THE PREVALENCE AND DISEASE PROFILE OF HUMAN IMMUNODEFICIENCY VIRUS INFECTED CHILDREN ADMITTED TO CHRIS HANI BARAGWANATH HOSPITAL

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DECLARATION

I, TAMARA MICHELLE MEYERS, HEREBY DECLARE THAT THIS DISSERTATION IS MY OWN WORK AND HAS NOT BEEN PRESENTED FOR ANY DEGREE AT ANOTHER UNIVERSITY.

THE WORK REPORTED IN THIS DISSERTATION WAS PERFORMED AT CHRIS HANI BARAGWANTH HOSPITAL, DEPARTMENT OF PAEDIATRICS, UNIVERSITY OF THE WITWATERSRAND.

SIGNATURE

This work is dedicated to all children suffering from HIV infection, especially to those in underdeveloped countries where there seems little hope, in the near future, of stemming the tide of the greatest plague of modern times

"My life has been a little different than other children that I have known. I was born with AIDS. Some people think it's not okay to have AIDS. And some people know that it's okay to have AIDS because you are still a normal person."

Hydeia Broadbent

(Pediatric AIDS *The Challenge of HIV infection in Infants, Children, and Adolescents* 2nd edition. Philip A. Pizzo and Catherine M. Wilfert.)

SUMMARY

The prevalence of HIV infection is increasing in the developing world. Mother-to-child transmission rates are high in this region and the prevalence of the infection in children is rising concurrently.

In sub-Saharan Africa few studies have been done to look at the impact of HIV on the health of children. Where work has been done the prevalence rates of hospital admissions have varied in different regions. In addition, the impact of paediatric HIV disease on health services has not been investigated fully.

There has also been little work done to show whether children with HIV infection from the developing world present similarly to those in richer countries. The natural progression of illness in underdeveloped countries has not been assessed adequately.

HIV infection has resulted in increased admissions to Chris Hani Baragwanath Hospital (CHBH), and mortality rates have increased over the last few years. The true prevalence has not been accurately assessed, as patients are not routinely screened.

This study was therefore conducted with the aim of determining more accurately the prevalence of paediatric HIV admissions, to describe the disease profile of these children in comparison with their uninfected counterparts, and to estimate the impact of the disease on the health services.

Patients <5 years of age admitted to 1 of the children's wards at CHBH were enrolled over a 6 month period (June-December 1996). All were eligible for screening for HIV infection after parental consent was obtained. Data regarding demographics and disease profile were recorded for each patient. Children were considered HIV infected if they were ELISA positive and ≥15 months, ELISA positive and symptomatic for HIV infection <15 months of age, and ELISA and DNA PCR positive <15 months but asymptomatic for HIV infection.

During the study period, 549 patients were enrolled. Of these 164(29,9%) were HIV ELISA positive, 42(7,6%) patients were not tested. Using the criteria for true infection, 144(26.2%) patients were definitely infected. The odds ratio for being admitted if HIV infected was 7,7 (CI 4.94-12.07), assuming that approximately 5% of children in the population are HIV infected.

Almost 50% of the HIV infected children had been admitted previously, significantly higher than the HIV uninfected children (20.4%) ($p<0.01$). The HIV infected children were admitted at a younger age, >90% were admitted in the first 2 years of age and more than half were < 6 months of age. These children stayed longer in hospital, median of 8 compared to 6 days in the HIV uninfected ($p<0.01$). The nutritional status also differed significantly between the infected and uninfected groups. The HIV infected children were more likely to be malnourished with 35% being underweight for age and 24.5% marasmic. In the HIV uninfected group 66.9% were well-nourished ($p<0.01$).

Most of the HIV infected children were admitted with infectious diseases, and most of these were respiratory infections (85%) (odds ratio 5.657 CI 3.402-9.407). Admissions in the HIV uninfected group, were also mainly for infectious reasons but in this group 50.9% had respiratory infections. Gastroenteritis was also more common in HIV infected children (31.9% compared with 22.5%) ($p< 0.02$). When blood cultures were positive, 12/22(55%) of the HIV infected children were found to have invasive pneumococcal infection and 75% of these were penicillin resistant organisms. Only 18% of positive blood culture results in the HIV uninfected group showed pneumococcal bacteraemia and the rest were due to a wide range of organisms. In the HIV infected group 16,5% of children demised during the study period which was significantly higher ($p<0.01$) than the HIV uninfected group where 4.6% of children died (odds ratio 4.10 CI 1.97-8.54).

HIV-related illness in children now accounts for nearly a third of paediatric hospital admissions to CHBH. These children are younger, stay longer in hospital and are more likely to be readmitted, with obvious financial consequences to the health services. They are more likely to be malnourished and have more infections than their uninfected counterparts. Advances in child health care in the developing world, which have been achieved over the last few decades, are now threatened.

SUPPORTING SERVICES

In this study statistical analysis was done in consultation with the Department of Statistics and Actuarial Science, University of the Witwatersrand. In addition, HIV ELISA testing was done by staff of the Department of Microbiology, South African Institute for Medical Research (SAIMR), Chris Hani Baragwanath Hospital, and PCR testing was done at the National Instate of Virology (NIV), University of the Witwatersrand.

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CHAPTER 1

INTRODUCTION

1.1 Background

Infection with human immunodeficiency virus (HIV) was first described in children in 1983. The World Health Organisation (WHO) estimates that, as of late 1994, 1.5 million children were infected with HIV.[1] By the year 2000 it is predicted that 10 million children will be born with HIV infection; most of these will be living in sub-Saharan Africa, South and south-east Asia, and South America.[2] More than 3 million women and 2.7 million children will die from the disease. Millions of children will be orphaned and infant and child mortality rates will increase by 30%.[3]

In South Africa, population prevalence rates are based on annual sentinel surveillance conducted on antenatal attenders. In Gauteng antenatal clinics, the prevalence of HIV has increased from 6.44% in 1994 to 15.49% in 1996.[4] Most children who have HIV infection, acquire it from their mothers.[1] Transmission rates from mother-to-child vary from 13-42% world-wide, with higher rates being found in Africa compared to Europe.[5] Using the antenatal prevalence figures for 1996, and assuming the mother-to-child transmission rate to be about 30%, the estimated prevalence of HIV infection in children in Soweto, as in the rest of Gauteng, is likely to be about 5%.

Few studies have been done in Africa, looking at the prevalence of HIV infection in hospitalised children. In Uganda, in 1990, the seroprevalence in hospitalised children <5 years of age was 16.8%.[6] In a study done in Abidjan, Ivory Coast, over a year period from August 1991 to July 1992, the prevalence of HIV seropositivity was 8.2% in hospitalised children.[7] From September 1992 to September 1994, in Maiduguri, Nigeria, the seroprevalence of HIV in hospitalised paediatric patients was 20.6%.[8] The seroprevalence of HIV in Zambia 1990-1991 in hospitalised children was 28%.[9] These studies demonstrate a geographic variation in seroprevalence rates of HIV but further work needs to be done to show changes over time.

The first patient diagnosed with HIV infection at Chris Hani Baragwanath Hospital (CHBH) in 1985, was a 9-year old haemophiliac patient who acquired it from a transfusion in 1982. The first symptomatic perinatally acquired infection in an infant was reported in 1989. In 1990 about 3-5 new and 2-4 previously admitted HIV infected children were admitted to the general paediatric wards monthly (comprising slightly more than 1% of admissions).[10] Subsequently there has been an increase in HIV positive children admitted to the general wards to 9% of admissions reported from hospital records in 1995. Retrospective data from these records at CHBH do not accurately reflect the true prevalence of HIV infection as children are not routinely screened and only those suspected of being infected with HIV are tested. The full impact of the disease on hospitalised children at CHBH has therefore not yet been fully defined.

