Original Article

Duration of hospitalization and appetite of HIV-infected South African children

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Abstract

Human immunodeficiency virus (HIV)-infected children generally show poor growth. Episodes of diarrhoea and pneumonia in HIV-infected children are thought to be more severe than in HIV-uninfected children. The objective of this study was to compare duration of hospitalization, appetite and nutritional status of HIV-infected children with that of uninfected children. A cross-sectional study was performed on children (2–24 months) admitted with diarrhoea or pneumonia to the university hospital. Children were tested for HIV, and the duration of hospitalization was noted for 189 children. Follow-up for blood analysis ($n = 154$) and appetite measurement ($n = 48$) was performed 4–8 weeks after discharge. Appetite was measured as *ad libitum* intake of a commercial infant cereal using highly standardized procedures. Hospitalization (in days) was significantly longer in HIV-infected children; among children admitted with diarrhoea (5.9 ± 1.9 vs. 3.8 ± 1.5) (mean $\pm$ standard deviation) and with pneumonia (9.0 ± 2.5 vs. 5.9 ± 1.9). Serum zinc, iron and transferrin concentrations, and haemoglobin levels were significantly lower in HIV-infected children compared with uninfected children. Appetites [amounts eaten (g) per kg body weight] of HIV-infected children were significantly poorer than those of HIV-uninfected children (18.6 ± 5.8 vs. 25.2 ± 7.4). The eating rates (g min^{-1}) of HIV-infected children were also slower (17.6 ± 6.2 vs. 10.1 ± 3.7). Mean Z-scores for length-for-age were significantly lower among HIV-infected children compared with HIV-uninfected children. Weight-for-length Z-scores were not significantly different. In summary, HIV-infected children had a 55% longer duration of hospitalization and a 21% lower appetite.

Keywords: HIV/AIDS, length of hospitalization, appetite, nutritional status.

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Introduction

It is estimated that in 2006 there were 36 million people infected with the human immunodeficiency virus (HIV) worldwide; 24 million of these infected people were in Sub-Saharan Africa (UNAIDS 2007). The number of HIV-infected persons in South Africa is estimated at 5.4 million, of whom approximately 294 000 are children under 15 years

(Dorrington *et al.* 2006). Infection with HIV has had a major impact on the admission of children to South African hospitals (Zwi *et al.* 2000). In one of South Africa's academic hospitals, approximately 60% of children admitted were HIV infected (Pillay *et al.* 2001). The commonest admission diagnosis among HIV-infected South African children is reported to be pneumonia, followed by diarrhoea (van Deventer *et al.* 2005).

The duration of hospitalization may be longer in HIV-infected children compared with uninfected children. An evaluation of a database that accounted for approximately 73% of all US hospital discharges of children in 2000 indicated that HIV-infected children had a significantly longer mean duration of hospitalization (7.8 days vs. 3.9 days) when compared with HIV-uninfected children (Kourtis *et al.* 2006). In a group of children who were younger than 5 years and were admitted to a tertiary hospital in Johannesburg, South Africa, those who are HIV infected had an average 33% longer hospital stay than uninfected children (Meyers *et al.* 2000). HIV-infected children, who were admitted to a hospital in Cape Town, South Africa, with pneumonia had an average 33% longer duration of hospitalization when compared with HIV-uninfected children (Zar *et al.* 2001). In yet another group of children who were admitted with diarrhoea to a hospital in Johannesburg, South Africa, it was noted that the median duration of hospital stay was 8 days for HIV-infected children, as opposed to 3 days for HIV-uninfected children (Johnson *et al.* 2000). HIV-infected children from Durban, South Africa, had a slightly longer duration of hospitalization than uninfected children; the difference approached but did not reach statistical significance (Pillay *et al.* 2001).

Persistent anorexia (loss of appetite) has been reported to be common among HIV-infected children (Heikens *et al.* 2008). In fact, loss of appetite was reported to be a common symptom in a group of HIV-infected Indian children, being reported in 59% of these children (Pol *et al.* 2007). Reduced energy intake is known to be common among HIV-infected people. Indeed, a study conducted in England on

HIV-infected men concluded that reduced energy intake was the prime determinant of weight in HIV-associated wasting (Macallan *et al.* 1995). Loss of appetite is an important cause of reduced food intake. Oropharyngeal and oesophageal candidiasis are common with HIV infection and may lead to dysphagia (difficulty in swallowing) and odynophagia (painful swallowing) (Semba & Tang 1999). These problems also contribute to the poor food intake that occurs in these children.

