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Evaluation of a Nutritional Support Intervention in Malnourished HIV-Infected Children in Bamako, Mali

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Background: We assessed a nutritional support intervention in malnourished HIV-infected children in a HIV-care program of the University Hospital Gabriel Touré, Bamako, Mali.

Methods: All HIV-infected children younger than 15 years were diagnosed for malnutrition between 07 and 12, 2014. Malnutrition was defined according to the WHO growth standards with Z-scores. Two types were studied: acute malnutrition (AM) and chronic malnutrition (CM). All participants were enrolled in a 6-month prospective interventional cohort, receiving Ready-To-Use Therapeutic Food, according to type of malnutrition. The nutritional intervention was offered until child growth reached -1.5 SD threshold. Six-month probability to catch up growth (>-2 SD) was assessed for AM using Kaplan-Meier curves and Cox model.

Results: Among the 348 children screened, 198 (57%) were malnourished of whom 158 (80%) children were included: 97 (61%) for AM (35 with associated CM) and 61 (39%) with CM. Fifty-nine percent were boys, 97% were on antiretroviral therapy, median age was 9.5 years (Interquartile Range: 6.7–12.3). Among children with AM, 74% catch-up their growth at 6-month; probability to catch-up growth was greater for those without associated CM (adjusted Hazard Ratio = 1.97, CI 95%: 1.13 to 3.44). Anemia decreased significantly from 40% to 12% at the end of intervention ($P < 0.001$).

Conclusions: This macronutrient intervention showed 6-month benefits for weight gain and reduced anemia among these children

mainly on antiretroviral therapy for years and aged greater than 5 years at inclusion. Associated CM slows down AM recovery and needs longer support. Integration of nutritional screening and care in the pediatric HIV-care package is needed to optimize growth and prevent metabolic disorders.

Key Words: HIV, malnutrition, Children, Adolescents, nutritional support, Africa

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INTRODUCTION

Malnutrition is highly prevalent among children living in resource-limited settings and constitutes an even more important burden for children infected by Human Immunodeficiency Virus (HIV). Several forms of malnutrition can occur. Wasting, or acute malnutrition (AM), is a weight deficiency, because of a rapid weight loss from an acute infection or famine. The body mass is reduced and vital functions are impaired, leading to a high risk of death. Stunting, or chronic malnutrition (CM), is a height deficiency, because of repeated episodes of malnutrition, food insecurity, or chronic infection. If weight deficiency is not reversed, growth starts to slowdown and even stop, leading to stunting. Underweight is also a weight deficiency, but it can determine the type of malnutrition, acute or chronic.¹ In sub-Saharan Africa in 2014, 8% of children <5 years were wasted, 36% were stunted, and 20% were underweight.² In Mali, the prevalence estimates of malnutrition in 2012 were 9%, 28%, and 19% for wasting, stunting, and underweight, respectively.³ Among HIV-infected children, high rates of malnutrition are found, in those not yet on antiretroviral therapy (ART) as well as for those on ART. Indeed, at ART initiation, 50 percent of children were underweight or wasted, and up to two-third were stunted in many African studies.^{4–7} In a cross-sectional study conducted in 2011 in HIV-care programs in West and Central Africa among HIV-infected children and adolescents, 33% suffered from CM and 16% from AM, whereas most of them were already on ART.⁸

HIV-infected children are more vulnerable to malnutrition than non-HIV-infected children and have a 3-times higher risk of mortality in case of severe AM (SAM).⁹ Children perinatally HIV-infected often face severe CM problems that can impair their social and cognitive development remaining beyond adolescence.^{10–12} In addition, although a growth improvement is observed in HIV-infected children after ART initiation, a substantial proportion

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of children remain malnourished even on ART.^{4–7} Thus, a routine nutritional support should be offered in these HIV-infected children on the top of ART to optimize their growth response.

However, specific nutritional recommendations in HIV-infected children are currently still limited, complex and nutritional care is not fully integrated to the pediatric HIV-care package. The World Health Organization (WHO) stated that children with HIV-infection should increase their energetic needs by 10% when asymptomatic, by 20%–30% during symptomatic phases, and by 50%–100% for an episode of SAM.¹³ Moreover, for the general pediatric population, nutritional protocols, as those used by the National Nutritional Program of Mali,¹⁴ are well defined for SAM until the age of 5 years. Recommendations for nutritional support among underweight children aged 6 months to 14 years are also part of the WHO guidelines for HIV-infected children,¹³ with the use of fortified porridge for example. No specific recommendations for chronic forms of malnutrition are available to our knowledge, especially for HIV-infected children or children older than 5 years. Recommendations for moderate acute malnutrition (MAM) are not developed as those for SAM.

Questions remain in 2016 on how to support nutritionally all malnourished HIV-infected children on ART regardless to their type/form of malnutrition. The objective of this study was to assess the effectiveness of a nutritional intervention among all malnourished HIV-infected children enrolled in a pediatric HIV-care program in Bamako, Mali and to identify their associated factors to catch up growth after 6 months.

