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REGULAR ARTICLE

The effect of nutritional support on weight gain of HIV-infected children with prolonged diarrhoea

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Abstract

Aim: To examine the effect on growth and immunity of enhanced calorie and protein provision to HIV-infected children presenting with prolonged diarrhoea.

Methods: A total of 169 HIV-infected children aged 6–36 months with diarrhoea for 7 days or more were randomly assigned to either standard nutrition support for children with prolonged diarrhoea or an enhanced diet started during hospitalisation and continued after discharge. The change in weight between enrolment and 8, 14 and 26 weeks and changes in plasma HIV-RNA and CD4 cell count at 8 and 26 weeks were estimated.

Results: Children receiving enhanced nutrition achieved significantly more weight gain ($p < 0.001$) between enrolment and 8 weeks than children on the standard diet (median increase in weight-for-age standard deviation score +1.02 vs. +0.01). After 8 weeks median weight velocity was normal and similar in both groups. The change in median CD4 count was similar in both groups. The 26-week mortality rate was high in both groups (standard support: 22%, enhanced support: 29%).

Conclusions: Nutrition support of children with advanced HIV infection and prolonged diarrhoea resulted in significant and sustained weight gain, but did not improve CD4 counts or survival. These results support integrated nutrition interventions for HIV-infected children.

INTRODUCTION

Approximately 58 000 children in South Africa become infected with HIV each year (1), and AIDS related complications account for 60% of paediatric admissions to hospitals in the Province of KwaZulu Natal (2). The HIV epidemic is superimposed on widespread food insecurity and chronic malnutrition.

Wasting and prolonged diarrhoea are frequent symptoms of HIV disease and are indications for anti-retroviral therapy (ART) in the SA national programme (3). Our study assessed the effect of enhanced nutrition on weight gain and immune competence in HIV-infected children with prolonged diarrhoea.

PATIENTS AND METHODS

Study population

HIV-infected children 6–36 months of age with diarrhoea lasting longer than 7 days presenting to King Edward VIII Hospital (KEH), Durban were recruited into this study. The hospital serves primarily persons of Zulu origin residing in urban and periurban townships.

Study design

This was a randomised non-blinded study. Parents or guardians of children with diarrhoea of 5 or more days duration and suspected HIV infection received pre-test counselling for HIV testing of their child. The child's HIV status was determined and routine history, examination and laboratory tests were performed. Children were either admitted to hospital, depending on clinical status, bed availability, home circumstances and caregiver's preference, or managed as outpatients. Caregivers of children not admitted were requested to return after 2 days. All children received standard management for prolonged diarrhoea, namely fluid and electrolytes, low lactose feeds and micronutrient supplements (4). Other infections and complications were treated as required.

Within 72 h of presentation, HIV-infected children were offered entry into the study if they were clinically stable, diarrhoea had lasted for at least 7 days and the mother or legal guardian gave written informed consent. Children given antibiotics before a stool sample was obtained were ineligible. Enrolled children were consecutively assigned a study number from a randomisation list that was prepared using a computer generated block randomization method with a block size of six that corresponded to standard treatment and either subsequent normal home diet or enhanced nutrition support at home. Hospitalised children were discharged when they had no watery stools, <4 loose stools/day, no vomiting and an oral calorie intake of ≥100 kcal/kg/day. After discharge, all children were followed up weekly. Outpatients were seen every 3 days until the diarrhoea resolved, after which they were seen weekly. Caregivers were

reimbursed for travel costs. After 3 months, the enhanced nutrition support group was again randomised to either continue with enhanced support or return to their normal home diet. Children were recruited into the study between 1 May 1998 and 31 March 2000.

Antiretroviral treatment was only introduced as standard of care in South Africa in 2005 and was not otherwise provided as sustainability, and appropriate long-term management could not be guaranteed. The study was approved by the Research Ethics Committee of the University of KwaZulu-Natal and the Institutional Review Board of the Tufts-New England Medical Centre.