The nutritional status in terms of weight, height and micronutrient status of HIV-infected children is reported to be poor compared with uninfected children. A study that followed up a group of children born to HIV-infected mothers in 11 centres in eight European countries showed that between 6 and 12 months of age, uninfected children on average grew 1.6% and 6.2% faster in height and weight respectively, than infected children (The European Collaborative Study 2003). In Rwanda, where children born to HIV 1-infected and uninfected women were followed for 36 months, it was noted that the mean Z-scores for weight-for-age and height-for-age were lower among HIV-infected children compared with uninfected children (Lepage *et al.* 1996). The assertion that HIV-infected children have a poor micronutrient status is supported by a study that showed that approximately 60% of stable (antiretroviral naïve) HIV-infected children from Cape Town, South Africa, had multiple micronutrient deficiencies (Eley *et al.* 2002a). HIV-infected adults from the Free State province in South Africa were shown to be deficient in several micronutrients (van Staden *et al.* 1998).

Key messages

- Episodes of diarrhoea and of pneumonia have a longer duration in HIV-infected than in uninfected children.
- HIV-infected children had poorer appetites and a more vulnerable micronutrient status than uninfected children.
- Poor growth is common in HIV-infected children and may be partly explained by the poor appetite and the poor micronutrient status of these children.
- These findings were observed in antiretroviral naïve HIV-infected children; effects in children treated with ARV are still to be studied.
- Appropriate interventions in HIV-infected children should include, in addition to ARV, an improvement of food intake and of micronutrient status.

Micronutrients are thought to play a role in infectious diseases, in particular diarrhoea and pneumonia. They are also thought to be important in growth and appetite. Deficiencies of zinc and vitamin A are associated with increased risk of diarrhoea and respiratory infections (Bloem *et al.* 1990; Bahl *et al.* 1998). Micronutrient deficiencies, in particular of zinc, have been associated with stunting and poor appetite (Umeta *et al.* 2000). Iron deficiency is also associated with poor appetite (Lawless *et al.* 1994).

HIV-infected children are thus more likely to have longer hospital stays and poorer appetites than uninfected children. Children with HIV infection are also likely to have poor growth and micronutrient status. The increased duration of hospitalization and poor appetites may be influenced by the poor nutritional status that is thought to be common in these children.

Antiretroviral therapy (ARV) was not available in South African public hospitals when the study was designed, and even at the conclusion of the study, only a modest number of patients were on ARVs. However, there is evidence that ARVs have an influence on the duration of hospitalization of HIV-infected children. This is supported by a retrospective study that was conducted in Italy that showed that the duration of hospitalization was longer in HIV-infected children who did not receive ARV compared with those who received the therapy (Resino *et al.* 2006). It was therefore decided to exclude children who were on ARVs.

The objective of the study was to compare duration of hospitalization, appetite and nutritional status of HIV-infected children with that of uninfected children.

Subjects and methods

Subjects and study area

The study was conducted between August 2004 and March 2005. The subjects were children aged 2 months–2 years who were admitted with diarrhoea and/or pneumonia to the Dr George Mukhari Hospital (previously GaRankuwa hospital), the teaching hospital for the Medunsa campus of the University of Limpopo. This government-owned peri-urban hospi-

tal is about 35 km north-west of Pretoria, the capital city of South Africa. The subjects were mainly from the townships surrounding the hospital. More than 80% of the patients who visit the hospital have no medical insurance and attend state-owned clinics and hospitals. Children under 6 years of age are not required to pay for hospital visits. Children admitted with acute lower respiratory tract infection (pneumonia) or acute diarrhoea were recruited to take part in the study.

Exclusion criteria

All children who had received vitamin or mineral supplements in the past 2 months were excluded. As we were assessing the length of hospitalization in children with acute pneumonia or diarrhoea, it was decided to exclude children whose pneumonia or diarrhoeal episode was longer than 72 h on admission. Children with pneumonia and respiratory failure, i.e. hypoxia on supplemental oxygen, were not included. Children who had both diarrhoea and pneumonia were also excluded. Any child who was on ARV was not eligible for inclusion.

Study design

A cross-sectional study was performed. The subjects were enrolled on admission or within 24 h of admission. At enrolment, the following information was obtained: age, gender, body weight and length. The HIV status of all the subjects was determined (after counselling and informed consent) using the enzyme-linked immunosorbent assay (ELISA) method in children older than 18 months, and by polymerase chain reaction (PCR) (Gene Amp 2400, Applied Biosystems, Foster City, CA, USA) in those younger than 18 months who had a positive ELISA. Children who had a documented previous positive HIV test result were not retested.