METHODS

Settings and Study Population

The study took place at the pediatric HIV-care service of the University Hospital Center Gabriel Touré in Bamako, Mali. All HIV-infected children included in the program were seen routinely 3 monthly with data collection on clinical events and anthropometric indicators. From July to December 2014, all HIV-infected children younger than 15 years attending the program and diagnosed with malnutrition (definitions below) during follow-up were eligible to receive a nutritional supplementation intervention. The formal written approval of the main caregiver of the child and written approval of all children older than 7 years have been collected before intervention. The study was conducted with the approval of the Institutional Review Board of the faculty of medicine and stomatology of Mali, obtained on March 2014.

Study Design, Definitions of Malnutrition, and Intervention

We conducted a 6-month prospective interventional cohort consisting of nutritional supplementation of all malnourished HIV-infected children.

Malnutrition was defined according to the WHO growth standards^{15,16} using Z-scores. A Z-score < -2 SD determine

malnutrition, which can be moderate [Z-score = $(-3; -2)$ SD] or severe (Z-score < -3 SD). Z-scores were determined with WHO Anthro and WHO Anthroplus softwares. AM was defined as Weight-for-Height Z-score (WHZ) of < -2 SD among children younger than 5 years and body mass index (BMI) for age Z-score (BAZ < -2) for older children. SAM was defined as WHZ/BAZ < -3 SD. CM was defined as Height-for-Age Z-score (HAZ) < -2 SD and severe CM as HAZ < -3 SD. Nutritional supplements were Ready-to-Use-Therapeutic Food (RUTF) (Plumpy Nut, Nutriset) offered until child growth reached the -1.5 SD threshold, because a threshold just reaching -2 SD was not considered as a sustainable catch-up growth. The duration was not defined as a standard but tailored according to the catch-up growth observed in each child.

Supplement doses were adjusted according to the age and weight of the child, the type and the severity of malnutrition. Quantities were based on the national recommendations on nutrition in Mali,¹⁴ as well as the WHO guidelines for nutritional support of HIV-infected children.¹³ Mean energetic supports for SAM were 80–180 kcal·kg⁻¹·d⁻¹ according to the child's weight. Children with MAM and CM followed the same nutritional support, with mean energetic supports of 30–90 kcal·kg⁻¹·d⁻¹ according to the child's weight. Children with both acute and chronic of malnutrition (AM + CM) were treated for AM in priority, as they were at high risk of morbidity and mortality.

Baseline was defined at the start of nutritional supplementation. All children were seen after 2 weeks of supplementation to control their nutritional status and the acceptance of the products. Then, they were followed and supplemented monthly until their catch-up growth reached -1.5 SD of WHZ/BAZ for children with AM or AM + CM, and -1.5 SD of HAZ for children with CM exclusively. The evaluation criterion was the catch-up growth measured after 6 months of support.

All health care professionals have been specifically trained to assess malnutrition with standardized anthropometric measures, and to provide the nutritional intervention.¹⁷

Data Management and Variables

At inclusion, data on sociodemographic characteristics, clinical events, anthropometric indicators, and treatments were recorded. Moreover, blood samples were collected to measure immunological, virological, and biological status, based on measures of CD4 count, viral load, fasting glycemia, hemoglobin, cholesterolemia, and triglyceridemia. Measures were done for each child at baseline, before the start of the nutritional support, as well as at the end of the support, and 6 months after the end of the support. Additional data on clinical events, treatment modifications occurring during follow-up were recorded, in addition to anthropometric measures and data on the consumption of the nutritional products.

Threshold for viral load undetectability, measured using Abbott M2000, was defined < 50 copies per milliliter. Immunodeficiency for age was based on the 2006 WHO definitions.¹⁸ Severe immunodeficiency was defined by

CD4% < 15 or CD4/μL < 350, and moderate immunodeficiency by CD4% = [15–25 (or CD4 cells/μL = 350–499)]. Levels of biological adverse events were based on the division of AIDS table for grading the severity of adult and pediatric adverse events.¹⁹

We described causes of death, lost to follow up and other clinical events occurring during the study. Nutritional habits (number of meals and snacks per day) and the consumption of RUTF at each visit were collected. The RUTF consumption was defined as the proportion of doses actually consumed on the number of doses prescribed initially. We defined the “good consumption of RUTF” as the actual consumption of >66% of the overall prescription offered.

Statistical Analyses

Interim database analyses were conducted to monitor the nutritional intervention, about every 3 months. The prevalence of each type of malnutrition, acute using WHZ/BAZ, and chronic using HAZ, among HIV-infected children included was determined with their 95% confidence interval (95% CI). Then, comparisons of the characteristics between malnourished and nonmalnourished children were made, as well as between those children included and nonincluded, using χ^2 and Fisher tests for qualitative variables, and Student and Mann-Whitney Wilcoxon tests for quantitative variables. The evolution of biological data was assessed using McNemar test, Student and Wilcoxon test for paired samples.

