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Review Article

Outcome of Severely Malnourished HIV Infected And uninfected Children in Mwanamugimu Nutrition Unit in Uganda

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Keywords

- Malnutrition
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Abstract

Background: The prevalence of severe malnutrition among people under five years of age worldwide is 11% and 7% in Uganda, while the prevalence of HIV infection among these children is high (29-48%).

Objectives: To establish the pattern of weight gain and duration of hospital stay among severely malnourished HIV-infected and uninfected individuals admitted to the Mwanamugimu Nutrition Unit (MNU).

Methods: A cohort of severely malnourished children was followed at MNU-Mulago Hospital until death or discharge. HIV tests, blood and urine cultures, and electrolyte and chest X-ray analyses were also performed. Children received standard management of severe malnutrition.

Results: Fifty-two of the 140 children (37.1%) were HIV positive. The overall mean weight gain in the MNU group during the study was 11.73 g/kg/day. HIV-infected children gained weight poorly (9.300 g/kg/day, SD = 6.66; 12.77 g/kg/day, SD = 7.40) for HIV negative patients (p = 0.023). Urinary tract infection associated with convulsions was a predictor of poor weight gain (p = 0.006). Oral thrush (p=0.003) and marasmus (p=0.04) were associated with prolonged hospital stays. Mortality was greater among HIV-infected children (RR = 2.940, CI 1.53–9.42, p=0.003).

Conclusions: HIV positive children gained weight poorly and had higher mortality than HIV negative children did. Given the high prevalence of HIV and the excess mortality, severely malnourished children, through their caretakers, should be offered voluntary counseling and testing for HIV.

ABBREVIATIONS

ACU: Acute Care Unit; AIDS: Acquired Immune Deficiency Syndrome; ART: Antiretroviral Therapy; CD4/CD8: Cluster of differentiation four/eight; CFR: Case Fatality Rates; CMI: Cell Mediated Immunity; CI: Confidence Interval; DNA PCR: deoxyribonucleic acid polymerase chain reaction; F-100: high energy diet; F-75: Low Protein Diet; HIV: Human Immunodeficiency Virus; MNU: Mwanamugimu Nutritional Unit; NCHS: National Center for health Statistics; OR: Odds ratio; PEM: Protein-energy Malnutrition; PCP: Pneumocyctis carinii pneumonia; PI: Principal Investigator; PIDC: Pediatric Infectious Disease Clinic; RR: Relative Risk; SD: Standard Deviation

INTRODUCTION

Malnutrition remains a global challenge among children and pregnant women. Approximately 150 million people under five years of age are stunted, and nutritional disorders contribute to 4.2% of the global burden of disease [1-3]. The prevalence of severe malnutrition worldwide is approximately 11%, and more than 20 million of these individuals are children [4,5]. Over 10.9 million deaths occur annually during the last few years in developing countries, 55% of which are due to malnutrition with kwashiorkor case fatality rates ranging between 20 and 30% [6,7].

In Uganda, severe malnutrition is among the leading causes of childhood morbidity and mortality. Malnutrition is an underlying cause of 40% of these deaths, and 7% of these individuals are under-fives and have severe forms of malnutrition [8]. Severe malnutrition contributed to 4.4% of all pediatric admissions in 2003 at Mulago Hospital, and 80% of the patients were under-fives with predominantly more marasmus than kwashiorkor [9-11].

An estimated 2000 children younger than 15 years of age became infected with human immunodeficiency virus (HIV) daily, and more than 5 million infections occurred worldwide during 2003, more than 95% of whom were in sub-Saharan Africa. The prevalence of HIV in Uganda is approximately 6.2% for all ages, and approximately 1.1 million people live with HIV [12]. At Mulago Hospital, 29-44% of severely malnourished children have HIV infection [13].

HIV infection contributes to slow recovery and high mortality among severely malnourished children [14]. HIV infection often presents with recurrent infections and failure to thrive, leading to growth failure and severe malnutrition [15,16]. Severe clinical malnutrition is classified by the WHO as advanced HIV disease stage IV and is associated with early death in children [16,17]. Several studies have shown that marasmus is more likely to be HIV-related than kwashiorkor [18-20].

In this study, the WHO classification of malnutrition was adopted. Weight-for-height is a measure of wasting, and severe wasting occurs if the value is <-3 SD from the reference population, usually due to malnutrition [21]. Weight-for-height was found to be the weakest predictor of death in malnourished children [11,22].

Perinatally acquired HIV infection is commonly associated with growth failure in children, which presents as stunting that begins early in life [16,23]. Growth failure in children perinatally infected with HIV might be an indicator of rapid disease progression. Studies have demonstrated a slower weight velocity in HIV-1-infected children than in HIV-1-uninfected children [23-25]. Earlier African studies reported seroprevalence rates ranging from 14-48.6% [15,18,19,26] among children. Researchers in Zambia and Côte d'Ivoire found that children admitted with severe malnutrition are more likely to be infected with HIV than children with other diagnoses [27,28]. This high prevalence of HIV infection among severely malnourished children emphasizes the burden of HIV on childhood nutritional morbidity and mortality. Severe malnutrition is usually the final manifestation of AIDS. Severe wasting is a recognized feature of AIDS and has been observed to be associated with high morbidity and mortality [14,16,29].

Protein-energy malnutrition (PEM) has been identified as the most frequent cause of acquired immunodeficiency in children under-five [30]. It has been shown that malnutrition has deleterious effects on cellular immune competence [31], but humoral immune competence mediated by B-lymphocytes has been reported to be unaltered [32]. Altered cell-mediated immunity (CMI) in PEM has important implications, including increased susceptibility to infection and false negative skin hypersensitivity test results. The pathogenesis of such marked depression of the cell-mediated immune response is attributed to thymic and lymphatic atrophy [30,33,34], increased levels of cortisol in the circulation and decreased protein synthesis [30]. Hypoalbuminemia and hypoglycemia increase physiologically active unbound cortisol in blood which, either by direct effects or through gluconeogenesis, leads to thymolymphatic involution and subsequent CMI [34]; and the role of macrophages cannot be underscored [35]. Apart from antigen presentation to T cells, macrophages produce interleukin-1 (IL-1) or lymphocyte activation factor, which provides a maturational signal to primed T lymphocytes, leading to the elaboration of interleukin-2 (IL-2). Interleukin-2 amplifies the cell-mediated immune response. IL-1 activity is lower in children with PEM than in well-nourished children. HIV has been found to play a significant role in the slow recovery of CMI among severely malnourished children, particularly those with marasmus, compared to HIV negative children [19].

Inadequate protection from peroxidation due to deficiencies of vitamins, trace elements, enzymes and amino acids causes widespread biochemical and structural damage. This causes leaky membranes (edema), mitochondrial damage with impaired protein synthesis or accumulation of glycerides (fatty liver) and skin damage (dermatitis) [36]. Cellular glutathione is reduced in severe malnutrition, leading to alteration of the sodium-potassium pump, causing increased leakiness of cell membranes. This is responsible for hyponatremia and hypokalemia in severe malnutrition, especially in patients with kwashiorkor [37]. Diarrhea is commonly associated with weight loss. The lining of the intestines is a reservoir for HIV that interferes with the absorption of sugars and fats and subsequently leads to weight loss. Stress increases cytokine release in severe malnutrition. HIV-related tumor necrosis factor (TNF-α) interferes with fat metabolism, leading to wasting. HIV-related weight loss is also associated with increased production of cytokines such as IL-1 and interleukin-6 (IL-6), which cause inflammation and interfere with metabolism. The chronic nature of HIV significantly manifests more as marasmus than as kwashiorkor [18-20]. Clinical improvement and weight gain velocity are faster in HIV negative malnourished children than in their HIV positive counterparts. A European Collaboration Group study [24], revealed that there was a small difference in weight and height velocity between HIV-infected and HIV negative children.

