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Treatment and outcome of hospitalised, very young, HIV-infected children

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Aim. The aim of this study was to describe the disease severity and clinical course and outcome of hospitalised HIV-infected children aged <6 months.

Methods. A retrospective case review was completed at Red Cross Children's Hospital (RCCH) during the middle of 2006. Perinatal management, disease severity and hospital outcomes were analysed. In a sub-analysis, the disease profile and outcome of admitted children aged less than and more than 6 months were compared over the latter 3 months of the study.

Results. Seventy-five out of 121 (43.86%) of all HIV-infected children admitted over the study period were <6 months of age. Sixty-nine out of 72 (95.83%) of the children not receiving highly active antiretroviral therapy (HAART) at admission, qualified according to current WHO treatment criteria. The most frequent cause for admission was pneumonia (54.67%). The inpatient fatality rate was 28%, pneumonia being the most frequent cause of death (61.9%). Fifty-two out of 75 (69.33%) of the mothers reported having been tested for HIV during pregnancy. Thirty-four out of 37 (91.89%) who tested HIV-positive during pregnancy received prevention of mother-to-child transmission (PMTCT) prophylaxis. Children with confirmed/presumed *Pneumocystis jiroveci* pneumonia (PJP) were less likely to have mothers who received PMTCT prophylaxis (18.51% v. 61.7%, p=0.0004), and less likely to be receiving cotrimoxazole prophylaxis (14.81% v. 46.81%, p=0.006) at admission. Children >6 months were more likely to be receiving cotrimoxazole prophylaxis (65.4% v. 31.1%, p=0.0008) and HAART (42.3% v. 6.7%, p=0.00007) at the time of admission. Of those not on HAART, 27 out of 30 (90%) had WHO stage 3 or 4 disease. Inpatient fatality in this group was 13.5%.

Conclusions. Young children constitute a sizeable proportion of the inpatient paediatric HIV workload. Comprehensive PMTCT interventions and earlier introduction of HAART may reduce morbidity, hospitalisation rates and mortality.

Natural history studies in Africa have demonstrated that HIV-infected children are at risk of disease progression during their first years of life. Without appropriate intervention, more than 50% die before their second birthday.[1] Vulnerability of infected infants has been documented in European and North American settings, where 15 - 20% progress to AIDS and 10% die within the first year of life. The risk of disease progression during infancy is difficult to predict because of an absence of reliable prognostic markers. For example, HIV encephalopathy may only be recognisable beyond 3 months of life. Furthermore, CD4 percentage and viral load are poor predictors during the first year of life. Consequently, many treatment centres in the northern hemisphere commence antiretroviral therapy in infants immediately after their HIV status is confirmed.[2-4]

The Paediatric Infectious Diseases Unit at Red Cross Children's Hospital (RCCH) provides a regular inpatient consultation service for HIV-infected children admitted to the hospital's general wards. Recent anecdotal observation suggested that a large proportion of this work involved caring for very young children with vertically acquired HIV infection. To quantify the inpatient HIV workload in children less than 6 months of age, describe their perinatal course and disease severity, and document inpatient mortality, a brief audit of HIV-infected children admitted to the hospital's general wards was undertaken.

Methods

This retrospective descriptive study was conducted at RCCH. The Research Ethics Committee of the University of Cape Town approved the study (Reference number: 264/2006). Clinical data were extracted from the hospital case records of all HIV-infected children aged less than 6 months, who were admitted to the two general paediatric wards over a 4-month period during the second and third quarters of 2006. The HIV status of the children was confirmed by HIV-DNA polymerase chain reaction (PCR) testing. The World Health Organization (WHO) clinical staging system was used to classify disease severity.[5] CD4 counts and percentages were measured by the Panleucogating method, by the National Health Laboratory Services.[6]

Children admitted with pneumonia were classified into one of two groups: (*i*) those with confirmed *Pneumocystis jiroveci* pneumonia (PJP) or presumed PJP; and (*ii*) those with pneumonia considered to have been caused by a different aetiological agent. *P. jiroveci* pneumonia was diagnosed in HIV-infected children <6 months old if the causative organism was identified by indirect qualitative immunofluorescence using the Detect IF Pneumocystis Carinii test (Axis-Shield diagnostics Limited, UK) on respiratory secretions collected at broncho-alveolar lavage or nasopharyngeal aspirate, or was presumed to be present when they fulfilled the following criteria: Either an oxygen saturation <90% on hospital admission and/or required a fraction of inspired oxygen (FIO_2)