Nutrition interventions

Standard nutritional support provided to all children consisted of a casein maltodextrin-based milk formula (AL110, Nestlé S.A., Randburg, SA) with 67 kcal/100 mL offered at least four times per day, and a maize porridge/pureed vegetable/oil diet with fermented milk offered at least four times per day. This provided at least 100–110 kcal/kg/day containing ~2.2 g protein/kg/day and 9.5% of calories as protein, and a total lactose content of <3.2 g/kg. Any child taking <100 kcal/kg/day for three consecutive days was fed by nasogastric tube. Children over 12 months of age were given a predominantly soft diet of porridge and vegetable purees with an equivalent protein and energy content; this diet continued until discharge from hospital. The same casein-maltodextrin–based formula was supplied to children who were not admitted until the child had no watery stools and less than four loose stools per day. There was unrestricted access to food for all children during hospitalisation. Following discharge, however, unless a child required a specialised feed because of persisting carbohydrate intolerance, no additional food support was offered. When household food insecurity was identified, caregivers were referred to the hospital social worker for assistance with welfare grants. During admission, outpatient visits and subsequent study visits a dietary assistant advised caregivers on food preparation, emphasizing a balanced diet and inexpensive but nutritious food choices, hygiene and advice for children with mouth sores or anorexia.

The group randomised to enhanced nutrition support received the same diet until the diarrhoea resolved and appetite was re-established. The amount of milk offered was then modified to provide at least 150 kcal/kg/day containing approximately 4.0–5.5 g protein/kg/day and 15% of calories as protein. Depending on age and weight of the child, this sometimes required a powdered protein supplement that was added to other food (Promod, Abbott Laboratories S.A. [Pty] Ltd. Aeroton, SA). This support was provided until the child was 3 months of age. Children randomized at 3 months to continued nutritional support received the same milk and supplements until 6 months of age. At home, caregivers were advised to provide their normal home foods and additionally give the milk and protein supplements as directed by the study dietician. The supplemented milk formula was provided in unlabelled tins, and intake was ascertained by examination of empty tins at follow-up.

All children received daily vitamin supplements (A, C, D, thiamine, riboflavin, pyridoxine, nicotinamide and B12) providing approximately twice the USDA-recommended daily requirement for 2 weeks. Children also received folate 5 mg daily for 7 days, zinc sulphate 15 mg daily for 14 days and a single oral dose of vitamin A (6–12 months: 100 000 IU; >12 months: 200 000 IU).

Study outcomes

The primary study outcome was weight change from enrolment until 8 weeks. Secondary outcomes were attained weight and height at 8, 14 and 26 weeks and the changes over the corresponding intervals. Other secondary outcome measures were changes in viral load and CD4 counts from enrolment to 8 and 26 weeks.

Laboratory methods

All children were tested for HIV infection initially by detecting HIV antibodies by ELISA (ABBOTT Axsym. HIV1/2 gO, 65205 Wiesbaden, Germany). In children ≤15 months, HIV status was confirmed by HIV RNA PCR (Amplicor HIV-1 RNA Monitor Test, Version 1.5, Roche, Indianapolis, IN, USA). If the HIV RNA load was less than 400 copies/mL, HIV status was confirmed using an in-house HIV DNA PCR test (Department of Virology, UKZN). CD4 cell counts were measured using a fluorescent activated cell sorter (Biometric Imaging 4T8 Assay Calibration Kit, Mountain View, CA, USA). HIV viral loads were quantified using the Roche Amplicor assay.

On admission and/or enrolment, the following laboratory tests were performed using standard methods at KEH: full blood count, serum electrolytes, total protein, albumin, bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma-glutaryl transferase and C-reactive protein (CRP), dipstix urinalysis, blood and urine cultures for bacterial pathogens, and gastric aspirate for *Mycobacterium tuberculosis* culture. Stool samples were examined macroscopically for blood, and microscopically for ova and parasites and cultured for bacterial pathogens; ELISA and electron microscopy were used to identify rotavirus, adenovirus and astrovirus infections. Chest radiographs were obtained at admission. Weight was measured to a precision of 100 gm (Seca, 22061 Hamburg), and length to 0.1 cm using a locally made measuring board.