Severe malnutrition is a risk factor for childhood mortality, particularly in developing countries. A total of 36.2 - 56% of childhood mortality is attributable to severe malnutrition [38,39]. Studies in Africa show similar trends of mortality in malnourished children as in other developing countries [40,41]. High mortality among hospitalized severely malnourished children is very common within the first week of admission and is usually associated with liver failure, over-hydration [42] infection, dehydration, and lack of interest by health workers [38]. Vella found in Uganda, a mortality rate of 10% in the first year of life, 3.1% in the second year of life, 4% in the third year of life and 0.5% thereafter [11]. Research in Mulago Hospital indicates a 20% mortality among HIV infected malnourished children [43,44].

Case fatality rates (CFR) are significantly greater for HIV-infected malnourished children (38.4%) than for HIV negative children (22.7%) [45]. Immunosuppression of HIV infection

together with severe malnutrition increases the risk of septicemia, especially due to gram-negative organisms [13,40]. However, Ticklay in Zimbabwe found no significant difference in CFR among HIV-infected severely malnourished children [46]. Studies have shown that perinatally acquired HIV infection is associated with early and progressive growth failure [16] and is associated with an increased risk of death in the first year of life compared to birth to HIV negative mothers [16,29,47]. Pulmonary tuberculosis, like HIV, is a major cause and outcome of severe PEM in children, and the strong epidemiological relationship between pulmonary tuberculosis and adult pulmonary tuberculosis puts contact with children at increased risk of both disease and death [48].

Successful management of malnutrition involves identifying and correcting both medical and social problems. All severely malnourished children were managed in the hospital. The WHO recommends three phases of management for severely malnourished children: the initial or stabilization phase begins with child admission to the hospital and starts with the standard F-75 diet for edematous malnutrition and F-100 for marasmus. Mortality is highest during this phase. The rehabilitation phase follows improved appetite and disappearance of edema. The child was advised to gain a weight >5 g/kg/d for 3 consecutive days. F-75 was replaced by F-100, and the child was fed a locally friendly diet to maintain a weight gain of 10-15 g/kg/day, as recommended by the WHO.

Weight gain is the most sensitive indicator of recovery from severe PEM [49]. Other outcome measures included good eating habits, improved mental status, resumption of motor activity, and disappearance or absence of diarrhea or vomiting. The overall duration of stay in the ward was also assessed.

Khanum, among inpatient children aged 12-60 months on a standardized diet in Dhaka, reported a mean weight gain of 11 g/kg/day compared to 6 g/kg/day and 4 g/kg/day for those managed on day care centers and at home, respectively. The median times to achieve 80% of weight-for-height for inpatients, day care and at home were 18, 23 and 35 days, respectively [50]. Hone & Fermor demonstrated a weight gain between 6.39 and 12.11 g/kg/day (mean of 8.93 g/kg/day) among children with severe PEM on a standardized diet of 150 kcal/kg/day. Landman demonstrated that individuals who consumed high-energy milk 150–250 kcal/kg/day earlier, showed an average weight gain of 6.9 g/kg/day [51].

This study was designed to determine the pattern of weight gain and duration of hospital stay among severely malnourished HIV-infected and uninfected children younger than 60 months admitted to the Mwanamugimu Nutrition Unit (MNU) and to describe the clinical characteristics of these children.

MATERIALS AND METHODS

Study sample

A prospective cohort study was carried out in the Acute Care Unit (ACU) and MNU of Mulago Hospital. The ACU is the pediatric emergency admission unit of the hospital. Very ill children up to the age of 12 years are admitted to the ACU, which includes severely malnourished children, for one day under close observation and intensive management. The patients were reviewed the next morning by the principal investigator (PI) to decide whether they could be transferred to other pediatric wards or discharged if in stable condition. At least two doctors stay in ACU throughout the night. The ACU receives patients from the assessment center or referrals from other hospitals in Uganda, as well as health units in and around Kampala city. The MNU is a 60-bed ward designed for the management of children with severe malnutrition. Children identified in the ACU with severe PEMs are transferred to the MNU for management. The daily admission to the MNU on average ranges between two and nine patients with variations throughout the year.

Selection criteria

Patient definition: Patients younger than 60 months who were admitted to Mulago Hospital within the study period and had severe malnutrition and were either HIV positive (proved to be by rapid HIV test or DNA PCR for children < 18 months) or HIV negative. A severely malnourished child is defined as one whose weight-for-height is less than –3 SD or less than 70% of the median NCHS/WHO reference values (severe wasting) or who has edema of at least both feet.

1. **Inclusion of the exposed group (HIV pos**Children younger than 60 years who presented to the MNU during the study period with a Z score weight for height < -3 SD or with edematous malnutrition and were tested positive for HIV by rapid HIV test for children > 18 months or DNA PCR for children < 18 months.

2. The children whose caretakers gave informed consent to the study and accepted an HIV test or provided credible evidence that it has been done and was HIV positive.

Inclusion of the unexposed group (HIV negative)

1. Children younger than 60 months were admitted to Mulago Hospital with severe malnutrition, but HIV negative results were tested by rapid HIV test for children > 18 months or DNA PCR for children < 18 months.

2. The children whose caretakers provided informed consent to participate in the study agreed to participate and accepted an HIV test or provided credible evidence that it was done and was negative.

Exclusion: Children with congenital abnormalities associated with failure to thrive.

Sample size: The minimum sample size was 138 patients.

Data collection

The study instrument was a precoded, pretested questionnaire. It was written in English but translated and

administered in Luganda (local dialect). The PI or his assistants administered the questionnaire. The sampling was performed by consecutive enrollment of the children who fulfilled the inclusion criteria until the minimum sample size was obtained. The triage nurse in the ACU urgently called for the research assistant or the PI, who identified severely malnourished children consecutively. Either the research assistant or the principal investigator carried out a quick general assessment, which included weight, height, the presence of visible severe wasting and edema. Any complications of severe malnutrition were identified, including severe anemia, dehydration or shock and signs of severe infection. Emergency resuscitation was performed for those children who were seriously sick. All identified children were stabilized in ACU for one day before transfer to MNU.

The purpose of the study was explained to the caretakers, and informed consent was obtained for participation in the study during the stabilization phase. A trained counsellor provided HIV counseling to the caretakers of the children and obtained HIV test consent. A sample of blood was obtained for rapid HIV testing and other tests, including CD4/CD8 counts to determine the immunological status of HIV positive children, full blood count, and serum albumin and electrolyte levels. For children younger than 18 months with a positive Rapid HIV test, a sample of blood was taken for confirmatory DNA PCR. Posttest counseling was provided as soon as results were obtained.

Recruitment of the participants into the study began in the initial phase after obtaining the results of the rapid HIV test and when patients were being stabilized.

All severely malnourished children with a positive Rapid HIV test (for those older than 18 months) and a positive DNA PCR (for those younger than 18 months) whose caretakers provided consent were exposed (HIV positive) participants recruited for the study. All severely malnourished children ≥ aged 18 months with a negative rapid HIV test plus those younger than 18 months with negative DNA PCR were unexposed (HIV negative) participants. Both groups were followed up for weight gain while on a standard diet, until discharge or for 30 days. All severely malnourished children who did not meet the inclusion criteria were not recruited for the study but provided routine care.

Urine was collected in a sterile container, and urinalysis, including microscopy and culture, was performed.

