa, the majority of them rely on clinical diagnoses (6, 9-16). In the past decade, studies investigating pathologic causes of death and evaluating the outcomes of efforts to prevent HIV infected associated preventable diseases have been published (7, 8, 17-21). In studies of HIV-infected children from West and Southern African countries, HIV infected children were found to develop pulmonary and neurological diseases, including pneumocystis carinii pneumonia (PCP), tuberculosis, interstitial pneumonitis, meningitis, and cytomegalovirus. However, no study has described the situation in the East African region. Better information on the causes of hospitalisation, morbidity, and mortality for HIV infected children in particular resource-limited settings is needed. In addition, in a system of care where appropriate diagnostic capabilities for HIV-infected children are limited by few referral facilities and other resource limitations, there is a need for evidence-based decisions and guidelines to help clinicians use available treatment options wisely. Accurate, up-to-date, and regionally specific clinical and pathologic data are, therefore, needed to improve clinical management of HIV-infected children.

The United States Agency for International Development (USAID) - Academic Model Providing Access to Healthcare (AMPATH) Partnership in collaboration between Moi University, MTRH, partner institutions from the United States (led by Indiana University) and was originally established to provide HIV infection care within public sector clinics in western Kenya (22). The AMPATH partnership currently provides HIV infection prevention and treatment services at 23 clinics in western Kenya, all but one of which is Ministry of Health (MOH)-affiliated. All USAID-AMPATH HIV infection clinics refer patients for admission to nearby sub-district or District Hospitals. More complex and difficult cases that require more advanced laboratory and radiological tests are referred to the MTRH in Eldoret. AMPATH's largest HIV clinic, which currently cares for over 4,600 children, is also located on the grounds of MTRH, and children from this clinic and other distant clinics requiring specialist care are referred to MTRH for admission.

The purpose of this study was to describe the characteristics and outcomes of hospitalisation for HIV-infected children admitted to the Moi Teaching and Referral Hospital.

MATERIALS AND METHODS

Study Design: The study was approved by the Institutional Research and Ethics Committee of the Moi University School of Medicine and MTRH and the Institutional Review Board of the Indiana University School of Medicine. This was a combined cross-sectional and retrospective cohort study using data from charts of admitted patients and prospectively collected de-identified data stored in the computerised medical records system of paediatric patients already enrolled in the USAID-AMPATH clinics (23).

Study Population and Setting: Records from admission charts and the computerised medical records of HIV-infected children admitted to MTRH between December 2006 and May 2009 were reviewed for inclusion into this study.

During the study period, the USAID-AMPATH clinic system operated between 12 and 23 clinics in western Kenya. There has been a steady rise in the number of clinics operated by the programme, in 2004;

there were only four clinics, rising to 18 clinics in 2008 and 23 in 2010. The largest urban clinic is located at the MTRH in Eldoret. It serves the whole of western Kenya with a population of over 15 million people. The monthly admissions to the paediatric wards range between 100 to 160 children. Due to the comprehensive and widespread nature of USAID-AMPATH system of clinics, most HIV infected patients in the North Rift and western Kenya regions get care within the AMPATH clinics. HIV infection clinics for adults, children, or combined populations were conducted two to five days per week at all sites (24, 25). Those requiring admission were sent to the nearby district hospitals or MTRH. As of May 2009, AMPATH had 56(962) active patients, including 44,780 adults and 12,182 children. Of these patients, 30,854 were on combination anti-retroviral therapy (cART).