It was scheduled to enrol a total of 200 children, i.e. 100 HIV infected and 100 HIV uninfected. The treatment was as per standard hospital care, as determined by the attending physician. Children with diarrhoea were assessed for dehydration, and the dehydration

was corrected over 24 h if there was hypernatraemia, or if the age was 3 months or less; otherwise rehydration was performed over 6 h. Diarrhoea was defined as the passing of three or more loose stools per day (Al-Sonboli *et al.* 2003), and pneumonia as a period during which a child was reported to have a cough, had a temperature of 38°C or more, and had an elevated respiratory rate, above the age-specific value on a minute estimation (World Health Organization 1990). The children admitted with diarrhoea were considered to be ready for discharge when they had passed stools of normal consistency or had no stools in the past 24 h and were well hydrated. Children with pneumonia were also considered for discharge when their temperature had been normal for at least 24 h, their respiratory rate already normal (Beatty 1998), there was no intercostal or sternal recession, and when the child is already able to drink and feed. On discharge, the duration of hospital stay was noted (from admission date to date of discharge), and the caregiver of the child was given a follow-up calendar date, written on an appointment card. The follow-up date was 4–8 weeks post discharge. At follow-up, the weight was measured; the children were assessed clinically for acute illness by the investigator. Blood samples for serum zinc, iron, and ferritin and transferrin were taken in those who were not acutely ill. Children who were acutely ill were given another return date. All the caregivers of children who were 6 months or older (and were already consuming solids) were asked to participate with their children in the appetite-testing segment of the study, which required three additional follow-up days.

Anthropometry

The ages of the children were calculated in months by using their reported dates of birth. The weight was measured using a single beam balance scale, without the child's shoes on and with the child wearing only light clothing, to the nearest 0.1 kg. The scale was calibrated to zero before each measurement session. The children were not clinically dehydrated at the time of the weight measurements. The length was measured in the recumbent position to 0.1 cm, on a baby board, by the investigator with the help of an

assistant. One examiner held the child's head (with the chin in the neutral position) in contact with the fixed part of the board, while the other examiner stretched the child to maximum length and then brought the movable part of the board into contact with the heels. Z-scores for weight-for-age, length-for-age and weight-for-length were calculated based on the National Centre for Health Statistics by means of the Epi-Info software version 3.2.2 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) (Dean *et al.* 2000).

Blood sampling and analysis

Blood samples were collected by venepuncture (puncture site cleaned with trace element-free alcohol). The samples for zinc were collected in trace element-free tubes with removable lids. All the blood samples were collected by the investigator and were sent to the laboratory immediately after collection, protected from light and stored at –20°C after centrifugation, until analysis. All the blood samples were stored at the Medunsa branch of the National Health Laboratory Services and analysed within 3 months of collection.

Serum zinc was measured by atomic absorption spectrometry in $\mu\text{mol L}^{-1}$ (Perkin Elmer ICP/5500, Perkin Elmer Life and Analytical Sciences Inc., Waltham, Massachusetts, USA); separation from cells was conducted within 45 min. Serum iron was measured in $\mu\text{mol L}^{-1}$ (Synchron CX Systems Iron/TIBC Calibrator Kit, Beckman Instruments, Johannesburg, South Africa) by using rate spectrophotometry. Serum ferritin was measured using commercial ELISA kits in $\mu\text{g L}^{-1}$ (Access Ferritin assay, Access Immunoassay Systems, Beckman Coulter, Johannesburg, South Africa). Quality control for serum zinc, iron and ferritin was assessed by repeat analysis of standard reference material for low, normal and high values. Coefficients of variation of less than 5% were considered acceptable. Serum transferrin was measured in $\mu\text{g L}^{-1}$ using spectrophotometry (Beckman Image Immunochemistry Systems and Beckman Calibrator 1, Beckman Instruments, Johannesburg, South Africa). The C-reactive protein was measured by nephelometry using an international reference

standard for plasma proteins. CRP levels greater than 10 mg L⁻¹ were considered to be elevated. Haemoglobin was analysed on whole blood by means of an electronic coulter counter in grams per decilitre.

Appetite testing

Conditions prior to testing

The subjects were given appointments on three non-consecutive days within a period of 2 weeks. The transport costs of the children and their caregivers were reimbursed on arrival at the hospital for appetite testing. From the last meal of the day preceding the appetite test, the child was not allowed to eat any food, not even breast or formula milk, until after the appetite test (Dossa *et al.* 2002). The test was conducted early in the morning. The mothers were asked when the last meal of the child was. If for any reason the child had been fed prior to the appetite test, the mother was given another date for the appetite test.