The children included had chest X-rays taken and read by one radiologist.

Each child was then transferred to MNU and started on a standard diet. Treatment for each recruited child was administered according to the standard protocol of the Ministry of Health (MOH) guidelines, which are modifications of the WHO guidelines. Children with edematous malnutrition first received a low-energy, low-protein diet (F-75) calculated according to body weight at 2-hour intervals until their appetite improved, edema disappeared, and weight gain began. The participants were then fed a high-energy diet (F-100) at 3-hour intervals. Children with marasmus started on high energy on the first day unless they had persistent diarrhea. Multivitamin and vitamin A supplements and folic acid and zinc gluconate were given on the first day. Parenteral antibiotics were started on children with septicemia.

All children found to be HIV positive were referred to the pediatric infectious disease clinic (PIDC) for appropriate management. Any children already receiving antiretroviral therapy were recruited for the study and followed up.

Follow-up started after the stabilization phase when the patients were expected to start gaining weight, when a weight-for-height ratio of 85% was reached, or after up to 30 days. The following parameters were recorded daily: weight (kg), temperature, presence of edema and appetite. Discharge from the hospital was 85% of the patient's weight at height gain. The outcome measures included edema-free weight gain (in g/kg/day), duration of hospital stay (in days), loss to follow-up and mortality for both HIV positive and HIV negative children.

Study variables

Clinical history: The principal investigator (PI) or his assistants took the history using open-ended questions. The demographic characteristics, dietary history, previous or present illnesses, and immunization status were also recorded.

Clinical examination: Axillary temperature was recorded in degrees Celsius using a digital thermometer (Microlife Corporation CH-9442 Bermeck Switzerland). The PI or his assistants took the weight of the children with a salter-weighing machine to the nearest 0.1kg. The weighing machine was checked weekly and calibrated daily with standard weights. All the children were weighed naked for accuracy. Children who were younger than 24 months, less than 85 cm tall or too ill to stand had their length (heel-to-crown) measured to the nearest 0.5 cm while lying down using a stadiometer. The heights of those who were 24 months or older, 85 cm or taller and were able to stand were measured using a wall scale calibrated locally. The child was made to stand with heels against the wall, feet flat on the floor and a horizontal board placed against the head. The PI or his assistants performed general and systemic examinations to assess anemia, wasting, skin changes, dehydration, edema, oral candidiasis, and organ failure.

Laboratory investigation: These included HIV screening (DNA PCR test was performed for confirmation among children younger than 18 months), CD4 and CD8 levels, complete blood counts (using a Coulter counter machine and the Westergren method for determining the erythrocyte sedimentation rate), blood cultures (reported by a microbiologist), urine analysis (microscopy, protein and culture), and serum albumin and electrolytes. Every child had a chest x-ray which was reported on by a senior radiologist.

Management

Patient management: All children recruited in this study

were managed according to standard up to date MOH guidelines for the management of severe malnutrition.

Outcome measures: The main outcome measure was edema-free weight gain in both HIV positive and HIV negative children. Secondary outcomes included duration of hospital stay, loss to follow-up and mortality. Discharge was determined by attaining 85% of the expected weight for height.

Data Management and Analysis: All the completed questionnaires were cross-checked at the end of each day for completeness. The PI securely kept these in a lockable cabin to ensure confidentiality and data safety. At the end of collection, the data were entered into a computerized database using Epi-info 6.04 and analyzed by a statistical package for social sciences. The analysis was performed with the help of a statistician. The results are presented as tables, graphs and pie charts.

The data were grouped into two groups: HIV-infected and HIV-uninfected severely malnourished children. Comparisons of variables were performed for the two groups. The means, medians and standard deviations were calculated. Continuous variables such as the mean weight gain (g/kg/day) and mean hospital stay (days), were analyzed using Student's t test. Categorical data (such as age and differences in rates) were grouped and analyzed using the chi-square test or Fisher's exact test. Odds ratios (ORs) or relative risks were calculated with 95% confidence intervals (CIs) and used to measure the strength of association between predictor and outcome variables. A p value < 0.05 was considered to indicate statistical significance.

Quality control: The following criteria ensured the internal validity of the study: The questionnaire was pretested, and any improvements were made before it was put to use to minimize errors. The completed questionnaires were cross-checked before the investigator left the ward at the end of each day. All the children were weighed naked.

The weighing machine was calibrated daily and checked weekly with standard weights by the investigator. Selected laboratory technicians were used for consistency and to avoid interobserver error. The raw data were securely stored to maintain confidentiality and to ensure that no data were lost during the study. Coinvestigators underwent training before the data collection commenced. The questionnaire, though written in English, was translated into, and administered in the local language (Luganda dialect), which is commonly spoken at the study location.

Ethical considerations: Permission to carry out the study was obtained from the Department of Pediatrics and Child Health, the Makerere University College of Health Sciences Research Committee and the Uganda National Council for Science and Technology. Informed consent was obtained from the parents/caretakers of the children before they participated in the study after they were provided an explanation of the language they understood, the nature of the study, the potential risks and benefits to the child and the effects on the community. The parents/caretakers of the children endorsed their signatures or thumbprints in the presence of a witness. Confidentiality was observed throughout this study. A trained counsellor carried out pretest and posttest counseling for all parents/caretakers whose children had HIV tests. All the children who were found to be HIV positive were referred to the PIDC for further management. All children with a CD4 percentage of 15% or less were considered for antiretroviral therapy (ART) at the PIDC. Withdrawal from the study at any time was an option for those who so desired without penalty or affecting the treatment given to their children.

Limitations

1. Blood glucose levels were not measured due to cost since serial tests were needed.
2. Only one radiologist reported the chest X-rays, which could have caused bias in the diagnosis.
3. No postmortem imaging was performed on the patients who died, which could lead to an incorrect impression of the cause of death.
4. The children were followed up for only 30 days, which could have affected the average duration of stay.

RESULTS AND DISCUSSION

Background characteristics

The number of children admitted through ACU to all pediatric wards in Mulago Hospital from the 22nd of November 2004 to the 5th of March 2005 was 6470. Among these patients, 320 (4.9%) had severe malnutrition and were admitted to the MNU.

One hundred forty severely malnourished children were enrolled in this study (Figure 1). Seventy-six (54.3%) of the children were males, and 64 (45.7%) were females, for a male-to-female ratio (M: F) of 1.2:1. Forty-seven (33.6%) were first-born children, and the rest were of other birth orders. Only 55 (39.3%) children were reportedly fully immunized, 83 (59.3%) were not complete, and 2 (1.4%) were not known. Only 57 (40.7%) caretakers had child health cards. Seventy-four (52.9%) of the children were from Kampala suburbs, whereas 66 (47.1%) were from surrounding districts, particularly Wakiso, Mpigi, Mukono and Luwero.

None of the caretaker characteristics were significantly associated with HIV infection (p >0.05) (Table 1). Most of the caretakers for the children were mothers (n=123; 87.9%), whereas only 17 (12.1%) were cared for by others; these included fathers, grandmothers and aunties. Eighty caretakers (57.1%) were married, and 60 (42.9%) were single. The age of the patients ranged from 3–59 months, with the majority being younger than 24 months.