>0.4 for 4 or more consecutive days of the admission plus at least one of the following: a respiratory rate >60/minute on admission, a lactate dehydrogenase concentration >450 U/l shortly after admission, or the presence of a reticulonodular pattern on chest radiograph. These criteria were based on the WHO clinical case definition of PJP and local research findings.[5,7,8]

In a sub-analysis over the latter 3 months of the study, a comparison of HIV-infected children less than and more than 6 months old, who were admitted to the general wards, was completed. In accordance with established diagnostic guidelines, HIV status was established by HIV ELISA or HIV DNA PCR testing.[9]

The data were analysed using conventional descriptive statistical methods. The chi-square test was used to compare categorical data, and the Mann-Whitney U-test to compare continuous data. A *p*-value <0.05 was regarded as statistically significant. The analysis was completed using StatsDirect software, version 2.5.5, 2006, Cheshire, UK.

Results

Infected children <6 months. A total of 171 HIV-infected children were admitted to the two general wards over the 4-month period. Of these, 75 (43.86%) were <6 months of age. The baseline characteristics of these children appear in Table I. Absolute CD4 count or percentage was done on 64 children (85.3%) during the admission. The median (IQR) CD4 percentage was 17.8%(10.4, 33.3). Thirty-eight (59.4%) had a CD4 percentage <25%. The median (IQR) absolute CD4 count was 530 (198, 1 116) cells/µl. Fifty-three (82.8%) had a CD4 count <1 500 cells/µl. Only 3 out of 75 (4%) children were receiving HAART at the time of admission. Of the 72 children not receiving HAART, 69 (96%) qualified for HAART according to the current WHO clinical and immunological treatment criteria. Reasons for hospitalisation appear in Table II. Twenty-six out of 75 (34.67%) of the children had more than 1 clinical problem at the time of admission. The median (IQR) duration of admission was 17 (9, 34) days. The inpatient fatality rate was 21 out of 75 (28%). The cause of death was pneumonia in 61.9%, sepsis-related in 23.8%, and related to gastrointestinal causes in 14.3%.

TABLE I. BASELINE CHARACTERISTICS OF THE CHILDREN AGED <6 MONTHS (N=75)

Median (IQR) age	3.3 (2.13, 4.23) months
Female:male	38:37
Median (IQR) weight-for-age Z score	-2.05 (-2.98, -1.32)
Underweight-for-age	38 (50.7%)
Severe underweight-for-age	18 (24%)
WHO clinical staging	
Stage 1	2 (2.7%)
Stage 2	5 (6.7%)
Stage 3	9 (12%)
Stage 4	59 (78.7%)

TABLE II. PRINCIPAL REASONS FOR HOSTIPALISATION (N=75)

Indication	N (%)
Pneumonia	41 (54.67%)
PJP/presumed PJP	28 (37.33%)
Pneumonia (other causes)	13 (17.33%)
Gastroenteritis	18 (24%)
Confirmed sepsis	7 (9.34%)
Presumed sepsis	9 (12%)

Perinatal history of the 75 children. Fifty-two mothers (69.33%) reported having been tested for HIV infection during pregnancy. Thirty-seven of these women (71.15%) reported testing positive, and 34 out of 37 (91.89%) reported receiving PMTCT prophylaxis. The regimen of PMTCT prophylaxis was recorded in only 23 out of 34 (67.65%) of these women. Four out of 23 (17.39%) received nevirapine (NVP) monoprophylaxis, 18 out of 23 (78.27%) received dual NVP and zidovudine (AZT) prophylaxis, while one mother was receiving HAART (AZT, lamivudine and NVP) at the time of delivery. Although 26 of the children on the PMTCT programme were >6 weeks of age at the time of admission, only 21 (80.8%) were receiving cotrimoxazole (Fig. 1). The place of birth was recorded in 52 (69.33%) of the patients; 45 (86.5%) were born in the Western Cape (43 in the Cape Metro Region, 1 in the Cape Winelands region, and 1 in the Southern Cape), 6 (11.54%) in the Eastern Cape, and 1 in the Northern Province.

Outcome of PJP. Four children had confirmed PJP, and an additional 23 fulfilled the criteria for a presumptive diagnosis. These 27 children were compared with the remaining 47 who were admitted with other diagnoses. We had insufficient data to classify the pneumonia of one child. Therefore she was excluded from this analysis. Median CD4 counts between the two groups were similar (19.4% v. 17.3%); however, the children with PJP had a lower median absolute CD4 count (407 v. 643 cells/µl), although this did not reach clinical significance (p=0.2). Children with confirmed/presumed PJP were more likely to have been born to mothers who had not received PMTCT prophylaxis during pregnancy (18.51% v. 61.7%, p=0.0004) and were less likely to be receiving cotrimoxazole prophylaxis at the time of admission (14.81% v. 46.81%, p=0.006). There was a higher inpatient fatality rate in children with PJP (33.3% v. 23.5%) although this was not statistically significant (p=0.4) (see Table III).