1.2 Burden of Disease on Health Services

There has been relatively little research into the burden that paediatric HIV infection presents to the health services in the developing world. In Rwanda, infants born to HIV positive mothers experienced more hospitalisation and received more medication than uninfected subjects.[11] In a study from Abidjan, children with multiple admissions were more likely to be HIV positive than those who had not previously been admitted.[7] Further work needs to be done to look at the financial implications of this disease to the health services.

1.3 Timing of Presentation to Hospital and Progression of Illness

In Europe and the United States, rates of hospitalisation of HIV infected children are increased in the first 1-2 years of life compared with older ages.[12] In addition, from cohort studies, it has been found that patterns of disease progression differ amongst HIV infected children. Approximately one quarter develop a rapidly progressive downhill course with features of AIDS developing in the first year of life. The rest have a slowly progressive illness extending over a few years, while a few have still been found to be asymptomatic by the age of 8-10 years.[1] In Africa, it appears that many HIV infected children develop symptoms early and die within the first 5 years of life.[12] Again, further research needs to be done in the developing world to record the natural progression of illness in HIV infected children and how this affects the rates of hospitalisation at different ages.

1.4 Diagnosis of HIV Infection in Children

The most common method of diagnosing HIV infection is by detecting antibody to the infection by the enzyme linked immuno-sorbent antibody (ELISA) method. However, this method is problematic in infants as maternal IgG antibodies are transferred via the placenta in the third trimester of pregnancy and only disappear between 9 and 18 months of age. The introduction of more sensitive diagnostic techniques has, however made early diagnosis of infection possible. Viral culture remains the gold standard, but is not locally available.[13] The DNA polymerase chain reaction (DNA PCR) has a 50% sensitivity in the first week of life, rising to about 95% sensitivity by the first month of age.[3] Immune complex dissociated p24 antigen has a high specificity after the first week of life[14] but is not as sensitive as the PCR.[15] The cost of doing PCR and p24 antigen testing is prohibitive and beyond the means of most of the health services in resource-poor countries.

Certain characteristic signs with which HIV infected infants present make it possible to make the diagnosis without the means of these investigations. The signs that are frequently described include: failure to thrive, persistent generalised lymphadenopathy, hepatosplenomegaly, oral candidiasis, chronic otitis media, pulmonary infection, and pruritic dermatitis.[11] These signs together with the detection of antibody to HIV infection on ELISA testing are often sufficient to make the diagnosis. The Centre for Disease Control in Atlanta (CDC) has also produced clinical guidelines for the diagnosis and staging of HIV infection[16] (appendix).

1.5 Clinical Manifestations of HIV

Children with HIV infection present with similar conditions in both developing and developed countries, with a few exceptions. Severe protein-energy malnutrition (PEM) is more prevalent in developing countries. Signs of severe PEM have often been associated with HIV infection and malnutrition may aggravate the course of HIV infection.[3,11] The cause of malnutrition is probably multifactorial. Poor social circumstances, increased susceptibility to recurrent infections, and decreased intake of food all combine to impair adequate nutrition. Viral load itself has also been shown to be associated with fall off in weight and height.[17] Anecdotal evidence suggests that nutritional intervention can stabilise or improve immune function.[18]

Pneumocystis carinii pneumonia (PCP) is one of the most serious manifestations of HIV infection.[19] In the developed world, PCP has been found to be the most serious opportunistic infection affecting young HIV infected infants, with a peak incidence at 3-6 months of age.[20] Clinically this infection presents as a severe acute lower respiratory tract infection (ALRI), characterised by marked hypoxaemia, a lack of auscultatory findings on chest examination, and an elevated serum LDH.[21] The organism is difficult to isolate, and is usually best obtained from bronchoalveolar lavage (BAL)[21] or induced sputum.[22] PCP is probably an important cause of mortality in children in the developing world as well, although facilities for isolating this organism are often lacking. In Durban, where post mortem lung and liver biopsies were done on children who had demised from severe respiratory disease, *Pneumocystis carinii* and Cytomegalovirus (CMV) were the

organisms found most frequently in the HIV infected children.[23] Findings from the Ivory Coast have shown that PCP accounts for 31% of HIV related deaths in children <15 months of age.[24] This is hardly surprising since it appears that *Pneumocystis carinii* is ubiquitous as has been shown in the Gambia where the majority of children have been found to have antibodies to this organism by the age of 8 years.[25]

Severe recurrent bacterial infections are reported frequently in HIV infected children. This may be as a result of impaired humoral immunity prior to exposure to bacterial antigens in an immature immune system.[18] The organisms commonly isolated are, *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* (H. influenzae), *Staphylococcus aureus* (S.aureus) and Salmonellae.[11] Children over the age of 1 year are especially prone to invasive pneumococcal infection.[26] In Africa, non-typhoidal salmonellae are cultured in a high proportion of HIV infected children compared with the developed world.[11]

Lymphocytic Interstitial Pneumonitis (LIP), CMV and encephalopathy are more common in children than in adults.[1] Other opportunistic infections are rare in children. Mycobacterium avium intracellularae complex (MAI) has been described in transfusion related illness, but has been rarely reported in vertically acquired HIV infection.[19]

LIP is a lymphoproliferative disorder of the lungs presenting as a chronic progressive interstitial lung disease in the second or third year of life.[27]

Children usually present with an insidious onset of dyspnoea, digital clubbing, salivary gland enlargement, and lymphadenopathy and normal findings on chest examination.[28] Chest radiographs usually have bilateral abnormalities with a characteristic fine reticular-nodular pattern. It was recognised that children with LIP have a relatively improved survival compared to other AIDS defining illnesses.[1] In the 1994 revised CDC clinical classification LIP was therefore changed from a previously AIDS defining condition to a category B disorder (moderately symptomatic).[16] However children with LIP have been shown to have a higher incidence of ALRI as compared to children without LIP.[29]

Tuberculosis (TB) appears to be less prevalent in children with HIV infection than in adults.[7,11] However HIV infection has been reported to be more common in children with diagnosed TB. In Zambia the seroprevalence of HIV in children with TB increased from 24% in 1989 to 56% in 1991.[7] At CHBH, 37% of patients diagnosed with TB have been found to have HIV co-infection.[30] Tuberculosis is notoriously difficult to diagnose in children generally, and is particularly difficult in immunocompromised individuals.[31] At CHBH, many children are treated empirically with TB therapy, without a definitive diagnosis being made. Difficulties with making the diagnosis and the high prevalence of the disease in the community are responsible for this management.