The number of patients markedly decreased from 25-59 months. The mean age of the HIV positive children was 18.62 years (SD=12.77) older than that of the HIV negative children,

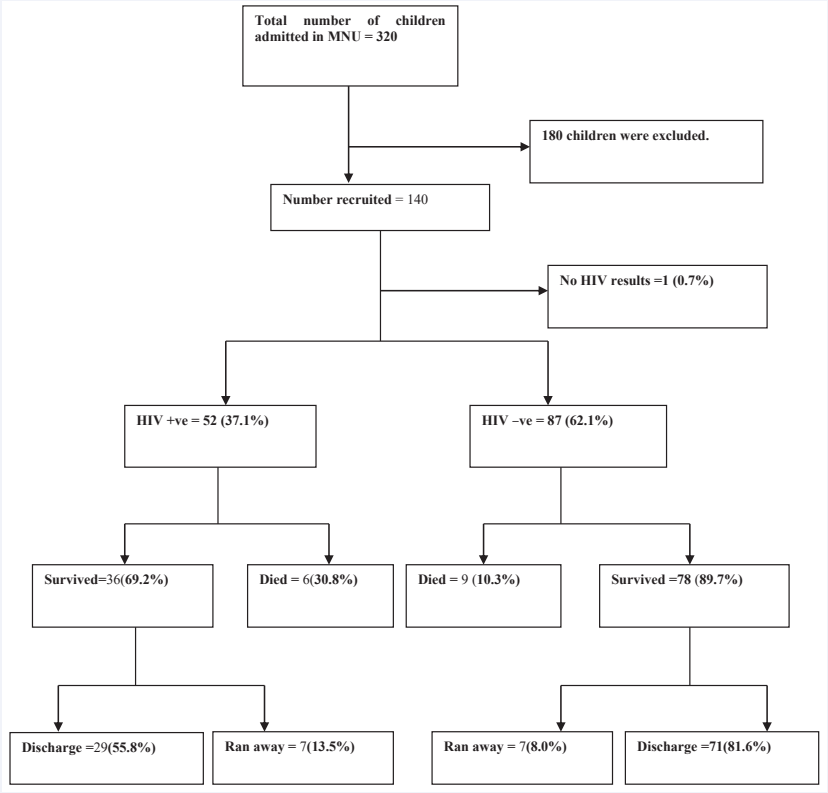

Figure 1 Client Flow Chart

Table 1: Associations between Caretaker characteristics and HIV status

Characteristic		HIV +ve N=52(%)	HIV –ve N=87(%)	OR	95%CI	P value
Sex:	Female Male	48 (92.3) 4 (7.7)	82 (94.3) 5 (5.7)	1.367	0.350-5.336	0.728
Relationship	Mother Other	47 (90.4) 5 (9.6)	76 (87.4) 11 (12.6)	1.361	0.445-4.161	0.588
Marital status[#]	Married Not married	27 (51.9) 25 (48.1)	53 (60.0) 34 (39.8)	0.727	0.364-1.453	0.366
Mother alive:	Yes No	49 (94.2) 3 (5.8)	86 (98.8) 1 (1.2)	0.194	0.020-1.921	0.153

Abbreviations: N: number of participants; OD: odds ratio; CI: 95% confidence interval; HIV +ve: HIV positive test result; HIV -ve: HIV negative test result; [#]caretaker marital status

with a mean age of 14.69 years (SD=8.197). The difference was not statistically significant (p =0.051). On admission, HIV positive children had a significantly lower mean weight-for-age Z score (-3.992; SD=0.954) than did their HIV negative counterparts (-3.524; SD=1.434) (p =0.038). The weight for height Z score was lower in HIV positive children (-3.085; SD=0.857) than in the HIV negative (-2.500; SD=1.061) (p =0.001).

A weight for height Z score <-2 SD, a measure of wasting, was more common among children with HIV infection than among those without (OR=3.091 [95% CI 1.173-8.149]; p=0.018). There were two and a half more HIV-infected children than HIV negative children (OR=2.593 [95% CI 1.275-5.271]; p=0.008). The prevalence of stunting and underweight was not significantly different between HIV positive and HIV negative children (Table 2).

HIV status among severely malnourished children

Of the severely malnourished children enrolled in the study, 52 (37.1%) were HIV positive, while 87 (62.1%) were HIV negative. One patient (0.7%) had no HIV test results. Twenty-eight (36.8%) of the males were HIV positive, whereas 25 (39.2%) of the females were HIV positive.

Marasmus was more likely to be associated with HIV infection in severely malnourished children than edematous malnutrition was (p=0.037). Among those with edematous malnutrition, the marasmic-kwashiorkor type was equally distributed among HIV-infected and uninfected children. Kwashiorkor was significantly more prevalent among HIV negative children than among HIV positive children (p=0.012). HIV infection is chronic and manifests over time as marasmus. Kwashiorkor, on the other

hand, is an acute form of severe malnutrition that manifests at a later age and often results in initially less stunting and better nourished children, precipitated by cessation of breastfeeding or sudden food shortage or deprivation.

The age group most affected by HIV infection was 13–24 months, which was markedly reduced from 25–59 months. This trend is the same as that for the prevalence of severe malnutrition. Although the incidence of HIV was reduced in children aged 25 months and older, the number of HIV positive children was significantly greater than the number of HIV negative children.

Clinical characteristics of severely malnourished children

Persistent diarrhea (lasting > 2 weeks), chronic cough (lasting >2 weeks) and persistent fever (for more than 1 month) were more prevalent among the HIV-infected children than among the HIV-uninfected children (Table 3).

Forty-one children (78.8%) who presented with diarrhea were HIV positive, whereas 54 (62.1%) were HIV negative (predictive value = 43.2%), and the difference was statistically significant (OR=2.278 [95% CI 1.030-5.039]; p=0.040). Cough was also more prevalent in 42 (80.8%) HIV-infected children than in 56 (64.4%) HIV negative children, with a predictive value = 42.9%. This difference was statistically significant (OR=2.325 [95% CI 1.027-5.265]; p=0.040). Children with a history of oral thrush were more likely to be HIV positive (32; 62.7%) than HIV negative (27; 31.8%). The difference was statistically significant (OR=3.618 [95% CI 1.746-7.4.496]; p=0.002). The number of children who were febrile with a temperature ≥ 37.5^{0}C was significantly greater for HIV-infected children (OR=2.269 [95% CI=0.138-2.418]; p=0.030). The other clinical features were not significantly different between the 2 groups.

Eleven (7.9%) patients had chest X-rays highly suggestive of pulmonary tuberculosis, and all of them were started on anti-tuberculosis drugs. Four (2.9%) patients had evidence of consolidation pneumonia. Twenty-six (19%) of the children had bronchopneumonia, and 21 (15%) had nonspecific pneumonitis. Two children (1.4%), indicated as others, had pleural effusion. Fifty-three percent of the severely malnourished children had normal chest X-rays.

Laboratory results

There was a significant difference between total protein in the HIV positive 60.24 (SD 16.64) and HIV negative 54.21 (SD 15.96) patients (p =0.037), although the mean values for both groups were below the normal ranges of 64–83 g/l..

The HIV positive children had lower mean CD4 counts

Table 2: Prevalence of stunting, wasting and underweight by HIV status

	HIV +ve N=52(%)	HIV-ve N=87(%)	OR	95% CI	P value
WHZ <-2 SD -2+ SD	46 (88.5) 6 (11.5)	62 (71.3) 25 (28.7)	3.091 2.201	1.173-8.149 1.038-4.664	**0.018***
WHZ <-3 SD -3+ SD	28 (53.8) 24 (46.2)	27 (31.0) 60 (69.0)	2.593 1.782	1.275-5.271 1.163-2.729	**0.008***
WAZ <-2 SD -2+ SD	50 (96.2) 2 (3.8)	78 (89.7) 9 (10.3)	2.885 2.148	0.598-13.904 0.602-7.667	0.147
WAZ <-3 SD -3+SD	44 (84.6) 8 (15.4)	63 (72.4) 24 (27.6)	2.095 1.645	0.862-5.092 0.866-3.124	0.098
HAZ <-2 SD -2+ SD	39 (75.0) 13 (25.0)	58 (66.7) 29 (33.3)	1.500 1.299	0.695-3.239 0.778-2.169	0.301
HAZ <-3 SD -3+ SD	19 (36.5) 33 (63.5)	34 (39.1) 53 (60.9)	0.898 0.934	0.441-1.825 0.596-1.463	0.765

Abbreviations: *p value significant, OR= odds ratio, CI= 95% confidence interval, WHZ= weight for height Z score, WAZ= weight for age Z score, HAZ= height for age Z score, SD= standard deviation.