Clinical Procedures: Throughout the period of the study, clinicians followed detailed, locally developed protocols consistent with World Health Organisation guidelines. Children whose HIV infection status were not already known were tested for HIV infection at the sick child clinic at admission or in the wards after admission. This was the normal hospital policy during the period of the study. HIV infection was documented by DNA-PCR (Amplicor, Roche, Basel, Switzerland) for children greater than 18 months and by two parallel HIV rapid ELISA tests using Determine and Unigold kits for children less than 18 months. cART was initiated for any child more than six years of age with a CD4 cell percentage of greater than 15%, for any child lesser than six years of age with a CD4 count greater than 200 cells / mm3, and for all children with WHO clinical stages 3 or 4 or CDC stage C disease. The standard initial cART regimens used were zidovudine / lamivudine / nevirapine for those weighing greater than 10kg or stavudine / lamivudine / nevirapine for those weighing less than 10kg. All patients were started on cotrimoxazole preventive therapy if below the age of six years. Those above six years of age with a CD4 cell percentage of less than 25% and those with WHO stages 3 or 4 were also put on cotrimoxazole. Children started on cART were seen two weeks after initiation of therapy, and then every month thereafter. During these visits, patients undergo clinical assessments, including assessment of family and social characteristics, nutritional status, the degree of immuno-suppression, current or chronic infections, dietary intake, drug treatment history and adherence history. An orphan was defined as a child who had lost either both or one of his or her parents. Laboratory investigations included routine assessment of CD4 percentage every six months and investigations to evaluate haemoglobin level, liver and kidney functions every three months. Tests to evaluate for toxicities were performed as necessary. Our outcomes of interest were death or discharge. The independent variables included age, gender, orphan status, ever on ARV's, previously enrolled in AMPATH, CDC stage, recent CD4 cell count and percentage and admission diagnosis. Patients were admitted if they had clinical indications as diagnosed by the clinicians in the various sites.

Data Collection and Management: For patients already enrolled in AMPATH, clinicians normally completed standard initial and return encounter forms at all USAID-AMPATH clinic visits for the children. The AMPATH encounter forms included standard demographic, birth, past and present medical history, physical examination, laboratory data and medications provided including anti-retroviral drugs and opportunistic infection prophylaxis. Dedicated data entry clerks entered this information into the ambulatory USAID-AMPATH Medical Record System with data entry validated by random review of 10% of the data entered. The medical records system was MS-Access-based (Microsoft Corporation, Redmond, WA) until 2006, and currently uses MySQL based database.

Hospital admission notes from MTRH were entered into admission encounter forms by dedicated research assistants who traced all HIV infected children admitted to MTRH. The independent variables included demographic history (age, gender, clinic site, orphan status), AMPATH enrollment, CD4 cell percentage closest to admission, admission and discharge or death diagnosis and use of cART. The dependent variables included the outcome of discharge or death and duration of hospital stay. Information on children's hospital admissions from the distant clinic sites was collected from the AMRS.

Statistical methods: Descriptive statistics, such as mean, standard deviation, median and range, were used for the continuous variables, while frequency listings were used for categorical variables. The chi-square test was used to assess for associations between a categorical variable and each of the independent variables. Where the cell counts were below ten, the Fishers' exact test was used in two by two tables. The Kruskal-Wallis test was used to compare the medians for continuous variables. All statistical analyses were performed using SAS Institute version 9.1. A p-value of less than 0.05 was considered significant in all analyses.

RESULTS

Data were available for 396 HIV-infected patients of 11,972 children who were admitted in MTRH from the December 2006 to May 2009. This formed 3.3% of all admissions to the paediatric wards during the period. The median age at admission was two years (range:

0-15 years), with the majority having been previously enrolled in AMPATH (Table1). More than half of the children were boys 236 (59%) and 36 (15%) of 236 with recorded orphan status were orphaned at admission. For the 108 with documented immunologic status, the mean CD4 cell percentage closest to admission was 16% (Table 1). In the whole cohort, the majority of the children were in CDC category B 173 (43%) and C 81 (30%). Sixty one (16%) of the children were already on cART from AMPATH. Pneumonia was the most common final diagnosis for HIV-infected children admitted in the hospital. One hundred and four (15%) of the children were diagnosed with pneumonia, 92 (14%) with gastroenteritis, 36 (9%) with tuberculosis and 37 (9%) with malaria (Tables 1 and 2).