Statistical methods

Sixty-four patients were required in each treatment group to detect a difference of 10% in weight gain between study entry and the 8 week follow-up visit, with 80% power at a two-sided significance level of 0.05. The total sample size for enrolment was increased by 25% to allow for attrition. Study data were entered onto a database (Microsoft Access 2000)

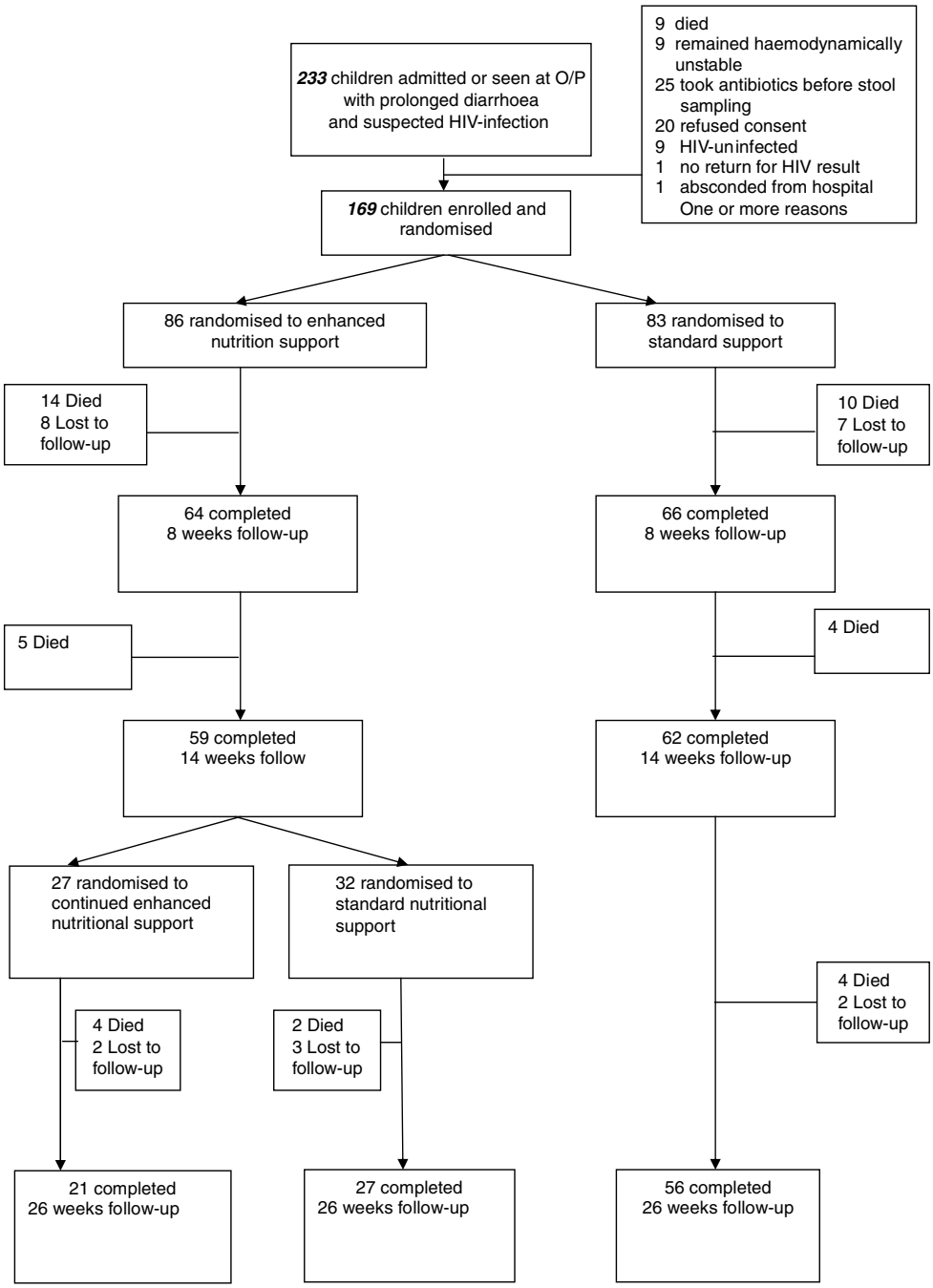

Figure 1 Study participant flow.