Test food

After interviewing the mothers, it was clear that the majority of the children consumed commercially manufactured infant cereals on a regular basis. The cereal Nestlé Nestum No. 2 [Nestlé (South Africa), South Africa] was used. For each participant, 25 g of dry porridge was weighed on an electronic load cell scale to the nearest 0.1 g. The cereal contains wheat and honey. Each 100 g of the dry cereal contains 9.3 g protein, 77.9 g carbohydrates, 1.7 g fat and 5.2 g fibre, and has 1634 kJ of energy. Fresh milk was warmed to 50°C (milk container put in a bowl of boiled water, until the milk temperature reached 50°C, measured by using a metal stem thermometer), and 160 mL of this milk was added to the dry porridge and mixed to a uniform consistency. One hundred millilitres of the milk contains 3.2 g protein, 4.8 g carbohydrates and 3.8 g fat, and yields 260 kJ. The preparation of the test cereal was standardized.

Test-feeding procedures

The weight of the wet cereal was measured. An empty porcelain bowl was weighed and then the bowl with

the cereal was weighed. The test was conducted in a quiet room, with three to five mother-and-child pairs at a time. Each pair sat apart from the next, and the mothers were not allowed to communicate with each other during the test. Plastic teaspoons were used for feeding the children. The mothers were informed that the child was not obliged to finish the test food and could stop eating at anytime. The mother helped her child such that the child was eating *ad libitum*; the mother was not allowed to verbally encourage the child to eat, nor apply any kind of pressure on the child. The child was not allowed to drink water or breast milk during the appetite-testing procedure. When a child was about to complete eating, a second bowl was prepared in the same manner, and this was offered to the child to eat. When the child stopped eating, the amount eaten and the duration of the eating episode was noted. A 5-min break was then given, after which the child was invited to continue eating. The total amount eaten and the total eating duration of the eating episode were noted. The investigator supervised the feeding episodes to ensure compliance. The eating environment and utensils for each mother and child pair were standard.

Ethical considerations

The Medunsa Research Ethics and Publications Committee approved the study; the permission of the Dr George Mukhari Hospital authorities was obtained, and the parents provided signed informed consent.

Statistical analysis

Anthropometric parameters, biochemical indices, duration of hospital stay and appetite test measurements were studied by means of analysis of variance (ANOVA). Among the children admitted with pneumonia, there was interaction between the variables 'HIV status' and 'admission diagnosis' in relation to 'age'. Consequently, the ages of HIV-infected children with pneumonia were compared with uninfected children with pneumonia by using independent-samples *t*-test.

Correlation between weight-for-length *Z*-scores and chronological age, and between serum ferritin

Table 1. Anthropometric characteristics and duration of hospitalization of all the study children

	Pneumonia		Diarrhoea		All HIV uninfected	All HIV infected
	HIV uninfected	HIV infected	HIV uninfected	HIV infected		
<i>n</i>	58	71	28	35	86	106
Gender (M/F)	35/23	30/41	10/18	16/19	45/41	46/60
Age (months)	7.4 ± 5.7*	11.1 ± 6.4	11.4 ± 7.6	9.1 ± 6.8	8.7 ± 6.3	10.4 ± 6.5
WAZ	-1.02 ± 0.97*	-1.88 ± 0.83	-0.89 ± 1.02 [†]	-1.46 ± 0.76	-0.97 ± 0.99*	-1.74 ± 1.20
HAZ	-0.65 ± 1.31*	-1.72 ± 0.85	-0.71 ± 1.1*	-1.62 ± 0.88	-0.67 ± 1.24*	-1.68 ± 0.86
WHZ	-0.61 ± 1.11	-0.78 ± 0.88	-0.59 ± 1.12	-0.46 ± 0.95	-0.60 ± 1.11	-0.67 ± 0.90
Duration (days)	6.1 ± 2.1*	9.3 ± 3.0	3.8 ± 1.5*	5.9 ± 1.9	5.4 ± 1.9*	8.2 ± 2.6

HIV, human immunodeficiency virus; WAZ, weight-for-age Z-score; HAZ, length-for-age Z-score; WHZ, weight-for-length Z-score. Mean ± standard deviation (*n*). *Significantly different from the HIV-infected group ($P < 0.01$). [†]Significantly different from the HIV-infected group ($P < 0.05$).

and CRP were assessed by the Pearson correlation coefficient. Correlation between anthropometric values, serum zinc and iron concentrations, and duration of hospitalization and amount eaten per kilogram body weight were also assessed using the same method (Pearson). All statistical tests were two tailed, and *P*-values less than 0.05 were considered statistically significant.

All data analyses were performed using SPSS (SPSS Inc., Chicago, Illinois, USA) statistical package for Windows version 11.0.

