

Hospitalization for severe malnutrition among HIV-infected children starting antiretroviral therapy

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Objective: To describe early hospitalization for severe malnutrition in HIV-infected children initiating antiretroviral therapy (ART).

Design: Randomized trial of induction-maintenance and monitoring strategies in HIV-infected children.

Setting: Three tertiary hospitals in Uganda and one in Zimbabwe.

Participants: 1207 HIV-infected children, median age 6 years (range, 3 months to 17 years).

Intervention: Abacavir, lamivudine and nevirapine or efavirenz were given; children in induction-maintenance arms also received zidovudine to week 36. Pre-ART inpatient/outpatient nutritional rehabilitation for children with baseline severe malnutrition.

Main outcome measures: Hospitalization for severe malnutrition and change in CD4 cell percentage by week 12 after ART. Mortality and change in weight-for-age Z-score (WAZ) by week 24 after ART.

Results: Thirty-nine of 1207 (3.2%) children were hospitalized for severe malnutrition (20 with oedema), median 28 days [interquartile range (IQR) 14, 36] after ART for marasmus and 26 days (IQR 14, 56) after ART for kwashiorkor. Hospitalized children had lower baseline and greater 24-week rise in WAZ than nonhospitalized children ($P < 0.001$). Twenty-nine of 39 (74%) children admitted for severe malnutrition had underlying infections. Of 220 children with advanced disease (baseline WAZ and CD4 cell Z-scores both < -3), 7.3% [95% confidence interval (CI) 3.8, 10.7] developed kwashiorkor and 3.6% (95% CI 1.2, 6.1) developed marasmus by week 12. CD4 cell percentage rise was similar among groups ($P = 0.37$). Twenty-four-week mortality was 32, 20 and 1.7% among children hospitalized with marasmus, kwashiorkor and not hospitalized, respectively, ($P < 0.001$).

Conclusion: One in nine children with advanced HIV required early hospitalization for severe malnutrition after ART, with a 15-fold increase in 6-month mortality compared with nonhospitalized children. Integration of HIV/malnutrition services and further research to determine optimal ART timing, role of supplementary feeding and antimicrobial prophylaxis are urgently required.

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Introduction

HIV and malnutrition overlap and interact in resource-limited settings [1]. There is high HIV prevalence among children with severe malnutrition, and mortality in these children is approximately three-fold higher than in HIV-uninfected children with severe malnutrition [2]. Similarly, malnutrition is a major risk factor for mortality in HIV-infected children. Studies from resource-limited settings, in which the majority of HIV-infected children have severe immunosuppression and poor nutritional status at presentation, consistently report 5–10% early mortality among HIV-infected children starting antiretroviral therapy (ART) [3,4].

Severe malnutrition presents as two main clinical syndromes: nonoedematous malnutrition (marasmus) and oedematous malnutrition (kwashiorkor and marasmic kwashiorkor) [5]. Although several studies report that HIV-infected children are more likely to present with nonoedematous malnutrition [6,7], there are anecdotal reports of oedematous malnutrition occurring soon after ART initiation in sub-Saharan Africa (J. Bunn, B. Amadi, personal communication); however, no study has described the frequency of this clinical observation. To better understand the interaction between malnutrition and HIV in children starting ART, we describe the frequency of hospital admissions for severe malnutrition and assess the impact of severe malnutrition on early mortality in a cohort of ART-treated children in Uganda and Zimbabwe.

Methods

Antiretroviral Research for Watoto (ARROW) is an open-label, randomized trial of induction-maintenance and monitoring strategies in 1207 HIV-infected children in Uganda and Zimbabwe (www.arrowtrial.org, ISCRTN number 24791884). Children aged 3 months to 17 years, meeting WHO criteria for ART initiation, were eligible. Children were assessed for severe malnutrition before enrolment and categorized as having kwashiorkor (60–80% weight-for-age with oedema), marasmus (<60% weight-for-age without oedema), or marasmic kwashiorkor (<60% weight-for-age with oedema), according to the Wellcome classification [8]. Children with severe malnutrition who were stable, had no concurrent infections and good appetite, or whose caregivers refused admission, received home supplementary feeding with high-energy milk (or Plumpy'nut, Nutriset, Rouen, France, from 2008). Children with severe malnutrition who were unstable, had concurrent infections or poor appetite were hospitalized for stabilization and inpatient therapeutic feeding. In general, children with severe malnutrition received 2–8 weeks of supplementary feeding prior to enrolment in the trial.