Haematological abnormalities are found relatively frequently in HIV infected children. Anaemia is the most common disorder observed with incidence

ranging between 16%-94%.[3] The cause of anaemia is multifactorial, often due to ineffective erythropoeisis. Iron deficiency may occur from a combination of nutritional privation, repeated phlebotomy or intestinal occult blood loss in association with infection.[3] Up to 40% of HIV infected children may have a positive direct Coomb's test although haemolysis is rare. Thrombocytopenia occurs in 30% of children. The mechanism of thrombocytopenia appears to be immune destruction of platelets.[32] Malignancies are rare in children compared to adults. Kaposi's sarcoma and other HIV related tumours are infrequently seen.[1]

1.6 Advances in the Management of HIV Infected Children

In recent years several advances in the management of HIV infected adults and children have altered the course of the disease. Mother-to-child transmission of virus has been significantly reduced by the administration of antiretroviral therapy to the mother during pregnancy, delivery, and to the infant for 6 weeks post partum.[33]

PCP prophylaxis started in early infancy has been shown to be effective in preventing this infection.[34] In the developed world infants born to HIV positive mothers are now started on PCP prophylaxis (usually in the form of cotrimoxazole) at 4-6 weeks of age for at least a year or until HIV infection has been excluded.[19] With improved treatment in addition to prevention, this disease is declining.[12]

The introduction, as part of routine vaccination schedules, of newer vaccines e.g. against H. influenzae, has resulted in a marked decline in childhood morbidity and mortality from meningitis in industrialised countries.[35] Currently a new nonavalent conjugated pneumococcal vaccine is under investigation in Soweto to prevent this infection in children <2 years of age. These vaccines should be of particular benefit to HIV infected children who are prone to invasive disease with the above organisms.

Treatment of HIV infection with antiretroviral agents has altered the course of the disease in adult and paediatric patients.[3] Combination therapy for HIV infected children with nucleoside analogues and protease inhibitors is still under investigation, although adult studies demonstrate improved outcomes with these therapies.[36]

In resource-poor countries where HIV prevalence levels are high, there is no provision for the implementation of expensive strategies to prevent mother-to-child transmission. Routine antenatal screening does not often occur, and therefore the opportunity to commence early PCP prophylaxis is often missed. Prevention for this infection at CHBH is usually only started subsequent to the first admission to hospital. In South Africa, vaccination against H. influenzae is still not routine procedure and only those who can afford to purchase the vaccine are immunised against this infection. Should the new pneumococcal vaccine be found to be efficacious, it is likely that it will be too costly to introduce into the routine vaccination schedule. In addition, antiretroviral therapy for the treatment of paediatric HIV infection is

also unlikely to be implemented given the high cost of these agents. Therefore despite these advances, the prospects for preventing the transmission of HIV to children, and for improving the outcome of infected children in the developing world remains bleak.

1.7 Mortality from HIV Infection

Mortality rates are higher in children born to HIV positive mothers in Africa than in children born to HIV positive women in Europe and the United States. Higher rates of perinatal transmission, increased risk of infection with ubiquitous and tropical pathogens due to poor social conditions, nutritional factors, poor access to general medical care and lack of specific therapies e.g. antiretroviral therapy, are all factors contributing to the higher mortality rates.[9]

Infant mortality rates have increased in parts of the developing world probably as a direct result of HIV infection. In Zaire, infant mortality rates have increased by 15% and in Haiti by 12%.[2] In-hospital mortality at CHBH has increased over the last few years from 4.3% in 1992 to 6% in 1997 and these deaths are directly attributable to HIV infection.[37] The major causes of death in HIV infected children are respiratory infections and gastroenteritis.[9] In addition malnutrition has been associated with a large proportion of HIV related deaths in children.[5,10]

More work needs to be done in the developing world and especially in sub-Saharan Africa, where the epidemic is most prevalent, to assess the threat that HIV infection is posing to child health.

CHAPTER 2

STUDY DESIGN

2.1 Aims

The aims of this study were therefore:

- To determine the prevalence of HIV infection in hospitalised children at CHBH.
- To describe the disease profile of HIV infected paediatric patients.
- To compare admission profiles of HIV infected with HIV uninfected children
- To estimate the impact of the disease on the health service

2.2 Methods and Definitions

All patients up to 5 years of age admitted to one of 4 general paediatrics wards over a 6-month period from 20/06/96-25/12/96 were eligible for enrolment into the study. Admissions to each ward occur on a 4-day cyclical basis, therefore admissions to one ward represent a random sample of admissions to the general wards. These wards contain 41 beds each, but there may be as many as 60 children in a ward at a time. All children who were readmitted to the ward during the study period were included in the study. CHBH serves the population of Soweto, however many children from other geographical regions of the country seek medical attention here. These patients often give a Soweto address making it difficult to assess accurately the areas of residence of all children admitted to the hospital.

Pre-test counselling was conducted, and parental consent for HIV testing of the children was obtained by attending doctors when the children were admitted. Clinical clerking of patients was done by medical officers and registrars at admission. Data regarding gender, age, previous hospital admissions, length of hospital stay from date of admission to date of discharge, and outcome were recorded for all admissions. Each admission was regarded as a separate event even if the patient had been admitted previously during the study period. Nutritional status, using weight for age, was defined according to the Welcome classification of protein-energy malnutrition and recorded for each patient.[38] The same scales were used to measure the weight of patients at admission. In addition, data regarding diagnosis were recorded for each patient at discharge from hospital.

Acute lower respiratory infection (ALRI) was diagnosed on clinical suspicion and confirmed on chest X-ray. Children with complicated gastroenteritis e.g. in association with severe metabolic abnormalities, malnutrition, or another infection, are admitted to the general wards, those with mild or moderate diarrhoea alone are usually admitted to a short-stay ward. The diagnosis of meningitis was made on clinical observation and a characteristic cerebro-spinal fluid result. Urinary tract infection was diagnosed if an organism was cultured from a suprapubic or catheter specimen in children <2 years or on a clean catch specimen in older children. TB was diagnosed on clinical suspicion together with either a positive Mantoux test (reaction of >15mm induration in immunocompetent children with previous BCG, >10mm in those without a previous BCG and >4mm in immunocompromised children),

positive gastric washings or sputum stain for acid fast bacilli or a positive TB culture on these specimens. Mantoux tests are done routinely on patients who present with respiratory signs. LIP was diagnosed in children presenting with clubbing or parotidomegaly, and a reticulo-nodular pattern on chest X-ray.

Routine blood testing at our hospital usually includes full blood count, urea and electrolytes, and blood cultures. These were done during the study period where indicated. HIV ELISA screening (3rd generation, testing HIV 1/HIV 2) was used (Abbott Diagnostic Products, Wiesbaden Germany). All positives were retested for HIV 1 + 2 (Murex Biotech Ltd. Kent, England). The screening was done at the South African Institute for Medical Research at CHBH and trained ward staff counselled the parents of ELISA positive patients.

HIV infection was defined as the presence of antibody in all children aged 15 months or older. Children under 15 months who were ELISA positive and had signs of HIV infection[16] (appendix) were also considered to be HIV infected. Those under 15 months and ELISA positive who were asymptomatic according to these criteria had HIV DNA PCR testing to look for the presence of viral DNA. These children were considered infected if the HIV DNA PCR was positive. PCR was considered positive if 2 or more primer pairs were positive. One primer pair positive was reported as indeterminate.

2.3 Statistical Methods

Frequency tables were examined for diseases and demographics versus HIV status, with chi-squared tests being used for tables with sufficient respondents. Follow-up loglinear models were used to determine where the significant differences lay. Odds ratios were calculated. Chi-squared automatic interaction detection (CHAID) was also used to investigate risk factors.

Descriptive methods and analysis of variance (ANOVA) were used to examine continuous variables such as haemoglobin, with follow-up multiple comparisons using the Bonferroni procedure. Where there was evidence of skewness in the data, the Kruskal Wallis test was used, again with follow up multiple comparison tests.

Testing was done at the 5% level throughout, with confidence intervals being at the 95% level.