Results

In total, 210 children were enrolled, but 18 refused consent for HIV testing, leaving 192 (106 HIV infected and 86 HIV uninfected) children. Of the 106 HIV infected, 71 were admitted with pneumonia and 35 with diarrhoea (see Table 1). The proportion of children admitted with pneumonia was 67%, and it was 33% for those admitted with diarrhoea. Similarly, two-thirds of the HIV-infected children had pneumonia as the admission diagnosis. The overall male-to-female ratio was 9:10. This ratio was independent of whether the children were the HIV-infected group or not and whether they were admitted with diarrhoea or with pneumonia. Of the full study population, 69% were younger than 1 year of age. ANOVA revealed a significant interaction between HIV status and admission diagnosis in relation to the subjects' ages. Age

was therefore used as a covariant in the ANOVA. It appeared that among the children admitted with pneumonia, the mean age was significantly higher in those who were HIV infected compared with the non-infected group (Table 1). The children were followed up 4–8 weeks after discharge for blood sampling and analysis, and the number of the children in the four subgroups is shown in Table 2. The data of appetite measurements were available for 50 children (Table 3).

Anthropometry

The anthropometric indices of the subjects are shown in Table 1. ANOVA showed that for all the anthropometric measurements, there was no significant interaction between HIV infection and admission diagnosis. Weight-for-age and length-for-age Z-scores were significantly lower among HIV-infected children compared with HIV-uninfected children. The admission diagnosis (i.e. pneumonia or diarrhoea) did not seem to significantly affect weight-for-age or length-for-age Z-scores. There was no significant difference in the weight-for-length Z-scores between HIV-infected and HIV-uninfected children. However, ANOVA showed a significant interaction between the subjects' ages and weight-for-length Z-scores (WHZ). Pearson's correlation coefficient showed a significant negative correlation between age and weight-for-length Z-scores ($P < 0.001$).

Table 2. Biochemical indices 4–8 weeks after hospital discharge

	Pneumonia		Diarrhoea	
	HIV uninfected	HIV infected	HIV uninfected	HIV infected
Serum zinc ($\mu\text{mol L}^{-1}$)	5.8 $\pm$ 2.9 (48)*	4.7 $\pm$ 2.8 (50)	6.7 $\pm$ 3.1 (24)*	5.3 $\pm$ 2.9 (28)
Serum iron ($\mu\text{mol L}^{-1}$)	7.0 $\pm$ 4.3 (48) [†]	5.2 $\pm$ 3.2 (51)	7.5 $\pm$ 4.4 (24) [†]	6.5 $\pm$ 4.6 (28)
Serum ferritin ($\mu\text{g L}^{-1}$)	76.5 $\pm$ 72.9 (43)	90.3 $\pm$ 83.8 (44)	67.3 $\pm$ 54.6 (25)*	143.0 $\pm$ 105.0 (26)
Transferrin (g L^{-1})	2.4 $\pm$ 0.9 (43)*	2.1 $\pm$ 1.1 (41)	2.7 $\pm$ 0.9 (19)*	2.1 $\pm$ 1.0 (25)
Haemoglobin (g dL^{-1})	10.8 $\pm$ 1.9 (50)*	9.5 $\pm$ 2.1 (47)	10.5 $\pm$ 2.0 (25)*	9.9 $\pm$ 2.0 (28)
CRP > 10 mg L^{-1} (%)	26% (26)*	35% (35)	12% (12)*	19% (19)

HIV, human immunodeficiency virus; CRP, C-reactive protein. Mean $\pm$ standard deviation (*n*). *Significantly different from the HIV-infected group ($P < 0.01$). [†]Significantly different from the HIV-infected group ($P = 0.05$).

Table 3. Appetite test 4–8 weeks after hospital discharge

	Pneumonia		Diarrhoea		All HIV uninfected	All HIV infected
	HIV uninfected	HIV infected	HIV uninfected	HIV infected		
<i>n</i>	13	17	11	9	24	26
Gender (M/F)	6/7	6/11	3/8	5/4	9/15	11/15
Age (months)	11.9 $\pm$ 4.1	14.1 $\pm$ 5.3	14.2 $\pm$ 6.3	12.0 $\pm$ 4.2	13.0 $\pm$ 5.1	13.4 $\pm$ 4.9
Weight (kg)	8.6 $\pm$ 1.8	7.9 $\pm$ 1.4	9.2 $\pm$ 1.7	8.1 $\pm$ 1.0	8.9 $\pm$ 1.8*	8.0 $\pm$ 1.3
Amount eaten (g)	190 $\pm$ 53*	153 $\pm$ 54	230 $\pm$ 99 [†]	148 $\pm$ 47	208 $\pm$ 74*	151 $\pm$ 52
Amount eaten (g kg^{-1} Bwt)	21.8 $\pm$ 7.1	18.8 $\pm$ 6.2	29.3 $\pm$ 7.8*	18.1 $\pm$ 4.9	25.2 $\pm$ 7.4*	18.6 $\pm$ 5.8
Duration of eating (min)	12.1 $\pm$ 3.2*	15.6 $\pm$ 3.0	14.9 $\pm$ 4.7	15.6 $\pm$ 3.1	13.4 $\pm$ 3.9 [†]	15.6 $\pm$ 3.0
Eating rate (g min^{-1})	16.5 $\pm$ 5.0*	10.3 $\pm$ 3.8	18.8 $\pm$ 7.7*	9.8 $\pm$ 3.4	17.6 $\pm$ 6.2*	10.1 $\pm$ 3.7