Among those already enrolled in AMPATH prior to admission, the median age was two (range 0-15), 33 (18%) were orphans among the 188 with documented orphan status and 58 (20%) of 297 were recorded ever having been on ARV's. They had a median CD4 cell percentage of 15 (range 0-45), with 166 (76%) being in CDC categories B and C (Table 2). Those not previously enrolled in AMPA TH tended to be younger, with a median age of 1.7 years (range 0-14) (Table 2). They were much less often orphaned, and only three (3%) of them had ever been on ARV's. Like the children enrolled in AMPATH, the majority of the un-enrolled children also had moderate and severe disease, with 29 (67%) of them being in CDC categories B and C.

More than half 220 (55%) of the children were discharged, 28 (7%) died with 152 missing entries. The median time to death after admission was six days (range 0-72). The median duration to discharge was seven days (range 1-516). Six (21%) of those on ART died compared to 22 (79 %) of those who had not been initiated on ART. The most common diagnosis for those who died was pneumonia (17%), followed by lymphoma (10%) and meningitis (7%). When comparing those who died to those who were discharged home, those previously enrolled in AMPATH were significantly less likely to die 14 (4.6%) than those not previously enrolled 14 (15%), p-value 0.0017. Gender, ever on ARV, orphan status, age at admission and recent CD4 cell percentage were not significantly different between the two groups (Tables 4 and 5).

Among the children already followed by AMPATH at the time of hospital admission, 14 (4.6%) died during their hospitalisation (Table 2). A significantly higher percentage of the children who were not previously enrolled in AMPATH died, with 14 deaths, signifying 15% mortality among this population of admitted patients, p-value 0.00017 (Table 3). The previously enrolled children who died were older, with a median age of 3.75 (range 0-12). The enrolled children who died were also more likely to be male (71 %), orphans (38%), and on ARV's (36%) than the enrolled children who did not die. The enrolled children who died also had immunological characteristics of more severe HIV infection disease. They had a median CD4 cell percentage of nine (range 1-21), and 90% were in CDC categories B and C.

Table 1

Characteristics of HIV-infected children admitted in the pediatric wards at Moi Teaching and Referral Hospital

Characteristic	Frequency N=396
Age at admission (years)	
Median (range)	2.0 (0 -15)
Mean (SD)	3.33 (3.86)
Gender	
Male	236 (59.15)
Missing	1
Orphan	
Yes	36 (15.00%)
Missing	160
Previously enrolled in AMPATH	305(76.63%)
Ever on ARV	
Yes	61 (15.64%)
Missing	10
Recent CD4	N=106
Mean (SD)	648.16(703.89)
Median (range)	420 (0,3696)
Recent CD4%	N=108
Mean (SD)	16.35(10.82)
Median(range)	15(0.45)

Admission outcome	
Discharged	220(55.14%
Died	28(7.02%
Unknown	152(37.84%)
CDC class at admission	
N	15(5.54%
A	58(21.40%
B	117 (43.17)
C	81(29.89%)
Missing	129
Time to death since admission (days)	N=26
Median (range)	6(0,72)
Mean (SD)	16.91(21.18)
Time to discharge since admission (days)	N=21 0
Median (range)	7.00 (1516)
Mean (SD)	23.36(58.55)
Diagnosis	N=400
Pneumonia	104
Malaria	37
Tuberculosis	36
Gastroenteritis/diarrhea	67
Meningitis	12
Dehydration	25
Immuno-suppression	37
Malnutrition	8
Lymphoma	5
Karposis sarcoma	4
Anemia	9
Brochiolitis	2

Table 2
Characteristics of children by previous enrolled in AMPATH

Characteristic	Frequency	
	Previously enrolled (N=305)	Not previously enrolled (N=93)
Age at admission (years)	N=302	N=92
Median (range)	2(0-15)	1.71 (0- 14)
Mean (SD)	3.36(3.86)	3.16(3.79)
Gender		
Male	171 (56.25%)	63 (67.74%)
Missing	1	
Orphan		
Yes	33 (17.55%)	2(3.92%)
No	155 (82.45%)	49 (96.08%)
Missing	117	42
Ever on ARV		
Yes	58 (19.53%)	3 (3.26)
No	239 (80.47%)	89(96.74%)
Missing	8	1
Recent CD4	N=105	
Mean (SD)	645 (706.51)	-
Median (range)	416 (0,3696)	
Recent CD4%	N=107	
Mean(SD)	16.31 (10.86)	-
Median (range)	15 (0,45)	
Admission outcome		
Discharged	145 (47.54%)	74 (80.43%)
Died	14 (4.59%)	14 (15.22%)
	146 (47.87%)	4 (4.35%)