CHAPTER 3

RESULTS

3.1 Prevalence

During the study period 549 patients were enrolled, 507(92%) of whom were tested for HIV antibodies, with 164/507(32.3%) being positive (table 1). Of tested children who were over 15 months, 33/133(25%), and 131/374(35%) under 15 months were ELISA positive. Table 1 shows the distribution of children according to HIV ELISA and HIV DNA PCR status. Two children under 15 months who appeared to be HIV infected on clinical grounds were PCR negative, as were four HIV asymptomatic children who had positive HIV EIA but negative DNA PCR.

There were therefore 349 uninfected patients, 144 infected, 42 untested, and 14 whose HIV status remained undetermined as PCR results were missing or indeterminate. The prevalence of HIV among children admitted during the study was 29.2% (144/493 excluding all patients not tested or PCR not known) with a confidence interval (CI) of 25.2% to 33.2%. The prevalence of HIV if all the untested and PCR unknown are assumed HIV uninfected was 26.2% (144/549) and 36% (200/549) if all HIV untested and PCR negative or unknown were infected.

Table 1 HIV ELISA and DNA PCR results showing the prevalence of infection in paediatric admissions

Total number of children in sample	549	
Untested	42	
Tested	507	
HIV ELISA negative	343/507 (67.7%)	
HIV ELISA positive	164/507 (32.3%)	
Over 15 months	33/133(25%)	
Under 15 months	131/374(35%)	
Under 15 months + symptomatic	101/374(27%)	
PCR Negative		2
Under 15 months + asymptomatic	28/374(7%)	
PCR positive		10
PCR indeterminate		4
PCR not found		10
PCR negative		4

A greater number of HIV infected than uninfected patients (47.9% compared with 20.4%) had had more than one admission to hospital ($p<0.01$). During the study period, 483 patients were first-time admissions, 103 HIV infected,

and 326 uninfected. The prevalence of HIV disease in these patients was 24%(103/429 patients who had HIV EIA and DNA PCR results) (CI 20.0-28.3) with the other estimates being 21.3% (103/483) and 32.5% (157/483) using criteria as above. Table 2 shows the proportion of readmissions in the different groups.

Table 2 Number of readmissions by HIV status.

	HIV uninfected	HIV infected	HIV unknown
Previous admissions	70 (20.4%)	69 (47.9%)	12 (28.6%)
No previous admissions	273 (79.6%)	75 (52.1%)	30 (71.4%)
Total	343	144	42

Of the HIV ELISA positive patients who were admitted for the first time, 71 were <15 months of age and symptomatic for HIV infection. There were 2 patients in this group who had negative PCR's, the presence of signs of HIV, and a positive ELISA was therefore predictive of HIV in 69/71(97.2%) of cases under 15 months of age.

Assuming the prevalence of HIV infected children in the general Soweto paediatric population to be 5%, the odds ratio for hospitalisation of HIV infected children was 7.724 (confidence interval 4.941-12.074), indicating that HIV infected children are about 8 times more likely to be hospitalised than the

uninfected children. The odds ratio for first admissions with HIV infection was 5.206 (CI=3.02-8.98).

3.2 Demographics

3.2.1 Gender Distribution

There were 310 (56.5%) males and 239 (43.5%) females. There was no significant difference (p=0.55) between the proportion of females and males in the HIV infected, uninfected and unknown groups (table 3).

Table 3 Gender breakdown by HIV status.

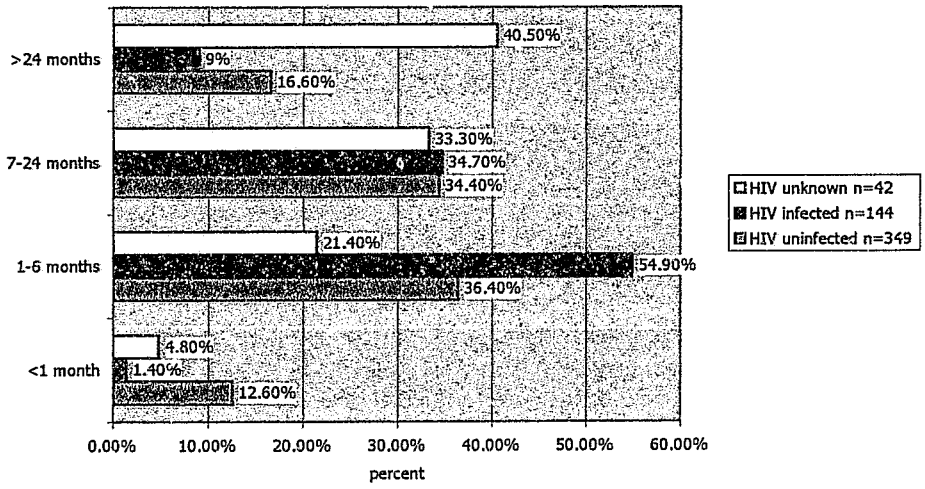
	HIV Uninfected	HIV infected	HIV unknown	PCR indet/unknown
Males	197 (56.4%)	79 (54.9%)	27 (64.3%)	7 (50%)
Females	152 (43.6%)	65 (45.1%)	15 (35.7%)	7 (50%)
Total	349	144	42	14

3.2.2 Age Distribution

HIV infected children were more likely ($p<0.01$) to be admitted at a younger age than the uninfected children (figure 1), with over 50% admitted under 6 months of age, and more than 90% being admitted under 24 months of age. However very few HIV infected children were

admitted in the first month of life. The majority of HIV infected children were admitted between 1-6 months of age [79/144 (54.9%)]. A loglinear model for the age group over 2 years, showed that, while there was no significant difference in the proportion of children admitted with or without HIV infection, there was a significantly higher percentage of children in the untested group who were admitted at this age. [All the patients in whom the HIV PCR was indeterminate or the result was missing were younger than 6 months, 4 were less than 1 month and the rest were between 1-6 months (not shown)

Figure 1 Age at Admission

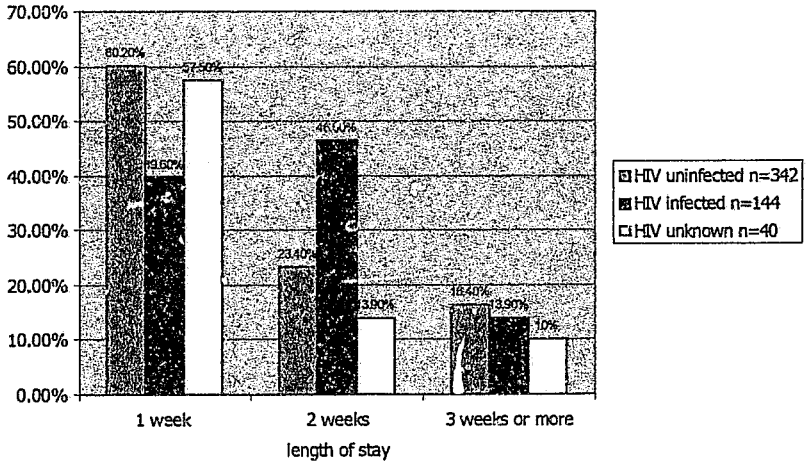


3.2.3 Length of Hospital Stay

The length of hospital stay was significantly longer ($p<0.01$) in the HIV infected children compared to the uninfected and not tested groups

(figure 2). Of the uninfected group, 60.2% (206/342) had a stay of less than one week, while 60% (87/144) of the infected group stayed in hospital for more than one week. The median stay in days for the HIV infected children was 8 compared to 6 in the HIV uninfected children, and this was significantly longer($p<0.01$).