Following written informed caregiver consent, children received cotrimoxazole prophylaxis and started abacavir, lamivudine and either nevirapine or efavirenz; children randomized to an induction-maintenance arm also received zidovudine for the first 36 weeks. Children with severe malnutrition who received Plumpy'nut prior to enrolment continued it following ART initiation; children without severe malnutrition received basic food supplements and multivitamins. Children were followed up 4-weekly in dedicated study clinics for clinical evaluation and measurement of weight, height and mid-upper arm circumference (MUAC). CD4 cell count/percentage was measured in accredited laboratories 12-weekly. Viral loads were not routinely measured in ARROW.

After ART initiation, children were hospitalized for severe malnutrition if they developed oedema, loss of appetite and/or concurrent infections requiring treatment. Hospitalized children received standard-of-care inpatient nutritional rehabilitation and continued ART. The case notes of all children admitted with severe malnutrition during the first 12 weeks of ART were reviewed. Baseline characteristics were compared among children admitted with oedematous malnutrition, nonoedematous malnutrition and those not admitted. CD4 cell percentage was compared at baseline and week 12 in each group. Mortality and growth parameters through 24 weeks were compared among groups. Reported causes of death were adjudicated by an end point review committee, with independent chair and membership.

Results

A total of 1207 children, median age 6 years (range, 3 months to 17 years), were recruited between March 2007 and November 2008. No child had oedema at ART initiation. During the first 12 weeks on ART, 39 of 1207 (3.2%) children were hospitalized for severe malnutrition, of whom 20 had oedematous malnutrition (11 kwashiorkor, nine marasmic kwashiorkor) and 19 had nonoedematous malnutrition (marasmus). Median time from ART initiation to admission was 26 days [interquartile range (IQR) 14, 56] for oedematous malnutrition and 28 days (IQR 14, 36) for nonoedematous malnutrition. Fourteen of 20 (70%) children admitted with oedematous malnutrition had underlying infections [pneumonia ($n=6$), pulmonary tuberculosis ($n=3$), oral thrush ($n=3$), upper respiratory tract infection ($n=3$), otitis media ($n=2$), gastroenteritis ($n=2$), septicaemia ($n=1$) and herpes simplex keratitis ($n=1$)]; seven children had multiple infections. A similar proportion of children with nonoedematous malnutrition (15 of 19, 79%) had underlying infections [pneumonia ($n=11$), oral thrush

($n=8$), gastroenteritis ($n=6$), pulmonary tuberculosis ($n=2$), herpes labialis ($n=1$) and oesophageal candidiasis ($n=1$); nine children had multiple infections.

There were significant baseline differences between children hospitalized for oedematous malnutrition, non-oedematous malnutrition or not hospitalized (Table 1). Children hospitalized for nonoedematous malnutrition were younger [median 2 years (IQR 1, 7), $P=0.04$]. Children hospitalized for oedematous malnutrition were more severely immunosuppressed (median CD4 cell percentage 2.5% (IQR 1.5, 12.8), $P=0.005$). Overall, children hospitalized for severe malnutrition had significantly lower baseline weight-for-age, height-for-age, weight-for-height and MUAC than nonhospitalized children, whereas differences between those with oedematous malnutrition and nonoedematous malnutrition were small (Table 1). Of the 39 hospitalized children, 34 (87%) had weight-for-age Z-score (WAZ) less than -3 at baseline; these children were clinically stable at trial entry, but deteriorated after ART initiation. Of 220 children with baseline WAZ and CD4-for-age Z-scores both less than -3 , 16 [7.3%; 95% confidence interval (CI) 3.8, 10.7] were hospitalized for oedematous malnutrition after starting ART and eight (3.6%; 95% CI 1.2, 6.1) for nonoedematous malnutrition. There were no significant differences among groups in primary caregiver (mother 57%, aunt 14% and grandmother 11%)

or percentage of household income spent on food [median 25% (IQR 10, 45)].

Mortality among children with severe malnutrition was high (Table 1). Two of 20 (10%) children hospitalized for oedematous malnutrition and four of 19 (21%) children hospitalized for nonoedematous malnutrition died within 12 weeks of starting ART, compared with 14 of 1168 (1.2%) children not hospitalized for severe malnutrition. Within 24 weeks, four of 20 (20%) children with oedematous malnutrition and six of 19 (32%) children with nonoedematous malnutrition had died, compared with 20 of 1168 (1.7%) children without severe malnutrition. However, those who survived recovered well. Rise in CD4 cell percentage 12 weeks after ART was not significantly different between children with or without severe malnutrition (Table 1), although those with oedematous malnutrition started from a lower level. Children with severe malnutrition had significantly greater increases in WAZ and MUAC over the first 24 weeks of ART, compared with those without severe malnutrition (Table 1).