Table 3: Clinical characteristics of the severely malnourished children

Variable	HIV +ve N=52(%)	HIV –ve N=87(%)	OR	95%CI	P value
Diarrhea:	41 (78.8)	54 (62.1)	2.278	(1.030-5.039)	0.040*
History of cough:	42 (80.8)	56 (64.4)	2.325	(1.027-5.265)	0.040*
History of fever:	35 (67.3)	53 (60.9)	1.321	(0.642-2.719)	0.450
Convulsions:	4 (7.7)	4 (4.6)	0.578	(0.138-2.418)	0.472
Temperature (>37.5^{0}C)	21 (40.4)	20 (23.0)	2.269	(1.076-4.784)	0.030*
Oedema:	20 (38.5)	45 (51.7)	1.714	(0.852-3.450)	0.129
Severe dehydration:	4 (7.8)	3 (3.4)	2.383	(0.511-11.10)	0.397
Skin lesions:	19 (36.5)	31 (35.6)	1.040	(0.509-2.126)	0.914
Oral thrush:	32 (61.5)	27 (31.0)	3.618	(1.746-7.496)	0.002*
Hepatomegaly:	20 (38.5)	22 (25.3)	0.542	(0.259-1.134)	0.102
Splenomegaly:	8 (15.4)	8 (9.2)	0.557	(0.195-1.587)	0.269
Heart failure:	1 (1.9)	2 (2.3)	1.20	(0.106-13.568)	1.000

Abbreviations: *p value significant, OR =odds ratio, CI=95% confidence interval

(868.72, SD = 722.78) and CD4% (22.91, SD = 12.49) than did the HIV negative children (CD4 counts 2079.41, SD = 1112.85 and CD% 39.33, SD = 9.49). The difference was statistically significant (p =0.000). Hemoglobin levels revealed that most of the children had different degrees of anemia; thirteen of them had severe anemia and were transfused with blood. Mild anemia was more prevalent in 103 (74.1%) children, 19 (13.7%) had moderate anemia, and only 5 (3.6%) children were classified as having no anemia. Only 1 (1.9%) of the 5 children with no anemia was HIV positive. The remaining laboratory results were not significantly different between the HIV positive and HIV negative children.

Pulmonary tuberculosis and pneumonia were more common among HIV-infected children than among uninfected children (p =0.002). The presence of diarrhea and vomiting during the initial phase were strong predictors of HIV infection, and most of the children were HIV positive, with the difference between the two being statistically significant (p =0.000 and 0.009, respectively). The remaining diagnoses were not significantly associated with HIV infection. The other infections were malaria; six cases of suspected *pneumocyctis jiroveci* pneumonia (formally called *pneumocyctis carinii* pneumonia PCP); one child who developed chicken pox; and one who had an injection abscess.

Outcome

Out of the 140 children recruited and followed up while on the ward, 101 (72.1%) were discharged, 25 (17.9%) died, and 14 (10%) ran away before recovery. A comparison of the outcomes according to HIV status (Table 4).

Discharge was more likely to be associated with HIV negative children than with HIV positive children. HIV negative children suffer fewer complications and have quicker recoveries than HIV positive children. The difference was statistically significant (OR=0.284 [95% CI 0.131-0.614]; p=0.001). On the other hand, death was significantly more strongly associated with HIV positive children (OR=3.802 [95% CI 1.534-9.423]; p=0.003). Loss to follow-up was not associated with HIV status (p =0.131). All clinical characteristics were compared for the children who were lost to follow-up and those who stayed until the outcome was determined, and the difference was not statistically significant (p >0.05). When children lost to follow-up were excluded from the analysis, there was no significant difference in the duration of stay.

Weight gain by HIV status

The average weight gain for severely malnourished children generally varies with HIV status. HIV positive children generally gained less mean body weight (9.300 g/kg/day; SD 6.6274) than did HIV negative children (12.767 g/kg/day; SD 7.3958). The difference between the mean weight gain among HIV positive and HIV negative children was statistically significant (p =0.023). The other factors that affect weight gain in severely malnourished children (Table 5).

HIV positive children on average gained 3.5g/kg/day less than their HIV negative counterparts. The difference between the 2 groups was statistically significant (p =0.023). Eight children presented with convulsions, and only 1 of them had neurological signs. The mean difference in weight gain between children who experienced convulsions and those who did not was 8.375 g/kg/day, and this difference was statistically significant (p =0.006). Other clinical features were not associated with reduced weight gain.

Laboratory characteristics were not associated with poor weight, and they were not reliable predictors of outcome. All children who either passed away or were lost to follow-up before admission to the rehabilitation phase were excluded from the analysis for weight gain. Eight children who were lost to follow-up during rehabilitation were included in the analysis because they gained weight. Children were followed up until discharge or for only 30 days, but this could not have affected weight gain since it was calculated as the rate of change in weight with time.

Compared with those without convulsions, children with convulsions had an average weight loss of 9.383 g/kg/day (coefficient = -9.383; p=0.005). HIV status and CD4 and CD8 counts were not significantly associated with poor weight gain. Oral thrush and age did not affect weight gain. A linear regression was performed for only HIV positive children, and convulsions and history of fever were found to be independent predictors of poor weight gain (coefficients -9.076; p =0.025 and 5.418; p =0.034, respectively).

On further analysis, with the children on antiretroviral drugs excluded from the regression model, convulsions remained the only independent predictor of poor weight gain (coefficient –9.387, [95% CI –15.762 to –3.013]; p=0.004). A positive urine culture was the only predictor of convulsions (OR=18.612;

Table 4: Analysis of outcomes by HIV status in severely malnourished children

	HIV+ve N=52(%)	HIV-ve N=87(%)	OR	95% CI	P value
Discharge$^{\psi}$	29 (57.7)	71 (81.8)	0.284	0.131-0.614	0.001*
Death	16 (30.8)	9 (10.2)	3.802	1.534-9.423	0.003*
Loss to f/up	7 (13.5)	7(8.0)	2.551	0.765-8.503	1.131

Abbreviations: *p value significant, OR= odds ratio, CI= 95% confidence interval, f/up = follow-up, $^{\psi}$discharge after attaining 85% weight for height or after 30 days of follow-up.

Table 5: Effect of clinical features on weight gain

Factor		N=109	Weight gain Mean (SD)	P value
HIV status:	positive negative	33 76	9.300 (6.6274) 12.767 (7.3958)	0.023*
Cough:	present absent	77 32	11.358 (7.3101) 12.628 (7.2781)	0.410
Diarrhea:	present absent	72 37	10.768 (6.6869) 13.605 (8.1030)	0.054
History of fever:	present absent	67 42	11.872 (7.0349) 11.507 (7.7546)	0.801
Temperature:	≥ 37.5^{0}C < 37.5^{0}C	29 80	10.545 (7.1261) 12.161 (7.3414)	0.308
Convulsions:	absent present	103 6	12.192 (7.2170) 3.817 (2.2266)	0.006*

Abbreviations: *p value significant according to ANOVA.

p=0.027). All the other variables were not predictive of convulsions.