Comparison with older children. Fifty-two HIV-infected children >6 months old were admitted during the final 3 months of the study. Their clinical and laboratory profiles were compared with the 45 younger children admitted over the same period. The most frequent reasons for admission in the older children were gastroenteritis (26.92%), pneumonia (excluding TB) (23.08%), tuberculosis (19.23%) and confirmed or presumed sepsis (13.46%). Ten out of 52 (19.23%) children had more than one diagnosis at the time of admission. In comparison with the younger group, older children were more likely to be receiving cotrimoxazole prophylaxis on admission (65.4% v. 31.1%, p=0.0008). However, they had a lower median z-score compared with the younger group (–2.82 v. –2.21, p=0.04). The older children were more likely to have started HAART prior to the admission (42.3% v. 6.7%, p=0.00007)

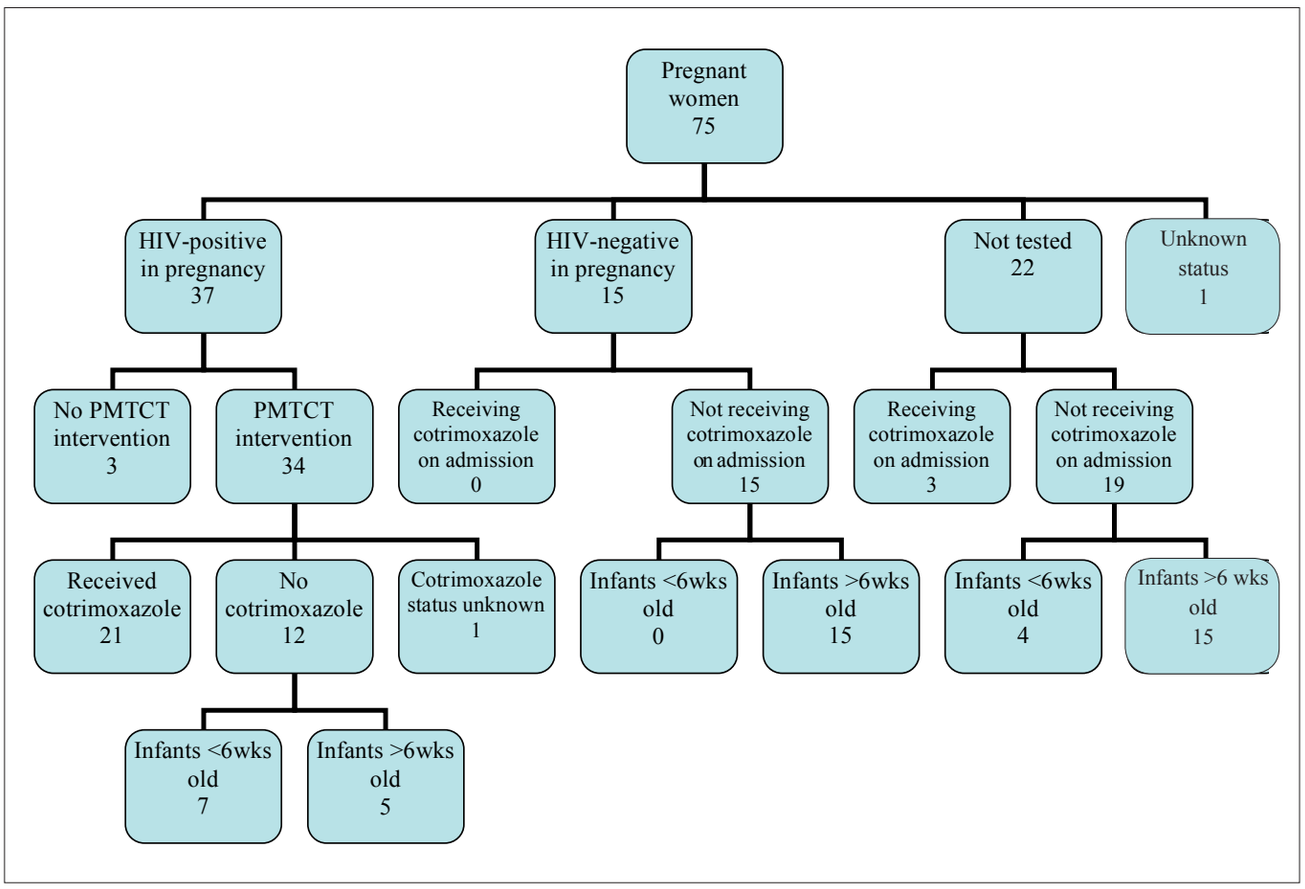

Fig. 1. Maternal and infant access to PMTCT intervention.