Our primary outcome was the proportion of children with AM or AM + CM who catch up their growth at a threshold of -2 SD, then -1.5 SD. A 6-month probability to catch up growth from AM was described using Kaplan-Meier estimates, and associated factors to probability to catch up growth were assessed with a Cox proportional hazards regression model. Event of interest was the probability to the first recovery from malnutrition. Children were followed up from start of the nutritional support to time to first catch up growth, death, last visit, 6 months of follow-up or end of the study on the April 30, 2015. Variables with a *P* value <0.25 in univariate analyses were selected and then kept in a full adjusted model. Co-variables were age, gender, immunodeficiency for age, viral load, orphan status, severity of malnutrition, associated CM, good consumption of RUTF, ART regimen and duration on ART. Age and immunodeficiency for age were forced in the adjusted model.

RESULTS

Selection Process and Characteristics of the Study Population at Inclusion

Between July and December 2014, 348 children attended at least once the pediatric HIV-care center in Bamako, and 339 (97%) were screened for malnutrition. Among them, 198 were diagnosed as malnourished (58%), 23% with exclusive CM, 23% with exclusive AM, and 12% with both chronic and AM, with for each type 1/3 of severe form (Fig. 1). Overall, median age was 9.1 [Interquartile

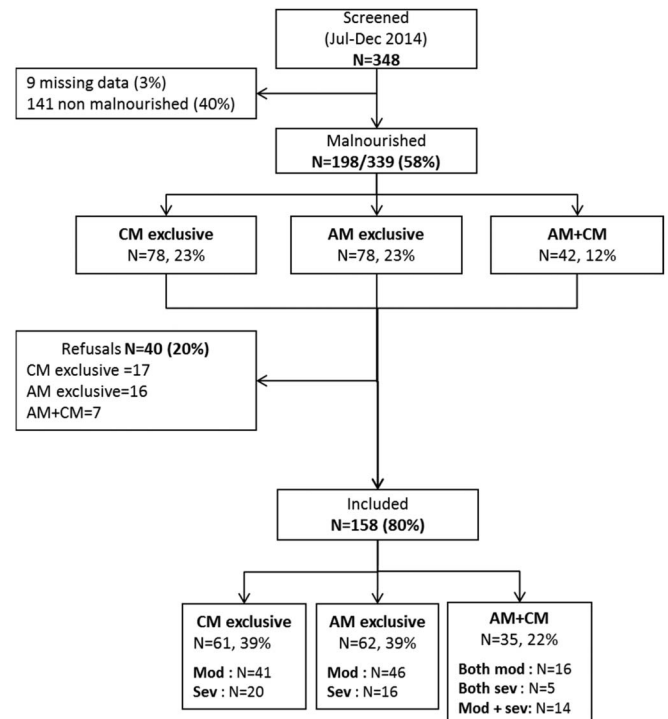


FIGURE 1. Flowdiagram of the selected population and prevalence of malnutrition, Bamako, Mali, 2014–2015. Mod, moderate; Sev, severe.

range IQR = (5.7–11.8)]. Malnourished children had initiated ART older than nonmalnourished children [median 3.7 years IQR = (1.8–6.9) vs 2.5 years, IQR = (1.5–4.7); *P* = 0.002], whatever the type of malnutrition (data not shown). The nutritional intervention has been proposed to the 198 malnourished children, of whom 158 (80%) have been included. Reasons of noninclusion were mainly due to refusals because of long distance from the clinical center, or fear of stigma. There were no differences between groups included and not included children according to immunological, virological, or sociodemographic data at inclusion and at ART initiation (data not shown).

Among the 158 children who received the nutritional support, 61 (39%) were supported for a chronic form of malnutrition and 97 (61%) for an acute form, of which 35 (36%) had an associated CM (Fig. 1). At inclusion, median age was 9.5 years (IQR 6.7–12.3). Sex-ratio was 1.4. Close to half of them lived in a household with more than 10 persons, 44% were orphans (Table 1). Approximately 97% of children were on ART at inclusion, with 43% since more than 5 years. Moreover, 55% of these children have initiated ART before 5 years of age. At inclusion in the study, half of children were no immunodeficient and 43% had an undetectable viral load (<50 c/mL), all children were on cotrimoxazole. Anemia was found in 40% of children, 20% of children had hypoglycemia, and 27% hypercholesterolemia (Table 1). Children with exclusive AM were younger than those with exclusive CM (aged 1–5 years: 7% vs 30%, *P* = 0.040), were on ART for a longer duration than the 2 other groups (≥5 years: 58% vs

TABLE 1. Baseline Characteristics of the 158 HIV-Infected Children Malnourished Included According to Their Type of Malnutrition, 2014, Bamako, Mali