HIV, human immunodeficiency virus. Mean $\pm$ standard deviation (*n*). *Significantly different from the HIV-infected group ($P < 0.01$). [†]Significantly different from the HIV-infected group ($P < 0.05$).

Duration of hospitalization

Table 1 also provides the results of the comparison of the duration of hospitalization of HIV-infected children with that of uninfected children. The duration of hospitalization was 51% longer (9.3 days compared with 6.1 days) in HIV-infected children admitted with pneumonia as compared with non-HIV-infected children with pneumonia; this difference was significant ($P < 0.001$). Among children admitted with diarrhoea, the duration of hospital stay was 55% longer (5.9 days compared with 3.8 days) in HIV-infected children ($P < 0.001$). Children admitted with pneumonia had a significantly longer hospital stay (53% longer) compared with those admitted with diarrhoea ($P < 0.001$). The Pearson correlation coefficient also revealed a significant negative correlation between serum zinc concentrations and duration of hospitalization, and

between weight-for-age Z-scores (WAZ), length-for-age Z-scores (HAZ) and duration of hospitalization.

Biochemical indices

The biochemical indices of the subjects are shown in Table 2. ANOVA showed no significant interaction between HIV status and admission diagnosis with respect to the concentrations of serum zinc, iron and transferrin, and the haemoglobin levels. Serum zinc, iron and transferrin concentrations, and haemoglobin levels were significantly lower in HIV-infected children compared with the uninfected children. ANOVA revealed a significant interaction between HIV status and admission diagnosis in relation to serum ferritin concentrations. Independent samples *t*-test done subsequently showed no significant difference in serum

ferritin concentrations of HIV-infected and non-HIV-infected children with pneumonia; however, HIV-infected children with diarrhoea had significantly higher serum ferritin concentrations compared with non-infected children with diarrhoea. A large proportion of both HIV-infected and non-infected children were anaemic ($Hb < 11 \text{ g dL}^{-1}$), 75% in HIV-infected children and 58% in HIV-uninfected children. ANOVA revealed that HIV-infected children had significantly higher CRP levels independent of admission diagnosis ($P < 0.05$). The percentage of children with CRP levels less than 10 mg L^{-1} among HIV-infected and HIV-uninfected children was 30% and 21%, respectively. Pearson's correlation coefficient showed a significant positive correlation between serum ferritin and CRP levels ($P < 0.01$).

Appetite test

The total intake of the test food eaten, the amount of test food per kilogram body weight, the eating duration and the eating rates are shown in Table 3. The amount of test food eaten was significantly lower in HIV-infected children compared with those who were uninfected. The duration of eating was significantly longer in children who were HIV infected than in the uninfected ones. ANOVA revealed that the amount of test food eaten per kilogram was 26% lower (statistically significant), and the eating rate was significantly lower in HIV-infected children compared with uninfected children, independent of the admission diagnosis. The admission diagnosis (pneumonia or diarrhoea) did not significantly affect the eating duration, eating rate or the amount eaten per kilogram body weight. The Pearson correlation coefficient also revealed a negative correlation between serum zinc concentrations and amount eaten per kilogram body weight, and between WAZ, HAZ and amount eaten per kilogram body weight, but these were not statistically significant.

Discussion

The objective of this study was to study the duration of hospital stay, appetites and nutritional status of HIV-infected South African children compared with

uninfected children. The length of hospital stay was significantly longer in children infected with HIV compared with those who were not infected. The appetites of HIV-infected children were significantly poorer than the non-infected children. The children with HIV infection were significantly more stunted, but not more wasted, compared with the uninfected ones. The micronutrient status of the children infected with HIV was poor compared with those who were uninfected.