Duration of stay

The duration of stay varied between 1 and 30 days. Children with severe malnutrition were followed up until they achieved 85% weight for 30 days. The overall mean duration of stay for both HIV positive and HIV negative children was 18.73 (SD 9.235). The age group with the longest duration of stay was 49-60 months (25.50; SD 5.196), and the group with the shortest duration of stay was 25–36 months (11.55; SD 6.890). Various factors affect the duration of hospital stay among hospitalized severely malnourished children.

On average, children with marasmus stayed in the hospital 3.2 days longer than did those with edematous malnutrition (p =0.040). HIV infected children on average stayed longer in the hospital (18.85 days) than did their HIV negative counterparts (18.61 days), but the difference was not significant (p =0.885). Oral thrush was significantly associated with a prolonged stay of 20.49 days compared to children without oral thrush (15.78) (p =0.003). The other factors were not significantly associated with prolonged hospital stays.

HIV positivity was the only independent factor according to linear regression and was shown to be associated with a long duration of hospital stay after controlling for other factors (p =0.041) (Table 6). The length of hospital stay was 3.915 days longer for HIV positive children than for HIV negative children, as indicated by the coefficient in Table 12. CD4 and CD8 levels were not associated with prolonged hospital stays (p =0.581 and 0.796, respectively). When linear regression was performed for only HIV positive children, none of the characteristics were significantly independently associated with prolonged hospital stay (p >0.05).

Mortality

Of the 140 children included in this study, 25 died (overall mortality rate 17.9%). Most of the deaths occurred within the first 48 hours after admission, and the patients were still in the stabilization phase. Sixteen children (64%) out of twenty-five who died were HIV positive, and nine (36%) were HIV negative. The difference was statistically significant (RR=2.940, p =0.003). The most likely causes of death included very severe pneumonia with respiratory distress (nineteen children), septicemia (five children) and electrolyte imbalance with features of shock and hypothermia (one child).

Table 6: Linear regression for factors affecting duration of stay

Variable	Coefficient	95% CI	P value
Age in months	-0.101	-0.295-0.092	0.302
Oral thrush	3.417	-0.300-7.134	0.71
Convulsions	3.558	-3.679-10.794	0.332
HIV positive	3.915	0.154-7.675	**0.041***
Sex	-0.201	-3.729-3.327	0.910
Fever	-1.191	-4.855-2.474	0.521
CD4	0.000	-0.001-0.002	0.581
CD8	0.000	-0.001-0.002	0.796

Abbreviations: *p value significant, OR = odds ratio, CI = 95% confidence interval.

Possible causes of death

All five patients who died of septicemia were confirmed by bacterial growth on the blood culture. Two patients had *Staphylococcus aureus*, 1 patient had *Klebsiella species*, one patient had *Escherichia coli*, and one patient had *Pseudomonas species*. Blood bacterial growth was not significantly associated with HIV infection. The child, who died of electrolyte imbalance and shock, also had severe anemia and received blood transfusion.

Sixteen out of the twenty-five children (64%) who died were HIV positive, whereas nine (36%) were HIV negative. HIV-infected severely malnourished children were three times more likely to die than HIV-uninfected children were (RR=2.940, p =0.003). Children with edematous malnutrition, especially marasmic-kwashiorkor, were more likely to die than were those with marasmus. Twelve children (27.9%) with marasmic-kwashiorkor (edematous) died, whereas nine (13.4%) with marasmus died (p =0.042). Only sixteen children had both HIV and marasmic-kwashiorkor, and twelve (75%) of those died. Children with purely edematous malnutrition (kwashiorkor) were less likely to die than were those with marasmic-kwashiorkor.

HIV status was the only independent factor associated with death (p =0.023). HIV positive children were three times more likely to die than HIV negative children were (OR=3.341). The type of malnutrition was not significantly associated with death according to logistic regression (p =0.055). On further analysis, with the children on antiretroviral drugs excluded from the regression model, positive HIV status remained the only independent factor associated with high mortality (OR=3.696 [95% CI 1.315-10.389]; p=0.013).

Figure 2 shows the Kaplan–Meier survival analysis curve for HIV infection. HIV infection was strongly associated with reduced survival compared to no HIV infection, as evidenced by the log rank test for equity of survival distributions for HIV status (p =0.0047). Most children died within the first five days.

Weight gain was slower within the first 24 months (ranging between 11.233 and 12.069 g/kg/day). After 24 months, weight gain is slower at less than 10 g/kg/day for up to 48 months. Between 49 and 60 months, the weight gain was normal (15.4 g/kg/day). Older children stayed longer than did the rest of the other age groups (average 25.5 days). Mortality was highest among those aged 13-24 months but sharply decreased to zero in those aged 49-60 months.

DISCUSSION

This study was carried out to establish the outcomes of severely malnourished (HIV-infected and uninfected) children presenting at Mulago Hospital and treated with the standard Ministry of Health protocol for severely malnourished children in

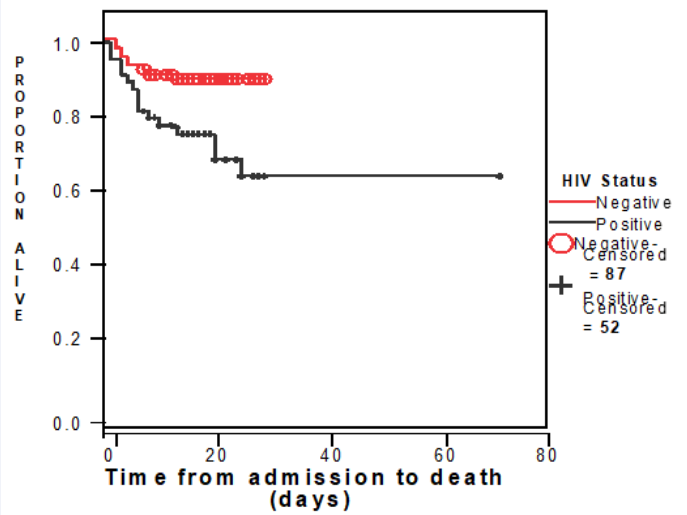

Figure 2 Kaplan-Meier survival analysis curves.

Uganda. One hundred forty severely malnourished children were recruited, 54.3% of whom were males and 45.7% of whom were females. These findings are similar to results from other studies performed earlier in Uganda [13], and other African countries [18,40]. Most children with severe malnutrition were younger than 25 months of age, possibly because of HIV infection, which manifests within this period if it is acquired perinatally.

Prevalence of HIV in severely malnourished children

In this study, the prevalence of HIV was 37.1%, contrary to the findings of an earlier study [13] in 2002, in which 44% of the participants were diagnosed. The difference could be due to the stepped-up health education against HIV/AIDS, increased availability of voluntary counseling and testing services for pregnant mothers, and availability of antiretroviral drugs that in effect reduce HIV prevalence rates in the country. The increase in the prevalence of HIV infection in pregnant women in Uganda is gradually decreasing, possibly explaining the reduction in HIV prevalence among severely malnourished children. Our findings are within the range of 14–48.6% reported from other countries [15,18,19,45,46].

The HIV status of one child was not determined by rapid testing, and the DNA PCR result was misplaced; however, this did not significantly change the final prevalence. The mean age of the HIV-infected malnourished children was 18.62 months. This finding may not be surprising, as HIV negative children may have recovered earlier, many did not become admitted or HIV positive children died earlier, and many did not appear in the older age group. A study by Mgone and colleagues found a slightly greater mean age of 24 months for HIV-infected malnourished children [15]. It is likely that these children became infected during the perinatal period.