	Total (N = 158)		CM Exclusive (n = 61)		AM Exclusive (n = 62)		AM + CM (n = 35)	
	N	%	N	%	N	%	N	%
A: Sociodemographic data								
Age groups, yrs								
1–5	29	18.4	18	29.5	4	6.5	7	20.0
5–10	55	34.8	19	31.1	25	40.3	11	31.4
>10	74	46.8	24	39.3	33	53.2	17	48.6
Boys	93	58.9	39	63.9	38	61.3	16	45.7
Number of persons living in the household ≥10	83	52.5	30	49.2	34	54.8	19	54.3
Orphanhood								
No	89	56.3	36	59.0	33	53.2	20	57.1
Yes, father	22	13.9	8	13.1	22	35.5	6	17.1
Yes, mother	33	20.9	12	19.7	33	53.2	6	17.1
Both parents	14	8.9	5	8.2	14	22.6	3	8.6
B: Data on treatment, immunology, and viral load								
On ART	153	96.8	59	96.7	60	96.8	34	97.1
Age groups at ART initiation, yrs								
0–2	34	22.2	18	30.5	11	18.3	5	14.7
2–5	51	33.3	17	28.8	24	40.0	10	29.4
5–10	55	35.9	18	30.5	23	38.3	14	41.2
>10	13	8.5	6	10.2	2	3.3	5	14.7
ART regimen								
2 NRTIS + 1 NNRTI	89	58.2	32	54.2	37	61.7	20	58.8
2 NRTIS + 1 PI (LPV/RIT)	64	41.8	27	45.8	23	38.3	14	41.2
Duration on ART								
<6 mo	28	18.3	13	22.0	5	8.3	10	29.4
6–12 mo	9	5.9	4	6.8	3	5.0	2	5.9
12–24 mo	17	11.1	9	15.3	5	8.3	3	8.8
2–5 yrs	33	21.6	13	22.0	12	20.0	8	23.5
≥5 yrs	66	43.1	20	33.9	35	58.3	11	32.4
Immunodeficiency for age at inclusion*								
No	87	55.1	30	49.2	41	66.1	16	45.7
Moderate	11	7.0	6	9.8	1	1.6	4	11.4
Severe	27	17.1	7	11.5	10	16.1	10	28.6
Undetermined	33	20.9	18	29.5	10	16.1	5	14.3
Undetectable viral load (< 50 c/mL) at inclusion (N = 124)	70	56.5	33	64.7	23	47.9	14	56.0
On cotrimoxazole	158	100.0	61	100.0	62	100.0	61	100.0
C: Biological data								
Hemoglobin level, g/dL, mean (SD) (N = 126)	10.1 (1.5)		47	9.8 (1.5)	52	10.4 (1.4)	27	10.2 (1.4)
Anemia								
No (≥10)	76	60.3	25	53.2	34	65.4	17	63.0
Grade 1 (mild) (8.5; 10)	34	27.0	15	31.9	12	23.1	7	25.9
Grade 2 (moderate) (7.5; 8.5)	7	5.6	3	6.4	3	5.8	1	3.7
Grade 3 (severe) (6.5; 7.5)	7	5.6	2	4.3	3	5.8	2	7.4
Grade 4 (potentially life-threatening) <6.5	2	1.6	2	4.3	0	0.0	0	0.0
Glycemia level, mmol/L, mean (SD) (N = 96)	4.2 (0.9)		38	4.3 (1.1)	34	4.1 (0.8)	24	4.3 (0.8)
Normal (3.56; 6.44)	74	77.1	30	78.9	24	70.6	20	83.3
Hypoglycemia grade 1 (3.06; 3.56)	16	16.7	4	10.5	9	26.5	3	12.5
Hypoglycemia grade 2 (2.22; 3.06)	2	2.1	1	2.6	1	2.9	0	0.0
Hypoglycemia grade 3 (1.67; 2.22)	1	1.0	0	0.0	0	0.0	1	4.2
Hyperglycemia grade 1 (6.44; 8.88)	3	3.1	3	7.9	0	0.0	0	0.0
Cholesterolemia level, mmol/L, mean (SD) (N = 93)	3.9 (1.1)		37	3.7 (1.0)	35	3.8 (1.2)	21	4.2 (1.0)
Normal <4.37	68	73.1	30	81.1	27	77.1	11	52.4
Grade 1 (4.37; 5.14)	15	16.1	5	13.5	3	8.6	7	33.3
Grade 2 (5.14; 7.70)	10	10.8	2	5.4	5	14.3	3	14.3

TABLE 1. (Continued) Baseline Characteristics of the 158 HIV-Infected Children Malnourished Included According to Their Type of Malnutrition, 2014, Bamako, Mali

	Total (N = 158)		CM Exclusive (n = 61)		AM Exclusive (n = 62)		AM + CM (n = 35)	
	N	%	N	%	N	%	N	%
Triglyceridemia, mmol/L, mean (SD) (N = 93)	1.3 (0.8)		37	1.5 (1.1)	35	1.2 (0.5)	21	1.2 (0.5)
Normal (<5.65)	92	98.9	36	97.3	35	100.0	21	100.0
Hypertriglyceridemia grade 1 (5.65–8.48)	1	1.1	1	2.7	0	0.0	0	0.0