Considering the objectives of the study, it was important to adequately define HIV-infected children in distinction to HIV-uninfected children, and this was done by the ELISA test and PCR as described in the Subjects and Methods section. However, within the group of children who were HIV infected, clinical and immunological staging of the HIV disease was not done. It is recognized that the outcome of the study could have been affected by the stage of HIV.

Approximately 55% of the study children were HIV infected; this is in keeping with the proportions observed at the hospital. There were more females than males among the subjects, and in the HIV-infected group of children, the proportion of females was also higher. However, there was no significant association between the gender of the child and whether the child was HIV infected or not. There was also no association between the gender of the children and whether they were admitted with diarrhoea or pneumonia, therefore the results of boys and girls were combined. HIV-infected children admitted with pneumonia were significantly older than HIV-uninfected children. This is thought to be as a result of the fact that diarrhoea and pneumonia occur more commonly in infants than in older children (Kosek *et al.* 2003; Zar *et al.* 2005). However, HIV-infected children remain vulnerable to these diseases for a longer period than the uninfected children, such that HIV-infected children with pneumonia or diarrhoea may on average be older than uninfected children. This may explain the age difference that we noted in the current study. Certainly, other authors have made a similar observation; a study performed on Ugandan children younger than 18 months admitted with sepsis noted that the median age of HIV-infected subjects

was higher than that of uninfected subjects (Bakaki *et al.* 2001). This was also noted in a group of HIV-infected children (aged 2 months–5 years) admitted with severe lower respiratory tract infection to a hospital in Johannesburg, South Africa, where the median age of HIV-infected children was significantly higher than that of uninfected children (Madhi *et al.* 2000a).

The duration of hospital stay was approximately 53% longer among HIV-infected children, compared with uninfected ones. Among children admitted with diarrhoea, those with HIV infection had a 55% longer hospital stay. Similarly, in the group of children admitted with pneumonia, it was 53% longer. The difference in duration of hospitalization of 2–3 days is also considered to be clinically significant. The longer duration of hospitalization among HIV-infected children is consistent with the findings of a number of studies. A study conducted in the United States, which evaluated a database that accounted for approximately 73% of all US hospital discharges of children in 2000, revealed that HIV-infected children had longer mean hospital stays (7.8 days vs. 3.9 days), when compared with HIV-uninfected children (Kourtis *et al.* 2006). South African studies have reported similar results. In Johannesburg, HIV-infected children admitted to a tertiary hospital had a 33% longer hospital stay (Meyers *et al.* 2000). Likewise, HIV-infected children who were admitted to hospitals in Cape Town and Johannesburg with lower respiratory tract infection had a longer duration of hospitalization than HIV-uninfected children (7–14 days compared with 6–10 days) (Madhi *et al.* 2000b; Zar *et al.* 2001). In the same way, the median duration of hospital stay was 8 days for HIV-infected children admitted to a hospital in Johannesburg with diarrhoea, as opposed to 3 days for HIV-uninfected children with diarrhoea (Johnson *et al.* 2000).

Children with HIV infection had significantly lower appetites compared with uninfected children in this study. This was in terms of total amount eaten, duration of eating episodes and eating rate, and was independent of the admission diagnosis. The total amount of test food eaten was 26% lower in the group of children who were HIV infected, compared with those who were uninfected. The children

who were infected with HIV also ate significantly less per kilogram body weight than the uninfected children. The amount eaten per kilogram body weight was 15%–20% lower in the HIV-infected group of children. The HIV-infected children took longer to complete eating the smaller amount of test food, and this resulted in an eating rate that was 60% slower than that of the HIV-uninfected children. The *ad libitum* consumption of the test food was used as a proxy for measuring appetite in this study. This appetite test has been validated as an appropriate tool in appetite evaluations (Dossa *et al.* 2002). However, it is recognized that there may be other reasons contributing to reduced food intake in HIV-infected children. Oropharyngeal candidiasis is known to be common in HIV-infected children (Pol *et al.* 2007), and this may lead to painful swallowing and thus reduced food intake. The proportion of children with oropharyngeal candidiasis was not assessed in this study. Reduced energy intake is thought to be common in HIV-infected children, and this reduced energy intake is thought to play a major role in the poor growth of HIV-infected people (Macallan *et al.* 1995). A study comparing HIV-infected American children with growth failure (growth velocity $\leq$ 5th percentile for age) with HIV-infected children without growth failure noted that the mean age-adjusted energy intake per day was significantly lower in the group of children with growth failure (Arpadi *et al.* 2000). Because of a lack of similar studies in young HIV-infected children, the results of the appetite test cannot be compared. Nonetheless, we believe that the poor appetites in HIV-infected children in our study were adequately demonstrated.