Discussion

Nutritional status, immune function and infectious burden interact in children, especially in the context of

Table 1. Baseline characteristics, mortality, change in CD4 cell count and growth parameters among HIV-infected children starting antiretroviral therapy.

Characteristic	Not hospitalized, <i>N</i> = 1168		Hospitalized with nonoedematous malnutrition, <i>N</i> = 19		Hospitalized with oedematous malnutrition, <i>N</i> = 20		<i>P</i> -value ^a
	Median	IQR	Median	IQR	Median	IQR	
Baseline							
Age (years)	6	2, 9	2	1, 7	4	1, 8	0.042
CD4 cell percentage (%)	12.3	7.5, 17.4	10.0	8.0, 15.5	2.5	1.5, 12.8	0.005
Weight-for-age Z-score	-2.1	-3.2, -1.2	-4.9	-6.1, -4.0	-4.9	-6.1, -3.9	<0.001
Height-for-age Z-score	-2.4	-3.3, -1.4	-3.6	-4.3, -2.3	-3.1	-4.1, -2.5	<0.001
Weight-for-height Z-score ^b	-0.5	-1.3, 0.3	-3.1	-3.6, -2.0	-2.9	-4.1, -2.3	<0.001
MUAC < 11 cm, <i>n</i> (%)	30	2.6%	4	21.0%	4	20.0%	<0.001
MUAC < 12.5 cm, <i>n</i> (%)	143	12.2%	12	63.2%	11	55.0%	<0.001
Change after 12-week ART							
CD4 cell percentage (%)	+8.5	4.5, 13.0	+6.9	2.8, 11.3	+6.3	2.9, 10.0	0.37
Mortality, <i>n</i> (%)	14	1.2%	4	21.1%	2	10.0%	<0.001
Change after 24-week ART							
Weight-for-age Z-score	+0.4	0.0, 1.0	+1.4	0.3, 2.0	+2.5	1.4, 3.2	<0.001
Height-for-age Z-score	+0.0	-0.2, 0.3	-0.3	-0.5, 0.3	-0.1	-0.4, 0.2	0.28
Change in MUAC (cm)	+0.8	0.1, 1.7	+1.3	1.0, 3.1	+2.9	1.3, 4.3	0.018
Mortality, <i>n</i> (%)	20	1.7%	6	31.6%	4	20.0%	<0.001

Baseline age, CD4 cell percentage and growth parameters are shown for children who were not hospitalized, hospitalized for nonoedematous malnutrition (marasmus) or hospitalized for oedematous malnutrition (kwashiorkor or marasmic kwashiorkor) after initiation of ART. Absolute increase in CD4 cell percentage at week 12 after ART, changes in growth parameters through 24 weeks of ART and mortality at 12 and 24 weeks are shown for the three groups of children. ART, antiretroviral therapy; IQR, interquartile range; MUAC, mid-upper arm circumference.

^aOne-way analysis of variance or Fisher's exact test used to compare baseline characteristics and change in CD4 cell percentage after 12 weeks. Generalized estimating equations used to compare changes in growth over 24 weeks with repeated measurements 4-weekly from each child, and Fisher's exact test to compare mortality within 24 weeks.

^bWHO 2007 weight-for-height Z-scores, only available for heights in 65–120 cm, 801 controls, 14 nonoedematous malnutrition cases and 13 oedematous malnutrition cases.

HIV infection [1], in which malnutrition and immunosuppression are compounding risk factors for early mortality following ART initiation [1,4]. In this study, a substantial proportion of HIV-infected children [10.9% (or one in nine) of those with advanced disease] were hospitalized for severe malnutrition within 12 weeks of starting ART. The majority had WAZ less than -3 , but were clinically stable at baseline; however, after starting ART they deteriorated. Children were hospitalized for severe malnutrition early (median 26 days after ART for oedematous malnutrition) and had 15-fold higher mortality by 6 months than nonhospitalized children.