*2006 WHO definitions.
 LPV/RIT, Lopinavir/Ritonavir; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

34% for exclusive CM and 32% for AM + CM, $P < 0.002$) and were more often nonimmunodeficient than the others (66% vs 49% exclusive CM and 46% AM + CM). They had also more often hypoglycemia than the others (29% vs 13% exclusive CM and 12% AM + CM, $P < 0.030$). Children with exclusive CM suffered more from anemia (45% vs 35% for exclusive AM and 37% for AM + CM, $P < 0.010$) and children with both AM and CM suffered more from hypercholesterolemia (48% vs 19% for exclusive CM and 23% for exclusive AM, $P < 0.040$).

Follow-up Characteristics

The median follow-up time was 6.3 months (IQR 3.0–8.6) and was longer for children with CM, exclusive or not [7.5 months (IQR 5.0–9.0) and 7.7 (IQR 5.1–9.0) vs 3.1 months (IQR 2.9–6.2), $P < 0.001$]. After 6 months, 26 children (16.5%) were lost to follow up, with 14 (8.8%) refusals to take RUTF [median cessation at 3.5 months (IQR 1.1–4.1)], and 12 (7.5%) withdrawals, related to fear of stigma, too long distance, or unavailability. Two children (1.3%) died at hospital after 3 months of follow-up (1 for repeated apyretic convulsive crisis, and 1 due to SAM) but

were not related to the nutritional intervention. Intercurrent infections and adverse events occurred in 48 children (30.4%) during follow-up: diarrhea (10.8%), malaria (9.5%), respiratory tract infection (8.2%), or other diseases (13.9%) (cold, otitis, anorexia, pyoderma, and dental pain). Children with CM, exclusive or not, had more intercurrent infections than children with exclusive AM (37.7% and 42.9%, respectively vs 16.1%, $P = 0.007$) (data not shown).

RUTF Consumption

We did not see any changes of the proportion of RUTF consumption over the 6-month period. Respectively, 60%, 58%, 49%, 45%, 42%, and 50% of children took all the dose prescribed at 1, 2, 3, 4, 5, and 6 months. In addition, approximately 10% took more than the dose prescribed at each visit. Among children who took less than the dose prescribed, the mean consumption was about 60%. Overall, 139 (88%) children were considered to have a good RUTF consumption, taking at least two-third of the prescription during the follow-up. There were no differences in socio-demographic characteristics (orphanhood, number of persons living in the household) comparing children according to their

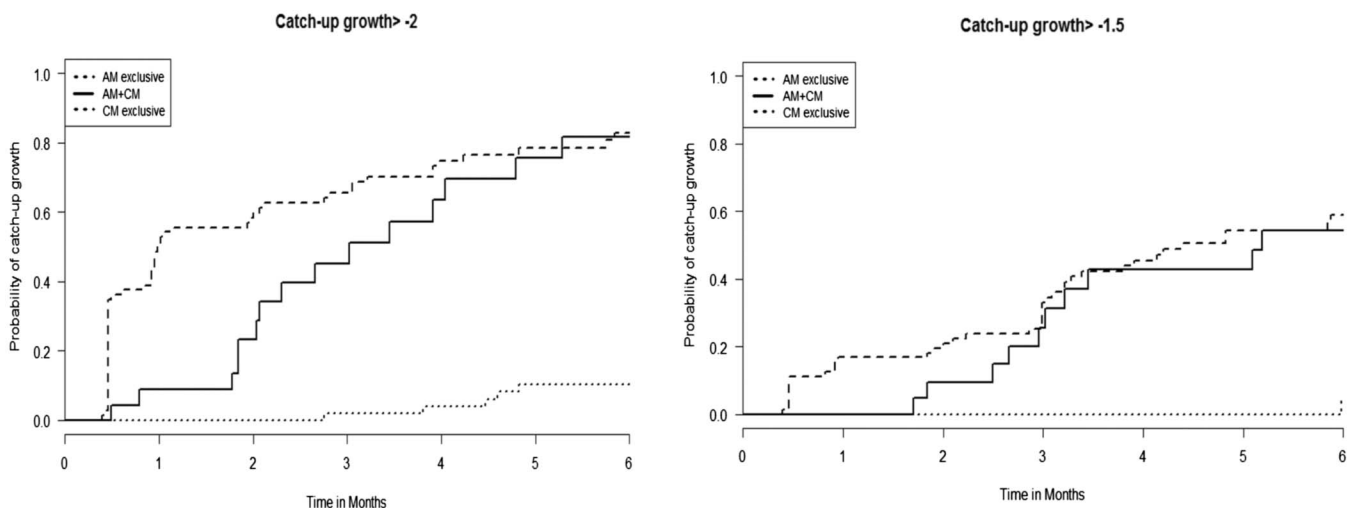


FIGURE 2. Estimated probabilities of catch-up growth (thresholds at -2 and -1.5 SD), based on Kaplan-Meier estimates, after nutritional supplementation among HIV-infected children, according to type of malnutrition: AM exclusive, AM + CM or CM exclusive, 2014–2015, Bamako, Mali.

profile of consumption. There was a nonsignificant tendency to a lower consumption for children supported for a SAM (76% of good RUTF consumption).