and analyses were performed with SPSS vs. 11.0 (SPSS Inc., Chicago, IL, USA).

Weight gain was expressed as change in age- and sex-specific weight standard deviation scores (SDS) (5) that were calculated using Growth Analyser software (6). Group differences in weight gain and CD4 counts at follow-up were tested using chi-square and Student's *t*-test, after normalizing transformation as required. Weight gains were correlated with, and regressed on determinant variables using Pearson correlations and multiple linear regression analysis, respectively.

Unfortunately, a batch of blood samples for follow-up viral load were lost during transportation to the United States so that follow-up viral loads could only be studied in the first 70 enrolled children. The analysis of viral load data is presented for descriptive purposes.

Table 1 Baseline characteristics by treatment group

Variable	Timing of measurement	Group 1 (standard nutrition support) n = 83 % or median (P10, P90)	Groups 2 (enhanced nutrition support) = 86 % or median (P10, P90)
Age (months)	Adm	13 (6.4, 29.6)	13 (7.0, 24.0)
% ≤ 24 months	Adm	89	93
Female	Adm	46	57
Weight-for-age SDS	Enr	−3.09 (−5.00, −1.17)	−3.25 (−4.94, −1.79)
Length-for-age SDS	Dis	−2.25 (−5.47, −0.59)	−2.66 (−4.92, −1.06)
Weight for length SDS	Dis	−3.08 (−5.42 to +001)	−2.70 (−5.81 to −0.19)
Head circ.-for-age-SDS	Dis	−0.97 (−2.49, +0.47)	−1.14 (−2.89, +0.61)
Underweight (WFA<−2 SDS)	Enr	71.8	86.0
Stunting (LFA < −2SDS)	Dis	51.8	64.3
Severely malnourished (WFL < −3SDS)	Dis	50.7	41.3
Pedal oedema	Adm	31.3	24.4
Dehydration	Adm	60.5	62.1
Macroscopic blood in stools	Adm	11.6	6.9
Days of diarrhoea before enrolment	Enr	15 (9, 32)	12 (8, 33)
Fever history	Adm	70.9	83.9
Mouth sores	Adm	66.3	71.3
Haemoglobin (g/dL)	Adm	8.7 (6.9, 10.8)	9.1 (7.2, 11.8)
	Enr	8.4 (6.3, 10.0)	8.3 (6.5, 10.2)
White cell count ($\times 10^9$) /L	Adm	13.4 (6.4, 24.4)	12.1 (7.3, 20.3)
	Enr	10.9 (5.4, 18.4)	9.9 (5.6, 17.7)
Platelet count ($\times 10^9$) /L	Adm	303 (131, 708)	314 (118, 602)
	Enr	293 (56, 632)	269 (39, 573)
Albumin (g/L)	Adm	23 (15, 35)	25 (17, 38)
	Enr	21 (12, 33)	23 (14, 31)
C-reactive protein (mg/L)	Enr	19 (5, 140)	21 (5, 106)
Log10-viral load	Adm	6.1 (5.2, 6.5)	6.1 (5.3, 6.6)
CD4 count/microlitre	Enr	834 (158, 1629)	705 (147, 1416)
CD4%	Enr	21.6 (6.1, 45.1)	18.85 (4.84, 50.5)
CD4%—≤24 months	Enr	21.6 (6.7, 47) (n = 74)	18.9 (4.9, 50.5) (n = 80)
CD4%—>24 months	Enr	17.4 (0.4, 43.8) (n = 9)	18.45 (2.8, 59.4) (n = 6)
Breastfed	Adm	12.0	9.3
Breast and formula fed		19.3	15.1
Formula fed		53.0	62.8
Other milk		15.7	12.8
Mother is main income provider	Adm	19.3	15.1
Treated as outpatient	Adm	27	23
Duration of hospital stay (days) (hospitalised patients)	Dis	10 (5, 23)	9 (4, 21)