Figure 2 Length of Hospital Stay

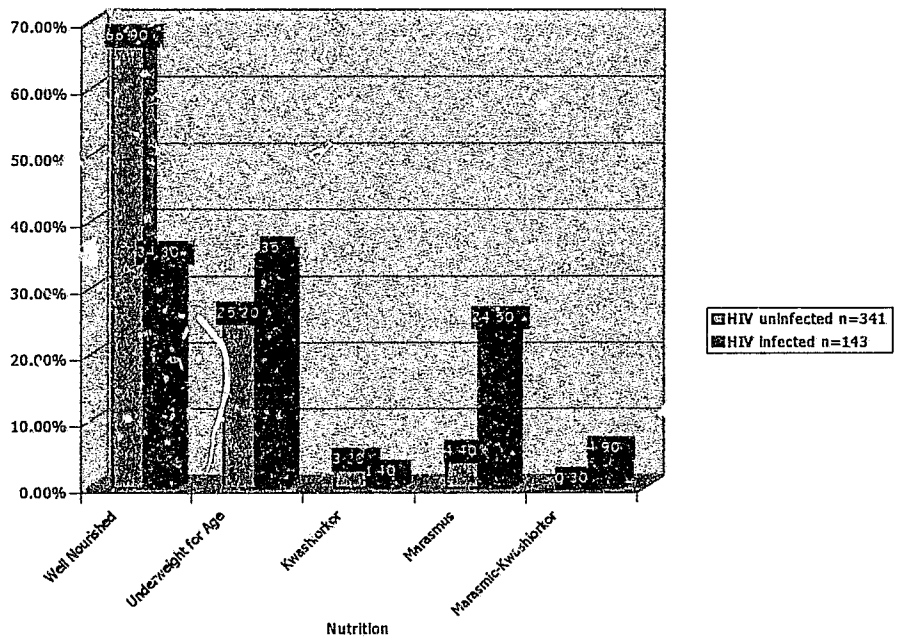


3.2 Nutritional Status

The nutritional status of the HIV uninfected children compared to the infected children was also significantly different ($p<0.01$), although this p value must be interpreted with caution owing to the small numbers of patients in some of the groups. Of the 524 patients where the nutritional status was recorded, figure 3 shows that 66.9% of the uninfected children were well nourished compared to 34.3% of the infected children, with 25.2% compared with 35% being underweight for age. The percentages in the uninfected and infected groups

who had kwashiorkor were 3.2% and 1.4% respectively, 4.4% and 24.5% had marasmus, and 0.3% and 4.9% had marasmic-kwashiorkor respectively. In the untested group (not shown), no children had kwashiorkor or marasmus, 70% were well nourished, and 30% were underweight for age.

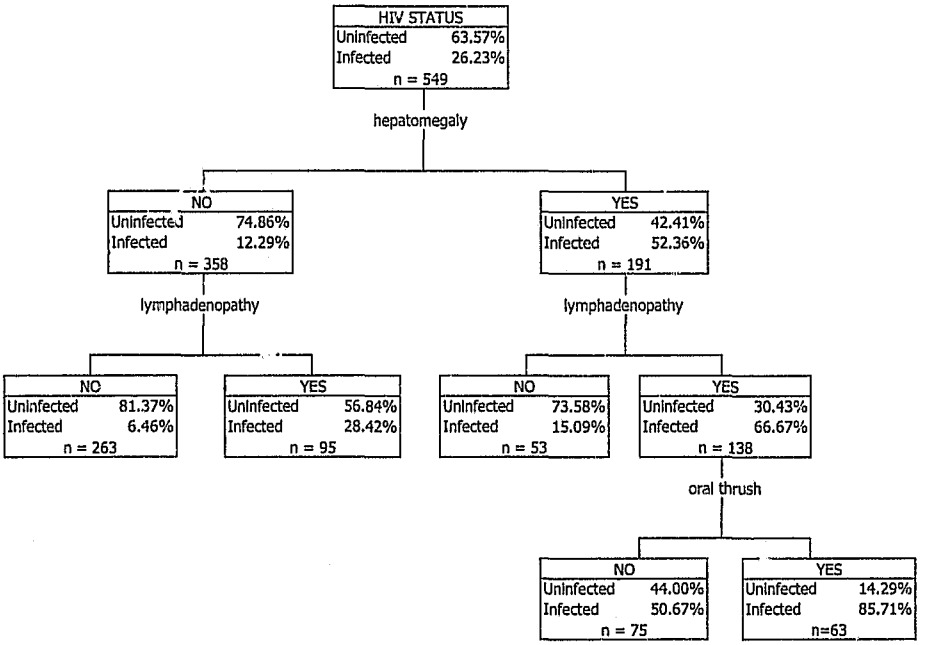
Figure 3 Nutritional Status



3.3 Disease Profile

Presenting clinical signs were examined for predictiveness of HIV status using CHAID, omitting figures for the HIV untested and unknown groups (figure 4).

Figure 4 Chi-squared automatic interaction detection (CHAID) analysis, to detect the probability of HIV infection on the basis of cumulative clinical signs.



Hepatomegaly is the most significant predictor (as measured by the significance of the chi-squared contingency table), with 52% of the group with hepatomegaly being HIV infected, versus 12% without hepatomegaly. The CHAID process then analyses the groups with and without hepatomegaly separately. In both these groups, lymphadenopathy is the most significant predictor variable. For the group with both hepatomegaly and lymphadenopathy, the chance of being HIV infected is 67%. Combining these signs with the presence of oral candidiasis, increased the likelihood of being HIV infected to 86%. The positive predictive value for the combination of these signs is 86%, with a high specificity (98%), but a low sensitivity (38%).

Infectious disease was the most common reason for hospital admission except in the HIV untested group (table 4). Of the infections, acute lower respiratory tract infections (ALRI) were the most frequent reason for hospital admission in all categories of patients. Proportions differed significantly between the uninfected, infected and untested groups ($p<0.01$). Of 532 patients in whom the presence or absence of pneumonia was recorded, 50.9% of the HIV uninfected children compared with 85.4% infected children had ALRI at admission. This gives an odds ratio of 5.657, with a confidence interval of 3.402 to 9.407. In the untested patients, 35.7% were admitted with pneumonia. In this group of patients 28/42 (66%) had a non-infectious underlying condition as a cause of admission (including poisonings, asthma congenital abnormalities, and seizure disorders).

Table 4 Number of patients presenting with different infectious disease by HIV status

	HIV Uninfected	HIV Infected	HIV not tested	PCR indet/ Unknown
Pneumonia	176/346 (50.9%)	123/144 (85.4%)*	15/42 (35.7%)	11/14 (78.6%)
Gastroentetritis	78/346 (22.5%)	46/144 (31.9%)♦	6/42 (14.3%)	1/14 (7.1%)
Gastroenteritis + Pneumonia	19/346 (5.5%)	27/144 (18.8%)+	1/42 (2.4%)	1/14 (7.1%)
Meningitis	12/346 (3.5%)	1/143 (0.7%)	1/42 (2.4%)	0
Urinary Tract Infection(UTI)	11/345 (3.2%)	6/144 (4.2%)	1/41 (2.5%)	0

* $p<0.01$
♦ $p<0.03$
+ $p<0.01$

The age groups in which children with pneumonia were admitted also differed significantly according to HIV status (table 5). Significantly more HIV infected infants were admitted with ALRI in the age group 1-6 months ($p<0.01$) with an odds ratio of 3.3 (confidence interval 1.67-6.37), and in the age group 6-24 months of age ($p<0.01$) odds ratio 13.4 (confidence interval 4.28-42.17). Over the age of 2 years no significant difference was found in the proportions admitted with ALRI.