Catch-up Growth and Associated Factors

Acute Malnutrition

Among the 97 children supported for an AM, mean WHZ/BAZ gain at 3 months was +0.61 SD for MAM and +1.67 SD for SAM. After 6 months, it was +0.95 SD and +2.05 SD for MAM and SAM, respectively. At the same time, HAZ decreased, illustrating a slowdown or a stop in height growth during weight recovery (Supplemental Digital Content, <http://links.lww.com/QAI/B53>).

After 6 months of supplementation, for a threshold at -2 SD, 72/97 (74%) children had to catch up their growth for an AM, 57/72 (79%) and 15/25 (60%) for MAM and SAM, respectively. Median time to catch up growth was 1.0 month (95% CI: 0.8 to 2.1) and 3.0 months (95% CI: 2.0 to 4.8) for MAM and SAM, respectively. Moreover, children with AM +CM had lower rates of catch-up growth compared with those with exclusive AM (81% vs 63% at 6 months) (Fig. 2). In Cox analysis, adjusted on sex, age, immunodeficiency for age, and severity of malnutrition, children with a good RUTF consumption had a higher probability to catch up growth, as

well as children without associated CM [adjusted hazard ratio (aHR) = 3.42, 95% CI: 1.19 to 9.71 and aHR = 1.97, 95% CI: 1.13 to 3.44, respectively]. Children with a severe immunodeficiency for age at inclusion tended to be more likely to catch up their growth compared with children no immunodeficiency (aHR = 2.15, 95% CI: 1.09 to 4.22) (Table 2).

Using a threshold at -1.5 SD, 49/97 (51%) of children had to catch up their growth for an AM, 39/72 (54%) and 10/25 (40%) for MAM and SAM, respectively, with a median time to catch up growth at 4-5 months of follow-up. In Cox analysis, the same trend to a higher probability to catch up growth for children without associated CM was found (aHR = 3.42, 95% CI: 1.56 to 7.48) (Table 2 and Fig. 2), as well as for children severely immunodeficient (aHR = 2.27, 95% CI: 1.05 to 4.91). A good RUTF consumption and the severity of malnutrition had no significant effect on the probability to catch up growth at this higher threshold. Moreover, younger children were significantly more likely to catch up growth (0-5 vs 10-15 years, aHR = 0.27, 95% CI: 0.10 to 0.71) (data not shown).

Chronic Malnutrition

Among the 61 children supported for a CM, we did not report any significant height gain during the intervention but weight improved (mean increase WHZ/BAZ +0.78 SD at 6 months), and 3 children became overweight (BAZ >2 SD)

TABLE 2. Factors Associated With 6-Month Catch-up Growth (Z-Score WHZ/BAZ > -2 SD) for the 97 Children With AM, Univariate and Multivariate Cox Model Analysis, 2014-2015 Bamako, Mali

Variables	Catch-up Growth for AM (Z-score > -2 SD)					
	HR	95% CI	P	aHR	95% CI	P
Girls/boys	0.69	0.43 to 1.12	0.132	0.61	0.37 to 1.01	0.055
Age groups at inclusion, yrs			0.703			0.549
1-5	1.00	—		1.00	—	
5-10	0.72	0.32 to 1.59		0.65	0.28 to 1.51	
10-15	0.81	0.38 to 1.74		0.64	0.28 to 1.46	
Immunodeficiency for age at inclusion*			0.709			0.137
No	1.00	—		1.00	—	
Moderate	0.63	0.20 to 2.04		0.86	0.26 to 2.81	
Severe	1.26	0.69 to 2.24		2.15	1.09 to 4.22	
Missing	0.94	0.49 to 1.79		0.97	0.50 to 1.89	
Viral load at inclusion (copies/mL)			0.348			
Undetectable	1.00	—				
50-1000	1.10	0.57 to 2.12				
>1000	0.62	0.32 to 1.21				
Missing	0.72	0.40 to 1.30				
ART regimen			0.575			
NNRTI-based	1.00	—				
PI-based	1.29	0.79 to 2.09				
Untreated	0.90	0.22 to 3.74				
Orphan (yes/no)	1.18	0.74 to 1.87	0.496			
Good RUTF consumption† (yes/no)	3.19	1.16 to 8.76	0.024	3.40	1.19 to 9.71	0.023
Severity of malnutrition (moderate/severe)	1.58	0.90 to 2.80	0.114	2.32	1.21 to 4.46	0.012
Associated CM (yes/no)	1.67	1.01 to 2.77	0.046	1.97	1.13 to 3.44	0.017

All the P-values highlighted in bold are P-values <0.05.