RESULTS

Patients enrolled in study

A total of 169 hemodynamically stable HIV-infected children were enrolled (Figure 1). Eighty-three were assigned to the standard nutrition group (Gp1) and 86 to the enhanced nutrition group (Gp2). Dropout rates at the end of the study were high in both groups (Gp1: 27/83 (33%); Gp2: 38/86 (44%); difference 11%, 95%CI: −3 to +26) and were primarily due to death; 8- and 26 weeks mortality rates were 10/83 (12%) and 18/83 (22%) in Gp1 and 14/86 (16%) and 25/86 (29%) in Gp2. Other dropouts (9 children from Gp1 and 13 from Gp2) included children who did not return for follow-up and two children who were started on antiretroviral treatment.

Baseline characteristics

Table 1 shows the baseline characteristics. Overall, severity of disease, baseline immunity and nutritional status were similar between groups, except for the presence of macroscopic blood in the stools (Gp1–11.6%, Gp2–6.9%). In both groups the majority of children were very low weight (weight-for-age [WFA] <60% expected mean, i.e. −3SDS) and showed signs of anaemia. Oedema, dehydration, fever and mouth sores were frequent.

Primary outcomes

Children who received enhanced nutrition support had significantly more weight gain in the first 8 weeks than

Table 2 Changes in weight and CD4 count over various follow-up intervals

Interval from enrolment	Nutrition intervention group		p-value*
	Group 1: standard nutrition support	Group 2: enhanced nutrition support	
Median change in weight-SDS (N)			
0–8 weeks	+0.01 (66)	+1.02 (64)	<0.0001
8–14 weeks	+0.00 (61)	+0.21 (58)	N.S.
14–26 weeks	+0.24 (54)	+0.12 (48)	N.S.
0–26 weeks	+0.40 (54)	+1.72 (48)	<0.0001
Median change in CD4 count (N)			
0–8 weeks	−40 (63)	−60 (62)	N.S.
8–26 weeks	−83 (52)	−100 (48)	N.S.
0–26 weeks	−90 (52)	−106 (48)	N.S.

**t*-test done after normalizing power transformation. N.S. = not significant ($p > 0.05$).

children receiving standard care ($p < 0.0001$), improving by an entire SD score (Table 2). Mean WFA-SDS at baseline of those who dropped out was not different between groups (Gp1 dropouts: –3.24; Gp2 dropouts: –3.39; $p > 0.05$), nor within each group (Gp1 completers: –3.00, $p > 0.05$; Gp2 completers: –3.19, $p > 0.05$). Hence, the observed outcome among the completers was unaffected by dropout bias or regression to the mean.

Secondary outcomes

After 8 weeks, weight gain was similar between groups, with only a slight increase in weight-SDS (Table 2). Table 3 shows the median attained WFA-SDS, CD4 count, viral load and the percentages of underweight and stunted children. WFA-SDS remained approximately stable in GP1 and far below the underweight cutoff (−2 SDS). In contrast, Gp2 showed a marked improvement of the median WFA-SDS, becoming statistically significant from 8 weeks onwards. Children in Gp2 who were randomised to continue with the enhanced nutrition support until 6 months (Gp2a), median attained WFA at 6 months increased to −1.01 SDS, whereas those who reverted back to standard home diet only maintained the same median value as at 3 months (−1.68 SDS). Changes in CD4 cell counts or viral load were similar between groups.