Table 5 Number of patients presenting with pneumonia by HIV status.

	< 1 month	1-6 months	7-24 months	>24 months
HIV uninfected	14/44 (31.8%)	74/126 (58.7%)	64/118 (54.2%)	24/58 (41.4%)
HIV infected	2/2 (100 %)	65/79 (82.3%)	47/50 (94.0%)	9/13 (69.2%)
HIV not tested	0/2 (0.00%)	3/9 (33.3%)	7/14 (50.0%)	5/17 (29.4%)

Gastroenteritis was the second most common reason for admission (table 4). There was a significant difference in proportions admitted with gastroenteritis ($p<0.02$), with a higher proportion of HIV infected children (31.9%). The odds ratio for gastroenteritis between infected and uninfected groups was 1.613 with confidence interval 1.047 to 2.483. There was no significant difference between the HIV uninfected, infected and untested groups when broken down into the different age groups.

Out of 546 patients where the diagnosis was recorded 48 were admitted with both gastroenteritis and ALRI. Of these, 19 were HIV uninfected and 27 were HIV infected ($p<0.01$) (table 4). Meningitis was diagnosed in 14 patients. The causes of meningitis are listed in table 6.

Table 6 Organisms causing meningitis.

	HIV Uninfected	HIV Infected	HIV Unknown
Haemophilis influenzae	7		
Streptococcus pneumoniae		1	
Neisseria meningitidis	2		1
Organism not identified	3		
Total	12	1	1

Urinary tract infections were demonstrated in 18 patients (table 4).. There was associated *Escherichia coli* (E.coli) septicaemia in 2 patients, 1 had kwashiorkor and was HIV uninfected and the other was an HIV infected child (not shown).

The diagnosis of TB was made in 20 patients. Of these 13 (3%) were HIV uninfected, 6 (4%) were HIV infected and 1 was ELISA positive but the HIV PCR result was missing. There were an additional 12 patients who were placed on TB treatment on clinical suspicion alone.

Lymphocytic Interstitial Pneumonitis (LIP) was suspected in 6 children. All but one was admitted for ALRI, the remaining one was admitted with E. coli bacteraemia and gastroenteritis. No patients had cardiomyopathy, nephropathy or malignancy diagnosed during the study period. Only one child under 5 years of age was admitted with a diagnosed malignancy in the 6-month period. This child was HIV uninfected, and had acute lymphocytic leukaemia (ALL).

Blood cultures were done on admission on most patients with suspected infection as part of routine investigation. Of these 43 were positive (table 7). Pneumococcal bacteraemia was most commonly diagnosed in the HIV infected children 12/22(55%) and 9/12(75%) of these were resistant organisms. In the HIV uninfected children there was a wider range of different organisms causing bacteraemia and of those where pneumococcus was grown 3/17(18%), 1/3(30%) were resistant organisms. Pneumococcus most commonly causes pneumonia, and all but one patient who had pneumococcal bacteraemia in this study had pneumonia. The remaining patient had meningitis. In the HIV infected group, bacteraemia was documented in only 5/22 (23%) of children over the age of one year, 3 of these patients had pneumococcal sepsis, 1 had E.coli and the remaining had *Streptococcus pyogenes* bacteraemia. Only 2 patients had non-typhoidal salmonella infection, 1 in each of the HIV infected and uninfected groups. All organisms are listed in table 7.

Table 7 Organisms causing bacteraemia.

	HIV Uninfected	HIV infected	HIV not tested	PCR indet/ Unknown
Streptococcus pneumoniae	3 (1)*	12 (9)	1 (0)	
Escherichia coli	3	2	1	
Staphylococcus aureus	3	1		
Streptococcus agalactiae	3	1		
Haemophilus influenzae	3			
Streptococcus pyogenes		3		
Salmonella species	1	1		
Enterococcus faecalis	1	1		
Pseudamonas aeruginosa		1		
Enterobacter species				1
Total	17	22	2	1

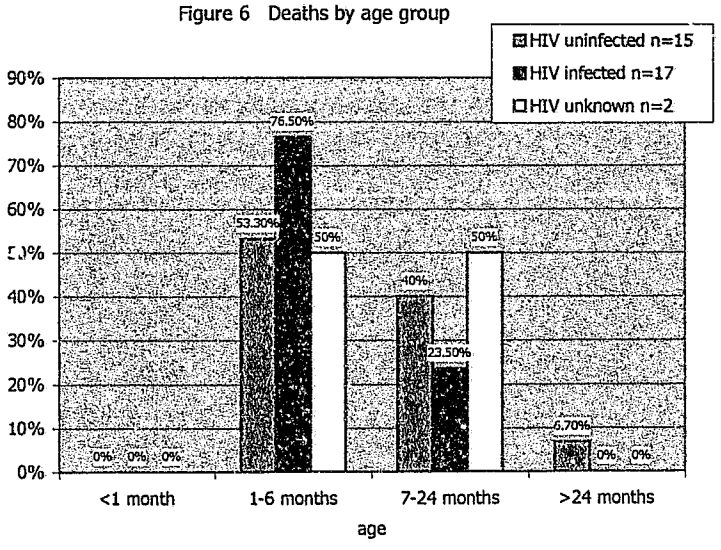
* Figures in parenthesis denote numbers of patients with penicillin resistant organisms.

3.4 Mortality

There were significantly more deaths among the HIV infected 17/103(16.5%) than the HIV uninfected 15/326(4.6%)($p<0.01$) (counting readmitted patients only once). No children in the PCR unknown group died and only 2 in the HIV untested group. The odds ratio for dying in the infected versus uninfected groups was 4.10 (CI 1.97-8.54).

None of the infants under 1 month of age died. Amongst those who died in the HIV uninfected group, 8/15 (53.3%) were aged 1-6 months, while in the HIV infected group 13/17 (76.5%) were in this age group (figure 6). One child in each of these age groups, 1 – 6 months and 7 – 24 months, died in the HIV untested group and these were the only 2 deaths in the untested group.

Figure 6 Deaths by age group



Of the children who died, ALRI was the most frequent diagnosis at death in the HIV infected group (64.7%). Among the uninfected children, the most frequent diagnoses at death (40%) were congenital anomalies (2 with heart defects, 1 with congenital nephrotic syndrome, 1 with hydrocephalus, 1 trisomy 13, and one with an undiagnosed syndrome), with half of these having associated ALRI. All the deaths in the HIV infected group were associated with intercurrent infection. In the HIV uninfected children who died, diagnoses not associated with infections were made in one third of the patients. In the HIV untested group one of the children who died had pneumonia and gram negative septicaemia. The other had unproven neonatal sepsis and renal failure (table 8). In addition, most of the HIV infected children 13/17 (76%) were malnourished when they died. Six were marasmic, 1 had marasmic-

kwashiorkor and 6 were underweight for age. In the HIV uninfected group, 8/15 (53%) were nutritionally compromised, 2 were marasmic, 6 were underweight for age and the rest were well nourished.

Table 8 Diagnosis of children who died.