*2006 WHO guidelines.

†At least two-third of the dose prescribed during the entire follow-up.

HR, hazard ratio; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; PI, Protease Inhibitor.

after 4 and 7 months of supplementation. Overall, after 6 months of intervention, 6 children catch up their growth (HAZ) at a threshold of -2 SD, including 1 child at a threshold of -1.5 SD. All of them had MCM (Fig. 2). Among these 6 children, 4 were older than 10 years, and 3 were on ART for more than 5 years at the start of the intervention, 4 were not immunodeficient for their age (the 2 others had missing data) and 2 had an undetectable viral load. HAZ evolution did not differ according to the age at the start of intervention.

Biological Evolution

Between the start and the end of the nutritional supplementation, there were no significant evolution of mean CD4 count and viral load, with no changes in the rate of severe immunodeficiency for age and undetectable viral load. Median hemoglobin level has increased of $+0.64$ g/dL ($n = 126$, $P < 0.001$). Rates of anemia were reduced significantly (from 39.7% to 11.7%), whatever the type of malnutrition (Table 3).

Between the start of the intervention and the first 6 months after the end, CD4 count did not evolve significantly, with no change in rates of severe immunodeficiency for age. Mean viral load did not evolved significantly, but less children had an undetectable viral load (from 56.5% to 43.6%, $P = 0.028$). Overall, 21/103, 32% of children with an undetectable viral load at inclusion get a detectable viral load in the 6 months after the end. Median hemoglobin level still has increased of $+1.39$ g/dL ($n = 110$, $P < 0.001$). Among acute malnourished children, those who catch up their growth had a better increase of hemoglobin in the 6 months after the end of the intervention (1.33 vs 0.30 g/dL, $P = 0.018$) (Table 3).

DISCUSSION

A high prevalence of malnutrition was found in this pediatric hospital, reaching 58%, whereas most of children were already enrolled in clinical care for a long time. The 6-month nutritional intervention was well accepted. Important weight gains were observed at 6-month for children supported for an AM, with a good probability to catch up growth reaching 74%. These weight gains could have concerned mainly fat mass in the first weeks of supplementation, before evolving in lean body mass. However, during this short nutritional intervention, height did not increase significantly among children with CM, whatever the age at the start of intervention. Indeed, we felt that we had an insufficient drawback to observe a significant increase, and we conclude that the intervention supplementation should be either longer or should have begun earlier.

For children with AM, several factors were associated with a higher probability to catch up growth at 6-month. Children with AM + CM had more difficulties to recover than those with exclusive AM. Reasons could be physiological: children chronically malnourished could have an affected metabolic system inhibiting the nutritional recovery; or socio-economical: experiencing repeated episodes of malnutrition and infections in their life, living in difficult conditions, with a high risk of food insecurity. A nutritional support in this context could be less efficient, because energetic needs, not being entirely covered by this support, could remain insufficient, or the nutritional products could also be distributed in the community.

Moreover, children under 5 years of age had a better probability to catch up growth at a threshold of -1.5 SD compared with older children (10–15 years). Younger age at ART initiation is known to be associated with a better growth reconstitution.^{4,20} In this study where the majority of children

TABLE 3. Biological Outcomes at Inclusion, at the End of the Nutritional Support (NS), and 6 Months After the End of Nutritional Support, According to the Type of Malnutrition Among Children Included, Bamako, Mali, N = 158

Biological Outcomes	Total (n = 158)			Exclusive CM (n = 61)			Exclusive AM (n = 62)			AM + CM (n = 35)		
	N	%	P	N	%	P	N	%	P	N	%	P
Anemia, <10 g/dL												
At inclusion (n = 126)	50	39.7		22	46.8		18	34.6		10	37.0	
At the end of nutritional support (NS) (n = 154)	18	11.7	<0.001*	7	11.9	<0.001	6	9.8	0.002	5	14.7	0.034
6 months after the end of NS (n = 158)	26	16.5	<0.001	13	21.3	0.003	5	8.1	<0.001	8	22.9	0.103
Hypoglycemia (<3.56 mmol/L)												
At inclusion (n = 96)	19	19.8		5	13.2		10	29.4		4	16.7	
6 mo after the end of NS (n = 130)	56	43.1	0.008	26	51.0	0.001	20	39.2	0.637	10	35.7	0.317
Severe immunodeficiency for age												
At inclusion	27	17.1		7	11.5		10	16.1		10	28.6	
At the end of NS	20	12.7	0.144	9	9.8	0.706	9	12.9	0.480	6	17.1	0.157
6 mo after the end of NS	23	14.6	0.371	7	11.5	1.000	8	12.9	0.317	8	22.9	0.479
Undetectable viral load (<50 c/mL)												
At inclusion (n = 124)	70	56.5		33	64.7		23	47.9		14	56.0	
At the end of nutritional support (NS) (n = 139)	66	47.5	0.353	25	49.0	0.285	24	42.1	0.366	17	54.8	0.317
6 mo after the end of NS (n = 133)	58	43.6	0.028	22	45.8	0.083	23	41.8	0.132	13	43.3	0.706

*McNemar test for paired samples, comparing end of NS or 6 months after end of NS versus inclusion. NS, nutritional support.

were already on ART at inclusion, an early treatment of malnutrition could be more efficient, because the nutritional status of these young children is not affected since such a long time compared with older children, helping to a complete recovery.