Table 3 summarizes the cumulative frequency of clinical signs during the follow-up intervals of 0–8, 8–14 and 14–26 weeks. The pattern of morbidity was similar between groups.

Table 3 Weight, length, CD4 count and HIV viral load and cumulative occurrence of clinical signs during follow-up intervals

	Group 1: standard nutrition support				Group 2: enhanced nutrition support			
	At baseline (n = 82)	8 weeks (n = 64)	14 weeks (n = 61)	26 weeks (n = 54)	At baseline (n = 84)	8 weeks (n = 62)	14 weeks (n = 58)	26 weeks[c] (n = 48)
Median attained value or%								
Weight-for-age-SDS	−3.10	−3.06	−2.96	−2.63	−3.13	−1.99[b]	−1.69[b]	−1.32[b] −1.01 (Group 2a) −1.68 (Group 2b)
Length-for-age-SDS	−2.25	−2.72	−2.98	−3.14	−2.66	−2.72	−2.91	−2.52
% Underweight	77	78	70	65	86	48	47	31
% Stunted	58	63	67	74	68	69	72	65
CD4 count	848	684	–	796	705	786	–	744
Log10 viral load[a]	6.2	5.9	–	6.0	6.2	6.1	–	6.0
Median (P10, P90) cumulative days since previous follow-up visit								
Diarrhea	–	3 (0, 19)	1 (0, 15)	5 (0, 21)	–	2 (0, 21)	1 (0, 8)	3 (0, 22)
Reported history since previous follow-up visit (%)								
Vomiting	–	53	44	69	–	56	51	65
Anorexia	–	65	50	67	–	68	47	83
Dyspnoea	–	47	45	66	–	56	42	71
Fever	–	87	88	86	–	76	70	92
Mouth sores	–	15	13	14	–	16	9	23

[a]Viral loads are based on a subgroup of the first 70 enrolled children (35 group 1, 35 group 2) for whom follow-up samples were available for analysis.
[b]$p < 0.05$ for *t*-test comparing the two groups at the same age. *t*-tests performed after normalizing transformation of the variables, that is square-root transformation of CD4 count and log10 transformation of viral load.
[c]At 14 weeks, patients from the enhanced support group were randomised into group 2a (continued enhanced support) and group 2b (standard support).

Additional analysis

We performed an additional analysis of factors associated with weight gain from enrolment to 8 weeks in children who received enhanced nutrition support. Change in WFA-SDS in this group correlated significantly with age ($r = +0.362$; $p = 0.004$), number of days of diarrhoea ($r = -0.465$; $p < 0.0001$), CRP at baseline ($r = +0.329$; $p = 0.035$); borderline correlation with initial WFA-SDS ($r = -0.241$; $p = 0.059$) but not significantly with initial degree of wasting, viral load or CD4 count or any other baseline clinical or laboratory feature. When analysed in a multiple regression analysis, age, days of diarrhoea and CRP remained significant independent determinants of weight gain.

DISCUSSION

This study demonstrates that substantial weight gain is possible in severely malnourished children with advanced HIV infection in resource-limited settings where ARV treatment was unavailable. Furthermore, the improved weight gain of children continued for as long as nutritional support was offered and was sustained even after support was stopped. This was in spite of several limitations including anorexia, co-infections, oropharyngeal candida and herpes, malabsorption and fever/catabolism (7–12). There are several possible reasons for these gains. First, we used a lactose- and sucrose-free commercially available modified formula milk. This feed was chosen to reduce the risk of disaccharide malabsorption, a frequent complication in HIV-infected children admitted with diarrhoea (13,14). Second, the milk provided was of relatively low osmolarity compared with the typical home-diet of children in this setting, where unmodified cows milk and maize porridge are common. The final potential renal solute load of the milk ranged between 195 and 280 mOsm/L depending on the age and weight of the child. The lower osmolarity might have averted sodium balance complications found in severely malnourished HIV-uninfected children (15,16). Third, the energy density and protein quality in the commercial supplements were significantly better, though more expensive, than home foods. Commercial formula feeds were chosen because they are easy to provide and audit in the home setting, and women in urban areas are familiar with them. They are also generally available in district hospitals throughout South Africa and are dispensed from government hospital pharmacies for use at home. While energy dense and micronutrient-enriched peanut butter pastes have produced marked weight gain in severely malnourished children in Malawi (17), further research is required to determine if a cheaper and less refined similar supplement would be equally advantageous in our study population. Micronutrients were provided for 2–4 weeks according to local protocols and may have contributed in part to cell mucosal recovery and repair. Because of the limited resources, we were unable to perform detailed assessments of micronutrient status that would have yielded greater insights to the mechanisms by which the intervention appeared to have an effect.