	HIV uninfected	HIV infected	HIV Not tested
Pneumonia		11	1
Gastroenteritis		1	
Meningitis	2		
Suspected sepsis	4	2	1
Pneumonia + Gastroenteritis	1	2	
Pneumonia + Meningitis		1	
Congenital Abnormalities (+ ALRI)	6 (3)		
Poisoning	1		
Status Epilepticus	1		
Total	15	17	2

CHAPTER 4

DISCUSSION

These results demonstrate a high prevalence of HIV infection in the children admitted to CHBH. Routine screening for HIV infection is not done at our hospital, and the true prevalence rate has not been previously determined. Despite the inaccuracy of previous records, there is no doubt that the prevalence of HIV at CHBH is increasing.[37] HIV infected children are often admitted to the short stay ward and are not included in the statistics of general admissions. This may result in an underestimation of the prevalence of infected children admitted to the hospital.

The children who were not screened for HIV were those who were accompanied by adults other than their parents. In addition some children were admitted with conditions which did not require blood tests at admission (e.g. poisoning or asthma) and were discharged the following day without being tested for HIV. This group of children was therefore an older group with a different disease profile to that of the other groups.

There was also a problem of missing and indeterminate PCR results for a number of asymptomatic HIV ELISA positive children. Logistical problems in ensuring that PCR's were done in the correct patients, together with difficulties in transporting specimens to the NIV which is some distance from CHBH confounded efforts to obtain these results. When PCR's were done in the correct patients, only 10/18 (56%) were positive, the rest being negative or

indeterminate. The children in the PCR indeterminate/missing group were very young (<6 months of age) and, at this age, the PCR is less sensitive than at older ages. The PCR testing in this study, therefore, was not found to be as helpful as has we had hoped. However, it does appear that clinical assessment and HIV ELISA testing alone are very useful in detecting HIV infection. In this study 28 patients under 15 months and 6 older than 15 months (6%) of all patients were considered to be asymptomatic but were HIV ELISA positive. It seems likely therefore, that only a small percentage of patients who are HIV infected but asymptomatic are being missed when routine screening is not performed. According to retrospective data (K. Zwi unpublished data) there has also not been an increase in the percentage of patients being tested for HIV over the last few years, despite the increasing prevalence, indicating that clinical skills in detecting infected children have improved. This is encouraging, in view of the fact that diagnostic methods to detect the presence of virus are expensive and are unlikely to come into routine use in the developing world.

Another problem that was encountered was that the criteria for diagnosing symptomatic HIV infection (especially category A)[16] are non-specific. It is a possibility that there may have been some children (as was found in the 2 who were considered symptomatic but had PCR's which were negative) who were not truly infected, but whom we have diagnosed as infected on the basis of clinical criteria alone. Nevertheless, the high HIV ELISA positivity rate (29.9%) 1(indicating maternal infection and infant exposure), and the fact that at least 26.2% were almost certainly infected is still grave cause for concern. Even

when readmissions were ignored in this study, the rate of HIV positivity (24.5%) remains worryingly high.

The children with HIV infection are more likely to have recurrent admissions and to stay in hospital longer than the HIV uninfected children. Most of these children receive antibiotics as they are admitted with infections. There is therefore significant cost both to the health service and in days at work lost by parents in caring for sick children or in getting them to health providers. With the rising prevalence of HIV in women of childbearing age, there is little doubt that the financial burden that HIV already presents is going to escalate. This problem will not only affect the health services but is likely to have an enormous impact on the economy of the country.

In this study over 90% of patients who were HIV infected, were less than 2 years of age at admission and more than half of them were under 6 months. This is similar to findings in Europe and the United States.[12] Very few patients with HIV infection presented in the first month of life. This has also been shown elsewhere where, because most children are only exposed to infection intrapartum, a very small proportion of neonates will be symptomatic for HIV infection.[1] With an estimated HIV prevalence of 5% in the local population of infants, it would be expected that this same proportion of neonates may be admitted with HIV unrelated conditions. Of the total number of neonates admitted during the study period, 2/48 (4%) were HIV infected, a figure similar to the expected population figure.

The significant difference in nutritional status between the infected and uninfected children in this study emphasises the impact of the illness on the general health of children. Interestingly, in this study, most of the HIV infected children were malnourished, with nearly 25% being marasmic but very few having kwashiorkor. In contrast, in the HIV uninfected group the majority were well nourished, and of the malnourished children most were underweight for age and a few had kwashiorkor. The fact that kwashiorkor appears to be rare in HIV infection has been shown in a retrospective analysis as well (K. Zwi). This interesting observation requires further investigation.

Hepatomegaly, lymphadenopathy and the presence of oral candidiasis, were the signs that correlated best with the presence of HIV infection. This is similar to that which has been documented elsewhere, where during the first year of life, lymphadenopathy, splenomegaly and hepatomegaly, singularly or combined, have been observed in over 50% of children.[1] These clinical signs predicted infection in 97,2% of our patients who were ELISA positive and admitted for the first time.

Infectious disease was the most common reason for admission in both the HIV infected and uninfected children. ALRI was the most common diagnosis in these admissions regardless of HIV status, however pneumonia was diagnosed in a significantly greater proportion of HIV infected children. Respiratory infections have been documented to be particularly common in HIV infected children.[5]

In our setting we have difficulty in establishing an aetiological diagnosis for the cause of ALRI. We do not have facilities for bronchoalveolar lavage or other invasive mechanisms for making an accurate diagnosis. In this study the majority of HIV infected children were admitted between 1-6 months of life and most of the remaining patients were under 2 years of age. Of these the vast majority had ALRI and, in fact, most of the children that were HIV infected who died, were in this age group. *Pneumocystis carinii* appears to be a ubiquitous organism,[25] and if the Durban and Ivory Coast findings[23,24] are anything to go by, it is quite likely that many of our patients in fact had PCP.

Gastroenteritis was the second most common reason for admission. There was a slightly greater percentage of HIV infected children with gastroenteritis than HIV uninfected children. An exact aetiological diagnosis is not routinely sought in children presenting with gastroenteritis at our hospital. Further, studies elsewhere have not demonstrated a significant difference in the pathogens causing diarrhoea in HIV positive and negative children.[11]

Few patients with HIV infection presented with meningitis in this study. even though HIV infected children were not discriminated in terms of investigations. Most of our patients who had meningitis were HIV negative and a large proportion of these were due to H. influenzae infection 7/12(58%). Immunisation against H influenzae is not routinely performed in our country, which explains the still high prevalence of this infection. Interpretation of our results is difficult due to the small numbers in these groups who had meningitis.

The number of patients with urinary tract infections was also small, and there was no significant increase in the proportion of UTI's in the HIV infected group. Although there has been an association between UTI and bacteraemia in HIV infected children,[39] this could not be demonstrated in our children, probably because of the small sample.

Few patients in this study had TB diagnosed on sputum or Mantoux testing. At CHBH, due to the high prevalence of TB in the community, patients are often started on TB treatment when the clinical picture is suggestive. This study does not demonstrate as high a prevalence of HIV in patients diagnosed with TB as has been shown at CHBH and elsewhere in Africa.[9,30] This may also be due to the fact that numbers were too small to assess the impact of HIV infection on childhood TB.

Despite small numbers, there were similar patterns of invasive bacterial infection in HIV infected children, to findings elsewhere.[11] There was a large percentage 12/22(55%) of children admitted with pneumococcal bacteraemia. The rate of penicillin resistance in these organisms was higher [9/12(75%)] than has previously been demonstrated in HIV infected children at CHBH (40.8%).[40] This may again be due to chance given the small numbers but, nevertheless, is cause for concern. The large number of recurrent bacterial infections to which these children are subject, and the high rate of penicillin usage by medical staff in the community probably explain this high resistance rate. Only 2 patients had non-typhiodal salmonellae bacteraemia, one from

each of the infected and uninfected groups. Higher rates of salmonella sepsis have been described elsewhere in the developing world,[11] but our findings may be attributable to small sample size.