Even if children reached the threshold of -2 SD and can be considered as no longer malnourished, we hypothesized that children could remain at high risk of relapse to malnutrition if they do not continue to improve their nutritional status, reaching a higher threshold of -1.5 SD for example. The use of this threshold for the nutritional supplementation could ensure a more sustainable catch-up growth.

RUTF are recognized as a safe product, providing beneficial effects for the management of SAM since a long time.²¹ Other studies have reported its positive effects on anemia among HIV-infected adults.²² However, these products have been specifically made for acute form of malnutrition, and seem not equally efficient to treat chronic form of malnutrition in the same time. A longer period of nutritional supplement should be used for children with CM. Moreover, we observed also an important rate of refusals to take RUTF, which emphasized the need to identify other nutritional options for these children, such as locally fortified-blended foods, supplementary foods etc... according to children's requirements. Other types of macronutrients as well as micronutrients could be used, but studies among HIV-infected people are still limited.^{23,24}

There are several limitations in this study. First, there was no comparative group without intervention for obvious ethical reasons, which limits our conclusions about the efficacy of this type of nutritional support, but allows us to appreciate the field effectiveness using a before/after intervention design. Second, the selected population was composed of children living mainly in urban areas, not representative of those in rural areas. Moreover, the sample size was quite small, which could have hindered to highlight some associations. Another limitation is the small number of children younger than 5 years and recently started on ART. But it also reflects the reality of late access to care in HIV-infected children below the age of 5 years in sub-Saharan Africa. Other tools such as dietary diversity questionnaires²⁵ or Household Food Insecurity Access Scale (HFIAS),²⁶ as well as more biological data, could have provided more information but requiring additional time and supplementary costs. We need to acknowledge that our cases were predominantly older children who have been on ART for years and have organic failure to thrive from their underlying disease. This makes the success in getting catch-up growth important and explains our failure to improve stunting within 6 months on supplements. One would not expect older children to catch up in height on supplementation. The interesting question that we cannot address (without further data on the dietary habits of the child, food insecurity as well as data on opportunistic infections and co-morbidities associated to HIV/AIDS) is how much of the stunting is related to CM (poor diet) and how much is attributed to HIV infection (chronic disease). Nevertheless, the data collection was well conducted, with few missing data, despite the geo-political

context in Mali during the study period. This study contributes to give more information on research on nutritional supplementation among HIV-infected children, focusing on an older population than in most studies, and highlighting the needs for this age group in terms of nutritional care.

This study provides encouraging results on the feasibility and field efficiency of a 6-month nutritional intervention integrated in the routine pediatric HIV-care package in sub-Saharan Africa. We can conclude that our 6-month intervention had a significant benefit in catch-up growth in HIV-infected children with AM before, but no measurable effect on CM. Many malnourished children in this study were older than 5 years, whereas the main international recommendations for malnutrition treatment are focused on children younger than 5 years. Other nutritional interventions need to be further developed, in particular among children older than 5 years, to determine the right product for the right type of malnutrition. Other type of interventions, such as cash transfer, community-based interventions, or nutrition training among caregivers and health care professionals could also explore to improve the child nutritional status.²⁷⁻²⁹ Moreover, long-term effects of such interventions in the metabolism and nutritional status in adulthood need to be assessed, to prevent risk of overweight, obesity and cardiovascular diseases.³⁰ The benefit of an integrated nutritional support on the first months of ART should also be investigated closely. In our study, most children were on ART for more than 5 years and no difference could be seen according to the duration on ART.

A systematic and early screening of malnutrition needs to be integrated to HIV pediatric programs, to prevent supplementary risks of morbidity and mortality among HIV-infected children. For the time being, Weight-for-Height, determining wasting, is the main anthropometric indicator used to assess malnutrition in programs, whereas Weight-for-age, defining underweight, could also be integrated, as it could show a rapid weight loss if it is regularly assessed during follow-up, independently of height. CM health care is still challenging, mechanisms associated with stunting are multifactorial and some of them not well known.^{31,32} Early height monitoring in the first years of life and combination of interventions including improvement of food security, hygiene, and appropriate nutritional supplementation are needed. In our study, a RUTF macronutrient intervention showed 6-month benefits for weight gain and reduced anemia. The integration of nutritional care in HIV-programs is already a long-standing issue,^{33,34} which requires appropriate and prompt answers to improve health of HIV-infected children.

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