The most obvious inference is, however, that food insufficiency is rife and that both HIV-infected and uninfected children, once discharged, receive a diet that is inadequate in energy, protein and micronutrients. Community-based studies in the region confirm that stunting, wasting and vitamin A deficiency are common (18). In other nutrition programmes, food supplements are often shared within the family or sold for cash. Although we could only monitor empty tins at study visits, and total energy and protein intake could not be measured, compliance with the recommendations appears to have been good and may be attributed to the discussions with parent and caregivers about the possible benefits of nutritional support. Nutrition counselling also included practical training, for example hygienic preparation of formula milk; such counselling for all caregivers may have accounted for similar follow-up rates between groups. Providing better supervision at home might have resulted in even more effective outcomes.

The study highlights the difficulty of distinguishing HIV-associated wasting due to anorexia, high metabolic demands and co-infections from severe malnutrition regardless of HIV status. The vast majority of children fulfilled local and international criteria for initiating ART, that is severely underweight (<60% of expected WFA) or CD4% less than 15–20% depending on age. WFA and CD4% are key determinants of HIV staging (19–21) and quantitative deterioration advances children between stages. This contrasts with most other criteria that are generally based on the presence or absence of clinical features such as HIV encephalopathy or specific opportunistic infections. If, as in this study, WFA were the only criteria used, some children might have changed classification from AIDS to symptomatic HIV. Response to the intervention might have indicated severe food insufficiency that compounded HIV-associated wasting. In contrast, 12–16% of children in both study groups died before 8 weeks' follow-up. These children may have been those whose malnutrition was primarily due to advanced HIV disease and were unlikely to respond to anything other than ARVs. Rather than suggesting that ARVs should be deferred until after a trial of nutritional support we would suggest that active nutritional support be provided to all children who require ARVs. Similar nutritional support should also be provided to underweight HIV-symptomatic children before they become severely malnourished, and indeed to any underweight children.

The absence of any effect of the intervention on CD4 counts or diarrhoeal morbidity should not be over-interpreted. The sample size and study methods were not designed to address these issues. Days of diarrhoea following discharge and enrolment CRP were significant independent determinants of weight gain. Some HIV-infected children were clearly able to enter a positive anabolic state once co-infections were treated and adequate energy and micronutrients provided. Any benefit that nutritional support conferred was seemingly mediated through mechanisms other than improved CD4 counts or reduced diarrhoeal morbidity. Unfortunately, we were unable to estimate changes in lean body mass and fat mass.

The results of the study were unexpectedly favourable and may appear obvious, that is if you feed a malnourished

child, he or she will gain weight. However, in hospital and clinic settings HIV-infected, severely malnourished children are sometimes regarded as beyond help and active support considered pointless. There are several programmatic implications. Nutrition support should be provided when food availability is assessed and deemed poor. Therapeutic responses to ARV treatment, for example growth may be compromised by inadequate macro- and micronutrient intake. Poor weight gain during hospitalisation should not necessarily be interpreted as a failure to respond; normal feeding patterns and improved intake might only return at home. Careful follow-up and support of mothers and other caregivers in active feeding practices once the child has returned home may yield significant benefits. Such nutritional support requires resources, infrastructure and commitment from parents, care providers and funders to ensure its sustainability.

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