It is particularly striking that half the children hospitalized for severe malnutrition developed oedema after starting ART, because kwashiorkor is less common than marasmus in HIV-infected children [6,7]. However, this finding supports anecdotal observations from clinicians in sub-Saharan Africa that kwashiorkor occurs in a proportion of children soon after starting ART. In our study, 7.3% (one in 14) children who had severe baseline immunosuppression and malnutrition were admitted for oedematous malnutrition by 12 weeks. As many children starting ART in resource-limited settings have advanced disease [4], a similar frequency of early hospitalization for oedematous malnutrition may be anticipated in treatment programmes. Although the mechanism underlying onset of kwashiorkor is unclear, there are several potential explanations. First, it has been proposed that a degree of immune competence is required to develop oedematous malnutrition [7]. The pro-inflammatory state that characterizes severe HIV infection without ART may limit development of oedema [9]. ART initiation, by decreasing immune activation and increasing CD4 cell count, may result in development of oedema. Second, onset of kwashiorkor soon after starting ART may be an example of the immune reconstitution inflammatory syndrome (IRIS). The timing of onset and picture of clinical worsening in children with profound immunosuppression and malnutrition at ART initiation are all very reminiscent of IRIS. Although it most frequently presents as unmasking or worsening of a pre-existing infection, protean manifestations of IRIS have been reported, including autoimmune, inflammatory and malignant disease [10]. Third, onset of oedema may be a variant of the refeeding syndrome which could occur due to increased appetite following ART initiation. Refeeding syndrome is characterized by fluid/electrolyte shifts and high mortality [11]. Fourth, this may be an unusual manifestation of antiretroviral toxicity in malnourished children. Frequency of toxicity is highest shortly after ART initiation [12], and may be more likely in individuals with a profound nadir CD4 cell count [13]. Although the clinical presentation is not typical of any known antiretroviral toxicity, it is possible that combination ART started in children with severe

malnutrition, immunosuppression and metabolic disturbance may have diverse clinical manifestations.

Hospitalization for nonoedematous malnutrition occurred with similar frequency and timing as hospitalization for oedematous malnutrition. Children with marasmus were younger than those with kwashiorkor and, although they had a similar baseline nutritional status, they were less severely immunosuppressed. However, mortality among children with marasmus was strikingly high. By 6 months after ART, almost one-third (31.6%) children hospitalized for marasmus had died, compared with 1.7% children not admitted for severe malnutrition. It is unclear why HIV-infected children with baseline marasmus should become more unstable after ART initiation. However, it is possible that the catabolic demands of immune reconstitution may precipitate frank protein-energy malnutrition in children with pre-existing wasting and stunting, particularly in those with profound immunosuppression at ART initiation.

There is an urgent need to integrate malnutrition and HIV services, as historically these have often been separated. As shown in this and previous studies [2,4,12], malnutrition is common in HIV-infected children and the two diseases cannot be treated in isolation. However, the optimal management of HIV in severely malnourished children remains uncertain. Recent WHO guidelines [14] emphasize the importance of early assessment and management of HIV-associated malnutrition, but acknowledge that there is a lack of evidence regarding its prevention and treatment. Malnourished children entering ART programmes require careful assessment and stabilization, as mortality is high; it is increasingly recognized that both the pathophysiology and optimal management of HIV-infected children with severe malnutrition differs from that of HIV-uninfected children [15].

There is an urgent need to understand better the complex interplay between malnutrition, infection and immunodeficiency. Future trials should address the optimal management of malnourished children starting ART, to reduce mortality [15]. Supplementary feeding may be expected to improve outcome, given the high prevalence of baseline malnutrition among children subsequently admitted for severe malnutrition. Current guidelines [14] recommend initial inpatient or outpatient therapeutic feeding of HIV-infected children presenting with severe malnutrition, followed by 50–100% increased energy intake for at least the first 6–10 weeks of ART, when immune reconstitution occurs rapidly. However, many children in this current study deteriorated clinically, despite receiving home-based nutritional rehabilitation while ART was started. Children may require a longer period of nutritional supplementation prior to ART, although the high mortality associated with profound

immunosuppression means that early ART initiation is a competing priority. The optimal timing and dosing of ART in malnourished children remains uncertain [15]. In addition, the majority of children hospitalized for severe malnutrition had underlying infections. Current WHO guidelines [16] recommend isoniazid preventive therapy for children starting ART; however, additional antimicrobial prophylaxis (particularly, against pneumonia and candidiasis) may help to reduce hospitalization further.

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