CDC class at admission		
N	11 (5.02%)	13 (25.49%)
A	42 (19.18%)	4 (7.84%)
B	98 (44.75%)	16 (31.37%)
C	68 (31.05%)	13 (35.29%)
Missing	86	42
Diagnosis	N=305	N=93
Pneumonia	77	27
Malaria	21	16
Tuberculosis	25	11
Gastroenteritis	31	26
Meningitis	7	5
Dehydration	15	9
Immuno-suppression	26	10
Malnutrition	5	3
Lymphoma	2	3
Kaposis Sarcoma	4	0
Diarrhea	8	1
Anemia	9	0

Table 3

Characteristics of children previously enrolled in AMPATH who died in the wards in MTRH

Characteristic	Frequency N=14
Age at admission (years)	N=14
Median (range)	3.75 (0 -12)
Mean (SD)	4.19 (3.58)
Gender	
Male	10 (71.43%)
Female	4 (28.57%)
Orphan	
Yes	3 (27.27%)
No	8 (72.73%)
Ever on ARV	
Yes	5 (35.71%)
No	9 (64.29%)
Recent CD4 count	N=5
Mean (SD)	403.80(399.04)
Median (range)	360(20.00,889.00)
Recent CD4%	N=5
Mean(SD)	9.8(9.12)
Median(range)	9.00(1.00,21.00)
CDC class at admission	
A	1(9.09%)
B	2(18.18%)
C	8(72.73%)
Missing	3
Diagnosis at admission (first admission)	N=14
Pneumonia	2
Malaria	0
Tuberculosis	1
Gastroenteritis	0
Meningitis	0
Malnutrition	0
Lymphoma	1
Kaposis Sarcoma	1

Table 4
Association between death and gender, ever on ART, orphan status, enrolled at AMPATH

Variable	Confirmed death N=28	Discharged / Unknown N=371	Fisher exact p-value
Gender			
Male	20 (71.43%)	216 (58.22%)	0.2314
Female	8 (43.75%)	155 (41.78%)	
Ever on ARV			
Yes	6 (21.43%)	55 (15.19%)	0.4155
No	22 (78.57%)	307 (84.81 %)	
Orphan			
Yes	3 (23.08%)	33 (14.54%)	0.4202
No	10 (76.92%)	194 (85.46%)	
Previously enrolled at AMPATH			
Yes	14 (50%)	291 (78.65%)	0.0017
No	14(50%)	79 (21.35%)	

Table 5
Median age and CD4% among those confirmed dead and those discharged or vital status unknown

Variable	Confirmed death N=28	Discharged / Unknown N=371	Kruskal wallis p-value
Age at admission (years)	N=28	N=368	
Mean (SD)	3.90 (4.01)	3.29 (3.84)	0.3915
Median range	2.91 (0.13)	2 (0.15)	
Recent CD4%	N=5	N=103	
Mean (SD)	9.80 (9.12)	16.67 (10.82)	0.1782
Median (range)	9 (1.21)	15 (0.45)	

DISCUSSION

In this paper, we describe the findings and outcomes of HIV-infected children admitted to the main referral hospital in western Kenya. We describe the general demographic characteristics, the clinical characteristics and then the outcomes. The main findings were the differences between HIV-infected children who had previously been enrolled in the AMPATH programme and those who had not been enrolled before admission. We found that those previously admitted to the AMPATH programme were less likely to die if admitted to the hospital. They also tended to have higher CDC classification and CD4 cell percentage, though these were not statistically significant.