and were more likely to have been started on HAART during the admission (60% v. 45%, p=0.2). The median duration of admission of the two groups was similar (17.5 v. 17 days, p=0.8). Although case fatality rate was higher in those <6 months of age (24.4% v. 13.5%), this difference was not significant (Table IV). Pneumonia was the most common cause of death in both the older and younger groups (57.14 v. 54.55%).

Discussion

The results of this study confirmed that children <6 months of age constituted a sizeable proportion of the RCCH inpatient HIV workload. They presented with advanced disease and experienced high inpatient mortality, particularly those with confirmed/presumed PJP. As the antiretroviral treatment

TABLE III. COMPARISONS OF CHILDREN WITH PJP OR PRESUMED PJP (GROUP A), AND THOSE WITH OTHER CONDITIONS (GROUP B)

Parameter	Group A (N=27)	Group B (N=47)	p-value
Median age (IQR*) months	3.2 (2.93, 3.87)	3.33 (1.53, 4.57)	0.5
WHO category 4 disease	27/27 (100%)	32/47 (68.09%)	0.001
Median (IQR) mass Z score	-1.94 (-2.66, -1.11)	-2.21 (-3.09, -1.41)	0.2
Moderate or severe underweight	12/27 (44.4%)	26/47 (55.3%)	0.4
Median (IQR) CD4 percentage	19.4 (10.3, 33.7)	17.3 (10.5, 32.7)	0.6
CD4 percentage <25%	14/23 (60.87%)	25/41 (60.98%)	1.0
Median (IQR) CD4 count (cells/µl)	407 (167, 737)	643 (257, 1126)	0.2
CD4 count <1 500 cells/µl	21/23 (91.30%)	32/41 (78.04%)	0.3
Mothers who received PMTCT intervention in pregnancy	5/27 (18.51%)	29/47 (61.7%)	0.0004
Children receiving cotrimoxazole prophylaxis at admission	4/27 (14.81%)	22/47 (46.81%)	0.006
On HAART at the time of admission	0/27	3/47 (6.4%)	0.18
HAART initiated during the admission	12/27 (44.44%)	17/47 (36.17%)	0.7
Duration (IQR) of hospitalisation (days)	16 (8, 32)	18 (11, 38)	0.5
Inpatient mortality rate	9/27 (33.33%)	11/47 (23.4%)	0.4

*IQR = interquartile range.

TABLE IV. COMPARISON OF CHILDREN WITH HIV INFECTION WHO WERE ≥6 MONTHS (GROUP I) AND YOUNGER HIV-INFECTED CHILDREN (GROUP II)

Parameter	Group I (*N*=52)	Group II (*N*=45)	*p*-value
Median (IQR*) age (months)	27.0 (11.9, 65.5)	3.3 (2.03, 2.2)	<0.0001
WHO clinical severity			
WHO stage 4	21/52 (40.4%)	35/45 (77.8%)	0.0002
WHO stage 3	28/52 (53.9%)	7/45 (15.6%)	
WHO stage 2	2/52 (3.9%)	2/45 (4.4%)	
WHO stage 1	1/52 (1.9%)	1/45 (2.2%)	
Median (IQR) mass Z score	-2.82 (-3.56, -1.81)	-2.21 (-2.97, -1.42)	0.04
Moderate or severe underweight	37/52 (71.2%)	26/45 (57.8%)	0.2
Median (IQR) CD4 percentage	15.2 (10.1, 23.1)	26.3 (14.3, 34.8)	0.01
Median (IQR) CD4 count (cells/µl)	427 (146, 1001)	635 (327, 1125)	0.06
Mothers who received PMTCT intervention during pregnancy	15/44 (34.1%)	20/45 (44.4%)	0.3
Children receiving cotrimoxazole prophylaxis at admission	34/52 (65.4%)	14/45 (31.1%)	0.0008
On HAART at the time of admission	22/52 (42.3%)	3/45 (6.7%)	0.00007
Median (IQR) time on HAART at the time of admission	204.5 (78, 471)	34 (22, 47%)	0.009
HAART initiated during the admission	18/30 (60%)	19/42 (45.24%)	0.2
Duration (IQR) of hospitalisation (days)	17.5 (9.5, 33.5)	17 (12, 35)	0.8
Inpatient mortality rate	7/52 (13.5%)	11/45 (24.4%)	0.2

*IQR = interquartile range.

programme in the Western Cape comes to include increasing numbers of adults and older children, a greater proportion of infected children with advanced disease presenting for medical care will be under 6 months of age. Therefore, improved care for these younger children should become a major focus for child health professionals.