In this study, the HIV positive children had a significantly lower weight for age Z score (-3.992) than did their HIV negative counterparts (-3.524), with p =0.038. Weight for age indicates underweight, which is a composite measure of stunting and wasting. These findings are similar to those of other studies [19,23,46]. The presence of infections such as persistent diarrhea, persistent fever, vomiting and pneumonia was suggested to be an important cause of poor growth in HIV-infected children. These infections were also common among the HIV positive children in this study and are possibly responsible for the low weight-for-age Z score. The weight for height Z score, a measure of wasting, was significantly lower in HIV positive children (-3.085, SD=0.857) than in HIV negative children (-2.500, SD=1.061), p =0.001. These findings are similar to those of a study in Malawi [46]. Rwanda found that weight-for-height was not common among HIV-infected children; possibly, they studied a younger age group (0-48 months) than the one in this study. The height for age Z score was not significantly different between the HIV positive and HIV negative children in this study, unlike in other studies involving young age groups [19,23,46]. This is not surprising since HIV is known to cause early stunting [16], but the mean age of the HIV positive children in this study was greater than that of the HIV negative individuals, who could also be taller.

Clinical characteristics of HIV-infected severely malnourished children

HIV infection was more prevalent among children with marasmus. Thirty-two percent of all children with marasmus had HIV infection. This is not surprising, as these results are similar to findings reported in other studies [18-20]. HIV infection has been found to be associated with early growth failure and wasting, possibly due to poor food intake, altered metabolism and poor absorption, subsequently leading to high morbidity and mortality [14,16,29]. In this study, pneumonia was more prevalent in HIV-infected children (p =0.002) than in HIV-uninfected children, as shown in earlier studies [28]. This explains the large number of HIV-infected children who needed oxygen compared to HIV-uninfected children (p =0.009).

Although pulmonary tuberculosis is difficult to diagnose in children [48], a history of contact with pulmonary tuberculosis in adults, clinical examination and chest X-ray findings were used to suspect infection in these children. Pulmonary tuberculosis was commonly associated with HIV infection (p =0.002). Similar results were reported in a South African study [52], in which 11% of HIV positive children were diagnosed with pulmonary tuberculosis, while 5% of HIV negative children were diagnosed with pulmonary tuberculosis (p <0.001). The percentage of 17.3% in this study is possibly due to the small sample size. However, therapy with anti-tuberculosis drugs has shown increased survival, increasing the likelihood of a provisional diagnosis of tuberculosis.

According to the WHO clinical case definition of childhood AIDS, severe malnutrition is a feature of severe immunosuppression; hence, all severely malnourished children need to be screened for HIV infection. The other clinical features of HIV infection may also be nonspecific, as they occur in uninfected children. In this study, the clinical features that correctly predicted HIV infection were a history of oral candidiasis, diarrhea and vomiting during the initial phase. However, oral candidiasis, as a sign, did not predict HIV infection. These clinical features have been found to be strong predictors of HIV infection in other studies [15,18,45,46]. This is not surprising since severe malnutrition is an AIDS-related condition [14,16]. Several clinical features, though more common in HIV-infected children, were not significantly different in this study. These included dermatitis, otitis media, splenomegaly and hepatomegaly. This finding contradicts findings from other studies [15,18,45,46]. This could be due to the small sample size in this study. Previous studies with larger sample sizes could explain the significant association between these factors and HIV infection.

All severely malnourished children were routinely treated with broad-spectrum antibiotics. HIV infection strongly influences the choice of other drugs given to severely malnourished children. Ketoconazole administration was associated with HIV infection (p=0.000), consistent with the high incidence of oral thrush in this and other studies [15,17]. Pulmonary tuberculosis was significantly associated with HIV infection (p=0.002). This result was similar to reports from other studies [27,48]. Most children develop pulmonary tuberculosis from adult patients. The high incidence of pulmonary tuberculosis corresponded to the significant number of HIV positive children receiving anti-tuberculosis drugs (p=0.001). Many studies have shown that diarrhea and pneumonia are responsible for poor growth in HIV-infected children [16,27,28,46]. These factors were strong predictors of HIV infection in this study, and most of the patients required oxygen therapy and ReSomal during their treatment (p =0.009 and p=0.035, respectively).

Oxygen was administered to all the children who had very severe pneumonia as classified by the WHO. Blood transfusion and fluid infusion were not significantly associated with HIV infection. Other drugs administered to these children included *cotrimoxazole for Pneumocyctis carinii* pneumonia (PCP) and antimalarials such as quinine, chloroquine and sulfadoxine-pyremethamine. PCP prophylaxis can delay the progression of the disease to severe symptoms, and it is given routinely in Uganda and other countries [29] for children with severe immunosuppression. All HIV positive children were receiving cotrimoxazole therapy; six of them were receiving PCP treatment, and the rest were receiving PCP prophylaxis.

Children with HIV infection had higher total protein levels than did their HIV-uninfected counterparts (p =0.037), a finding similar to that of Dramaix and colleagues in Zaire [53]. This is not surprising in this study, as most HIV-infected children were aged younger than 24 months, manifesting mainly as marasmus. Kwashiorkor, which is usually associated with marked hypoalbuminemia, peaked after 24 months, corresponding to the cessation of breastfeeding, and was least likely to be associated with HIV infection according to the present study and other studies. Another possibility for increased protein levels in HIV positive children could be increased levels of immunoglobulins, which were not specifically examined in this study.

The CD4+ T-cell count and percentage of CD4+ T cells were significantly lower in HIV-infected children (p =0.000). Although these parameters vary greatly in children younger than 5 years, these findings are not surprising. All the children were severely malnourished and expected to have reduced CD4 counts; hence, these tests are not very reliable. Previous studies have shown that the thymus and lymph nodes, which are responsible for cellular-mediated immunity, are involved in severe malnutrition [33-35]. HIV infection causes further depression of CD4+ T cells, as shown in this study.

Outcome of severely malnourished children

Mean weight gain: The mean weight gain for children recovering from severe malnutrition in MNU was 11.73 g/kg/day. This analysis excluded all children who died or were lost to follow-up before admission to the rehabilitation phase. For children who had edematous malnutrition, weight gain was determined after complete loss of edema. This is comparable to results from Bangladesh, where the weight gain for inpatients was 11.0 g/kg/day [50]. Earlier studies revealed markedly decreased weight gain after intensive high-energy feeding in severely malnourished children in Zambia (8.93 g/kg/day)[69] and Jamaica (6.9 g/kg/day) [54].

In the above studies, HIV was not mentioned as being responsible for the low weight gain. In the present study, on average, the HIV negative children gained 3.5 g/kg/day more than the HIV positive children did (p =0.023). However, according to our logistic regression, HIV status ceased to be significantly associated with poor weight gain (p =0.742). It was not an independent predictor of poor recovery or growth failure. This finding contradicts the significant associations found in earlier studies [23,24]. The lack of statistical significance may be due to the small sample size.

The children in our study doubled their average weight gain

(11.73 g/kg/day) compared to those in the pilot study. This could be because the research assistant closely observed the children in the present study during their feeding hours and compensated for any losses. The children who vomited food were fed through a nasogastric tube. Accurate weights were taken on a calibrated weighing scale. In the pilot study, data whose degree of accuracy could not be ascertained were retrospectively collected from the records. Children are usually not routinely supervised while being fed by their caretakers, which possibly caused the discrepancy during the pilot study.