LIP was diagnosed in 6 HIV infected children at admission. There were no patients with renal abnormalities, malignancies or cardiomyopathies associated with HIV infection. Patients are not routinely screened for cardiomyopathy with echocardiography, and urine screening is only done for patients with suspected infection or who have other signs of renal dysfunction. It is possible that with screening, more of these abnormalities would have been detected. In addition, children suspected of having a malignancy are often admitted directly to the paediatric haematology/oncology unit without being admitted to the general wards resulting in an underestimation of malignant disorders. HIV encephalopathy was not diagnosed accurately in this study as many of the children were extremely ill at the initial presentation, and the neurological status fluctuated during the hospital stay. HIV encephalopathy is often a progressive illness and diagnosis is made on observing the child over a period of time.[16]

There was a 4-fold increase in mortality rate in the HIV infected children compared with the HIV uninfected children. The cause of death in these children was largely due to infectious disease, respiratory infections being the most common. Similar findings were documented in Abidjan,[7] where a large proportion of deaths was due to respiratory infections in association with malnutrition. The causes of death in the HIV uninfected group, although also

commonly due to respiratory infections, was often in association with congenital abnormalities. Although numbers are small in this study, it appears that the prevalence of preventable morbidity and mortality in HIV uninfected children is declining. This has also been shown in a retrospective analysis of in-hospital deaths in the paediatric wards at CHBH.[37]

Although this study shows an alarmingly high prevalence of HIV admissions to CHBH, there were several limiting factors that deserve mention. The study was conducted over a 6-month period, which results in some bias as there is seasonal variation in admissions with the busiest months being late summer and autumn. This study however took place during winter and spring months. Counting all admissions as single events regardless of whether they had been readmitted during the study period created problems with analysis of the data regarding diagnoses. Where possible, this was taken into account, specifically when looking at numbers of new admissions with HIV and at mortality figures. The small numbers of children with different diseases resulted in difficulty in interpretation of some of the results. The diagnosis of HIV-related illnesses was poor in this study, partly due to the lack of screening for these conditions, and also due to the unavailability of invasive tests for diagnosing opportunistic infections, e.g. BAL, for diagnosing PCP. As a result of the lack of these diagnostic facilities, classification according to the CDC criteria was difficult except in the milder categories. This classification of HIV infection has limited use for developing countries where such investigations are unlikely to be done routinely.

CHAPTER 5

5.1 CONCLUSION

Paediatric HIV infection has reached epidemic proportions with most a third of all admissions to the children's wards at CHBH being admitted with HIV related illnesses. HIV infected children are more likely to have multiple admissions and to stay in hospital longer with enormous financial implications to the health services and the economy as a whole. The increasing prevalence of HIV infection in mothers attending antenatal clinics, indicates that the numbers of children admitted with the disease is likely to increase in the foreseeable future. The burden that this infection is placing on the health service is already enormous and likely to become overwhelming.

It appears that most patients admitted to CHBH who are HIV infected are diagnosed at admission, with very few being missed when routine screening is not conducted. This is encouraging as definitive investigations to detect the presence of virus are very expensive and beyond the means of our health budget.

HIV infected children who are admitted to hospital are often malnourished, suffer from more infectious illnesses e.g. respiratory infections and gastroenteritis, and have a 4-fold greater risk of dying than their uninfected counterparts. This disease, therefore, has devastating consequences to recent advances in child health care, which have occurred in the developing world over the last few decades.

5.2 RECOMMENDATIONS

- Further investigation and long term follow-up of HIV infected children needs to be undertaken to determine the natural history of the disease in our region.

- Implementation of measures to prevent the transmission of HIV from mother to children needs to be given urgent consideration.

- In addition steps should be taken to prevent the common illnesses with which these children present. The routine screening of pregnant women and the institution of cotrimoxazole as a preventive measure from early infancy needs to be strongly recommended.

- Widespread immunisation against *H. influenzae* and the development of a pneumococcal vaccine needs to be prioritised.

- Lastly, these small patients need to be managed with empathy and compassion, and every effort should be made to attain treatment levels equal to their counterparts in developed countries, so that they too can enjoy a better quality of life.

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APPENDIX

Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age (1994)

Clinical categories for children with human immunodeficiency virus (HIV) infection.

CATEGORY N: NOT SYMPTOMATIC

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

CATEGORY A: MILDY SYMPTOMATIC

Children with two or more of the conditions listed below but none of the conditions listed in categories B and C.

Lymphadenopathy (> 0.5 cm at more than two sites; bilateral = one site)

Hepatomegaly

Splenomegaly

Dermatitis

Parotitis

Recurrent or persistent upper respiratory infections, sinusitis, or otitis media

CATEGORY B: MODERATELY SYMPTOMATIC

Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to :

Anaemia (< 8gm/dL), neutropaenia (<1 000/mm3), or thrombocytopaenia (< 100 000/mm3) persisting > 30 days

Bacterial meningitis, pneumonia, or sepsis (single episode)

Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children < 6 months of age

Cardiomyopathy

Cytomegalovirus infection, with onset before 1 month of age

Diarrhoea, recurrent or chronic

Hepatitis

Herpes simplex virus (HSV) stomatitis, recurrent (more than 2 episodes within 1 year)

HSV bronchitis, pneumonitis, or oesophagitis with onset before 1 month of age

Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome

Leiomyosarcoma

Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex

Nephropathy

Nocardiosis

Persistent fever (lasting >1 month)

Toxolasmosis, onset before 1 month of age

Varicella, disseminated (complicated chickenpox)

CATEGORY C: SEVERELY SYMPTOMATIC

Children who have any condition listed in the 1987 surveillance case definition for Acquired Immune Deficiency Syndrome (AIDS) with the exception of LIP :

Serious bacterial infections, multiple or recurrent (i.e. any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)

Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs)

Coccidiomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)

Cryptococcosis, extra pulmonary

Cryptosporidiosis or isosporiasis with diarrhoea persisting > 1 month

Cytomegalovirus diseas with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes)

Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) imparied brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerised tomography or magnetic resonance imaging (serial imaging is required for children under 2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following : paresis, pathologic reflexes, ataxia, or gait disturbance

Herpes simplex virus infection causing a mucocutaneous ulcer that persists for > 1 month; or bronchitis, pneumonitis, or oesophagitis for any duration affecting a child > month of age

Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)

Kaposi's sarcoma

Lymphoma, primary in brain

Lymphoma, small. Noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunological phenotype

Mycobacterium tuberculosis, disseminated or extra pulmonary

Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)

Mycobacterium avium complex or *Mycobacterium kansii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)

Pneumocystis carinii pneumonia

Progressive multi focal leukoencephalopathy

Salmonella (nontyphoid) septicaemia, recurrent

Toxoplasmos of the brain with onset at > 1 month of age

Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss > 10% of baseline OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g. 95^{th}, 75^{th}, 50^{th}, 25^{th}, 5^{th}) in a child ≥ 1 year of age OR c) < 5^{th} percentile on weight-for-height chart on two consecutive measurements, ≥ 30 days apart PLUS a) chronic diarrhoea (i.e. at least 2 loose stools per day for ≥ 30 days) OR b) documented fever for ≥ 30 days, intermittent or constant.