The higher mortality among HIV-infected patients who present to the hospital without being previously enrolled to the AMPATH programme has also been described among the adult population of patients admitted to the same hospital (26). These findings are also consistent with other studies from Nairobi, which showed increased mortality among those presenting with low CD4 cell counts (27). It is plausible that the lower mortality among children that are enrolled earlier into care system from the fact that they are more likely to be evaluated for opportunistic infections and to be initiated on prophylaxis against the common causes of HIV infection, including PCP or TB. All HIV-infected children enrolled in AMPATH are initiated on cotrimoxazole for life. They should, therefore, be less sick and have better outcomes upon admission to the wards. Not only may the children not enrolled in this care programme be missing key prophylaxis regimens and routine medical evaluations, but they also may be a population that has shied away from care due to stigma. They may also be orphaned and lack other protective factors, such as supportive families and social environments, and this may not augur well for optimal outcomes to hospitalisation (28).

The majority of children who died after admission were in CDC categories B and C, suggesting they had more severe disease at admission than those who were ultimately discharged home alive. Similar findings have been described among HIV-infected children in South Africa (11) and in adults admitted in the same hospital (26). It is also important to note that the immunologic status of all those admitted was severely depleted, indicating the vulnerability to common infections and opportunistic infections. And, although it was not statistically significant, those who died tended to have lower CD4 cell percentage compared to those who were

discharged. This has been described in a paediatric cohort in Nairobi (27) and in the adult population of admitted HIV infected patients in AMPATH (26). These findings all point to the importance of careful monitoring and aggressive medical care for HIV-infected children with more severe disease staging and impaired immunological functioning.

The common admission diagnoses were pneumonia, gastroenteritis and tuberculosis, which is similar to other studies of HIV-infected children in sub-Saharan Africa (5, 6, 10, 12, 16). Zambia and South Africa have shown the benefits of these preventive strategies (17-19). The AMPATH programme has since introduced INH prophylaxis to all HIV-infected children seen in the programme who are evaluated and found not to have active TB.

Among the hospitalised children who died, pneumonia was the most common diagnosis, consistent with outcomes described for HIV-infected children in South Africa, Zimbabwe, Ivory Coast, Botswana and Uganda (6, 8, 9, 11, 12, 29). While we could not identify the causes of these pneumonia, it is known that HIV-infected children frequently get pneumonia caused by the common pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenza*, but these pathogens tend to cause more severe disease and higher mortality in children with HIV infection (30). HIV-infected children are also at risk for pneumonia cause by pathogens such as *Pneumocystis carinii*, reinforcing the importance of cotrimoxazole prophylaxis.

This study does have several limitations that bear consideration. No details regarding the treatments given to the children was available for analysis; however, we were still able to provide a description of the children's characteristics and their diagnoses. Moreover, these data rely on the admission and discharge or death diagnoses listed in the inpatient charts, which did not allow us to tease out the co-morbidities. The distant AMPATH related admissions to the district hospitals and health centres were not described although some few patients were referred for inpatient specialised care to MTRH; the outcomes might therefore not have been representative of the whole spectrum of AMPATH care. However, MTRH does cover a catchment's area of two million people. Because of the nature of MTRH as a referral hospital, these data probably allowed us to capture the HIV-infected children with more severe illnesses and, perhaps, with a higher likelihood of death. The fact that the analysis is for patients admitted in a national referral hospital means that it may not be as generalisable to outcomes in smaller health facilities. Nonetheless, these data provide a description of the HIV-infected children requiring or receiving referral care, and it is helpful for clinical programmes to be able to estimate the inpatient burden, as well as some of the risk factors for mortality.

In conclusion, the most common diagnoses at hospitalisation included pneumonia, gastroenteritis, malaria and tuberculosis. Higher mortality occurred among those diagnosed with pneumonia and those not previously enrolled in the HIV care programme. Recommendations: Aggressive treatment and prevention of the most prevalent diseases and early enrollment into HIV care are recommended for HIV-infected children. A follow-up study to investigate the pathological causes of death in this population is recommended.

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