Various mechanisms of poor weight gain in HIV-infected children have been suggested. These include reduced intake, malabsorption of nutrients from the gastrointestinal tract, abnormal energy utilization and psychosocial stress [23,24,55]. Reduced intake is mainly due to HIV-related symptoms such as oral candidiasis, anorexia, vomiting, diarrhea and other opportunistic infections [24,46,55]. Poverty may be a contributing factor to the nonavailability of food [47]. Previous studies have reported malabsorption to be a common feature of pediatric HIV infection, mainly due to the effect of HIV and other enteric pathogens on the intestinal epithelium [24,55]. HIV-infected children have high levels of cytokines, which cause hypermetabolism and excessive viral replication, and increased caloric intake leads to severe wasting or poor weight gain [55]. Children who lack parental care suffer from chronic psychosocial stress leading to hypopituitarism and other endocrine dysfunctions with reduced levels of growth hormone secretion and hence poor growth [23,55].

The use of antiretroviral drugs for the treatment of severely malnourished children did not affect weight gain in this study. Four children in this study were receiving antiretroviral therapy, and their exclusion from the linear regression analysis model did not change the predictors of poor weight gain. The lack of impact of antiretroviral drugs in this study could be due to the small number of patients receiving treatment. In the European Collaborative Study, antiretroviral drugs administered to children at 28% growth velocity without symptoms and 45% growth velocity with symptoms were suspected to cause poor weight and height gain [24].

The presence of convulsions was a strong independent predictor of poor weight gain according to logistic regression (p=0.005). Neither convulsions nor other neurological manifestations were significantly associated with HIV infection in this study (OR=0.578; p=0.472) or other studies [18,28,45]. However, together with recurrent infections, encephalopathy is recognized as a cause of growth failure [18]. Logistic regression analysis for predictors of convulsions showed that positive urine culture was an independent predictor of poor weight gain (OR=18.612 [95% CI 1.392-248.8]; p=0.027). The organisms cultured on urine included *Escherichia coli*, *Proteus mirabilis*, unidentified *coliforms*, *Klebsiella species*, *Staphylococcus aureus* and *Candida species*. Convulsions are not directly responsible for poor weight gain but are rather a marker of underlying urinary tract infection.

Antibiotics were routinely given to all severely malnourished children. *Escherichia coli*, which is the predominant bacterial isolate, was found to be less sensitive to gentamicin and ampicillin, which are commonly used antibiotics [13]. Most patients were not treated with ceftriaxone, which is effective for most organisms. Although three out of the eight children who presented with convulsions had bacterial growth on blood culture, there was no significant association with poor weight gain. Leukocytosis was evident in four out of the eight children with convulsions. Four of the children who had convulsions were suspected to have pulmonary tuberculosis and started anti-tuberculosis treatment. The convulsions could have been due to neurological involvement, such as tuberculous meningitis. One child who had severe immunosuppression and a CD4 level of 11% was treated for HIV encephalopathy and had a negative weight gain of 3.76 g/kg/day. In Malawi, Taha et al. reported that 100% of children with CD4+ cells < 15% died after progressive growth failure, mainly due to opportunistic infections [29]. The cause of her convulsions could have also been metabolic in origin and affected all the children, irrespective of their HIV status. Four children with convulsions had hyponatraemia, one had hypernatraemia, and one had hypokalemia.

HIV-infected children were more likely to have opportunistic infections such as oral thrush, diarrhea, vomiting, persistent fever and respiratory tract infections. Age extremes were associated with greater mean weight gain than was age. The mean weight gain in the first 12 months was within the normal range, similar to the findings of one study in which there was no difference between HIV positive and -negative children within the first 6 months [24]. This may be consistent with primary HIV infection with no severe immunosuppression. The slower weight gain after 24 months could largely be explained by HIV-related illnesses. In the present study, HIV-infected children with persistent diarrhea and tuberculosis had significantly lower weight velocities than did those without, but other HIV-related illnesses, such as oral thrush, persistent fever and chronic cough, were also associated with slow weight gain. This suggests that the cause of slow weight gain may be multifactorial [24].

Although all severely malnourished children with HIV infection qualified to be given antiretroviral drugs, only 4 children (7.7%) received these drugs, mainly based on their CD4+ T-cell counts. Treatment with antiretroviral drugs would have a transient benefit on weight gain if the number of patients was large, but the fact that only four patients were treated in this study could not explain the normal average weight gain among the older age group. The ages of the children on antiretroviral drugs were 18, 43, 50 and 53 months.

Mean duration of stay for severely malnourished children

The mean duration of hospital stay for all severely malnourished children was 18.73 (SD=9.235) days. This is slightly greater than that reported in an earlier study performed in the same setting, in which the mean hospital stay was 16

days [13]. Khanum and colleagues, in a controlled trial of three approaches to the treatment of 437 severely malnourished children in Bangladesh, found that inpatients on average stayed for 18 days [50].

In this study, the HIV-infected children stayed 0.24 days longer than the HIV-uninfected children did during the study period. Compared with HIV-uninfected children, HIV-infected children stayed for 18.85 (SD=11.914) days 18.61 (SD=7.306) days (p =0.885). Zwi et al., in a study assessing the impact of HIV on pediatric hospital admissions at a South African urban regional hospital, reported that HIV-infected children stayed 1.5 days longer than uninfected children [52]. The difference may be because the South African study examined all sick children and not only severely malnourished children.

Mortality of severely malnourished children

The overall mortality or case fatality rate in this study was 17.9%, which is lower than that reported in earlier studies in Uganda [13,43,44]. The case fatality rate in this study is much lower than that reported in other African countries, such as Côte d'Ivoire (20.8%) [28], Zimbabwe (22.8%) [46], Zambia (25.8%) [40], and Malawi (28.0%) [45]. These differences could be due to improved methods of managing severely malnourished children and the availability of antiretroviral drugs. In Bangladesh, however, Khanum and colleagues reported a mortality rate of only 3.5% among inpatients with severe malnutrition [50]. This low mortality rate was because the study was specifically carried out to optimize outcomes, unlike our study, which was performed during daily routine care without special attention given preferentially to patients. Critically ill children and those who needed blood transfusion and tuberculosis treatment were excluded from their study, as these conditions tremendously reduced their mortality rates.

In this study, HIV infection significantly contributed to most of the deaths (RR=2.94; p =0.003). This result, contrary to that found by Ticklay and colleagues in Zimbabwe [46], is similar to findings from other studies [18,19,28,52,45]. HIV is associated with increased morbidity with opportunistic infections, mainly pneumonia, persistent diarrhea, pulmonary tuberculosis and septicemia, which are usually associated with mortality.

CONCLUSION

The overall mean weight of children younger than 60 months admitted to the rehabilitation phase of MNU gain was 11.73 g/kg/day, and HIV negative children gained 3.5 g/kg/day more than HIV positive children.

1. On average, the duration of stay was 18.73 days, and there was no significant difference between HIV positive and HIV negative children.

2. The clinical features significantly associated with HIV infection among severely malnourished children included pulmonary tuberculosis, pneumonia, persistent diarrhea, vomiting, fever (with a temperature of 37.50°C) and a history of oral thrush.

3. Overall mortality was 17.9%, and HIV-infected children (30.8%) were three times more likely to die than HIV negative children (10.3%).

RECOMMENDATIONS

Considering that among severely malnourished children, HIV-infected individuals have slower weight gain and greater morbidity and mortality than HIV negative individuals, all severely malnourished children should receive voluntary counseling and testing for HIV and those found to be HIV positive be offered antiretroviral drugs.

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Conflict of Interest

The study was conducted with financial support from the Kulika Charitable Trust and Nuffield Foundation. The authors declare that they have no conflict of interest.

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