The weight-for-age and length-for-age Z-scores of the HIV-infected children were significantly poorer than that of uninfected children. However, there was no significant difference in the weight-for-length Z-scores. Our finding that length-for-age Z-scores were significantly lower among HIV-infected children compared with the non-infected children was consistent with other studies that have suggested that stunting is frequently an early finding in perinatal HIV infection. Bobat *et al.* (2001) observed a cohort of children born to HIV-infected South African women

and noted that by 3 months of age, the children who were HIV infected were significantly more stunted, but not more wasted than those who were not HIV infected. The poor weight-for-age Z-scores and stunting that occurs in these infants may be related to poor intrauterine growth as a result of poor maternal nutrition. Nonetheless, there are post-natal causes of stunting as well, including decreased energy intake (Arpadi *et al.* 2000), nutrient malabsorption (Knox *et al.* 2000) and increased resting energy expenditure per kg of fat-free mass (Batterham 2005). We may assume that the weights and lengths will be similarly affected by the poor maternal nutritional status, such that wasting is not evident in the first few months of life. However, as the child's own immunological status deteriorates, wasting may then ensue. Maternal nutritional status before and during gestation is thought to be one of the strongest determinants of pregnancy outcomes (Villamor *et al.* 2002). Pregnant HIV-infected women have been observed to be at higher risk than those who are not infected of intrauterine growth retardation and having low-birthweight babies (Iroha *et al.* 2007). Poor maternal weight, advanced-stage HIV disease and intrauterine HIV transmission were identified as significant determinants of having a low-birthweight baby in a group of pregnant HIV-infected Tanzanian women (Dreyfuss *et al.* 2001). The assertion that wasting is likely to be a late finding among children with HIV infection is supported by a study conducted among pregnant HIV-infected women in the Democratic Republic of Congo (DRC). In this study from the DRC, it was shown that when compared with pregnant HIV-uninfected women, the children of the HIV-infected women were significantly more stunted by 3 months of age, while they only became significantly more wasted by 12 months of age (Bailey *et al.* 1999). In our study, there was no significant difference in weight-for-length Z-scores between HIV-infected and uninfected children.

In the current study, the zinc and iron status of HIV-infected children was significantly poorer than that of uninfected children. Similar findings have been observed in a number of studies. Low concentrations of plasma zinc have been noted to be highly prevalent in HIV-infected female drug users (Baum *et al.* 2003).

Micronutrient deficiencies were also noted to be widespread in stable HIV-infected South African children (Eley *et al.* 2002a). Anaemia has also been shown to be common in HIV-infected children; another study from Cape Town, South Africa, indicated that 72% of HIV-infected children were anaemic (Eley *et al.* 2002b). The factors that result in micronutrient deficiencies in HIV-infected subjects include the following: (1) decreased intake of micronutrients as a result of poor appetite, central nervous system disease and dysphagia; and (2) diarrhoea and malabsorption of micronutrients, and altered metabolism with increased utilization of the micronutrients. These factors have been well described in the review by Semba & Tang (1999).

Micronutrient deficiencies are known to be associated with increased severity of infectious diseases, especially diarrhoea and respiratory tract infections (Bloem *et al.* 1990; Bahl *et al.* 1998). Deficiencies of micronutrients have also been observed to be associated with poor growth. This has been elucidated by a review by Rivera *et al.* (2003), which noted that there is strong evidence for the contribution of micronutrients to growth faltering, in particular deficiencies of zinc, vitamin A and iron. The longer duration of hospitalization observed in the current study is thought to be in part related to the poor nutritional status (anthropometry and micronutrient status) of the HIV-infected children. Indeed, we did show a significant negative correlation between anthropometric data (WAZ and HAZ), serum zinc concentrations and the duration of hospital stay. Micronutrient deficiencies, in particular zinc deficiency, have been associated with poor appetite (Baum *et al.* 2000). Moreover, zinc supplementation has been shown to significantly improve appetite in infants (Umeta *et al.* 2000). The poor growth observed in these children is thought to be partly related to reduced energy intake, which is influenced by appetite.

Results from this study show that children with HIV infection have a longer duration of hospitalization and were noted to have poorer appetites than the control group. The nutritional status of HIV-infected children as measured by growth and micronutrient status was significantly poorer than that of non-infected children.

A holistic approach is needed in the potential interventions in HIV-infected children. Potential interventions include early introduction and scaling up of antiretroviral therapy, focusing on appetite and food intake and possibly micronutrient supplementation. Future research will indicate whether improving the dietary intake of HIV-infected children and/or supplementation with multi-micronutrients will improve the nutritional status of these children.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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