This study had several limitations. It was conducted over a short period and included a small sample size. This was particularly true for the sub-analysis, which compared older children with those <6 months old. As with many retrospective studies, some of the data were not available, in particular information describing PMTCT interventions. Consequently, information on early postnatal feeding practices was not analysed. Furthermore, mortality after discharge from hospital was not described. Despite these limitations, we were able to provide a relatively detailed description of the disease severity of the young children and identify important management gaps.

The provincial PMTCT programme is important to reduce vertical transmission and improve access to medical care for babies who become infected. Although antenatal HIV testing is offered throughout the province, 22 out of 74 (29.7%) of the mothers reported that they had never been tested. More than 25% of mothers who were tested, reported a negative HIV test result during pregnancy. This finding questions the reliability of rapid testing. Furthermore, repeat testing under certain circumstances should be considered, such as in pregnant women who previously tested negative but develop clinical features suggestive of HIV infection, or who subsequently engage in unprotected sexual activity. A recent report from Tygerberg Hospital showed that rapid testing during pregnancy was reliable. However, our findings suggested that repeat testing during pregnancy should be revisited.[10] Alternatively, a recent proposal that HIV DNA PCR testing be offered to all infants at 6 weeks of age irrespective of their mothers' status during pregnancy should be considered as it could assist in overcoming PMTCT programmatic gaps and provide an entry route to diagnosis and care for children who fall outside the PMTCT intervention programme.[11]

HIV-exposed infants should receive cotrimoxazole prophylaxis from 6 weeks of age, coinciding with their second immunisation contact, to reduce the risk of PJP pneumonia.[12] Of the young children on the PMTCT intervention programme who qualified for prophylaxis, 5 out of 26 (19.2%) were not receiving cotrimoxazole on admission. Older children were more likely to be on cotrimoxazole prophylaxis at the time of admission. Furthermore, all of the older children who were not on prophylaxis at the time of their admission qualified on WHO criteria for HAART, indicating that health care providers should remain vigilant and determine the HIV status of all children who are admitted to hospital.

At RCCH, most cases of PJP are diagnosed on clinical grounds. Few HIV-infected infants with suspected PJP are admitted to the intensive care unit for assisted ventilation. Therefore, diagnostic bronchoalveolar lavage (BAL) is rarely performed. Although secretions obtained by nasopharyngeal aspirate (NPA) are frequently screened by indirect immunoflorescence, the sensitivity of identifying *P. jiroveci* by NPA is relatively low.[8] The WHO clinical definition of PJP is broad and often unhelpful in either including or excluding the diagnosis of PJP.[5] No other clinical diagnostic guidelines exist. However, a recent study established that four criteria were independently associated with PJP.[7] We used these criteria and other published data to classify our patients.[7,8] Predictably, children with confirmed/presumed PJP were less likely to be on

cotrimoxazole prophylaxis, and more likely to be born to mothers who had never received PMTCT prophylaxis.

Although 42.3% of the children >6 months of age were receiving HAART at the time of admission, 27 of the remaining 30 (90%) fulfilled WHO criteria for starting HAART.[5] Eighteen of these children (60%) were started on HAART during their admission. In contrast, fewer children <6 months of age were started on HAART during their admission. The reason for this difference was not clear. Since recognising this discrepancy, we have adjusted our clinical practice to ensure that most children <6 months of age start HAART before discharge. There is growing evidence that HIV-infected children on the African continent experience rapid disease progression.[13] Interim results of a South African clinical trial showed that, after an average of 32 weeks' follow-up, significantly more infants were alive after initiating HAART at diagnosis compared with infants who were started on HAART when the CD4 percentage had declined to <25% (96% v. 84%). Consequently, the deferred treatment arm of the trial was recently closed.[14] These findings should result in liberalisation of the antiretroviral start criteria for infants in South Africa.

Conclusion

This study documented PMTCT programmatic gaps and treatment discrepancies which increase the risk of disease progression in young HIV-infected children. A shift in clinical practice towards optimal administration of cotrimoxazole prophylaxis and the early introduction of HAART is required to reduce their vulnerability.

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