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Malnutrition, Growth Response and Metabolic Changes Within the First 24 Months After ART Initiation in HIV-infected Children Treated Before the Age of 2 Years in West Africa

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Background: There is limited information about malnutrition, growth evolution and metabolic changes among children initiated early on lopinavir-based antiretroviral therapy (ART) in Africa.

Methods: HIV-1-infected children, age <2 years were initiated on ART, as part of the MONOD ANRS 12206 project, conducted in Burkina Faso and Côte d'Ivoire. Weight-for-age, height-for-age and weight-for-height Z scores defined malnutrition [Z score less than -2 standard deviations (SDs)] using World Health Organization growth references. Biologic data were collected every 6 months. Factors associated with baseline malnutrition were evaluated using multivariate logistic regression, and with growth evolution in the first 24 months on ART using linear mixed models.

Results: Between 2011 and 2013, 161 children were enrolled: 64% were from Abidjan, 54% were girls. At ART initiation, median age was 13.7 months (interquartile range 7.7; 18.4), 52% were underweight (weight-for-age), 52% were stunted (height-for-age) and 36% were wasted (weight-for-height). Overall, baseline malnutrition was more likely for children living in Burkina Faso, with low birth weight, never breastfed and older age (12–24 months). Growth improved on ART, mainly within the first 6 months for weight, and was greater for the most severely malnourished children at baseline, but 8%–32% remained malnourished after 24 months. Over the 24-month period of ART, there was a significant increase of hypercholesterolemia and decrease of anemia and hypoalbuminemia.

Conclusions: Prevalence of malnutrition was high before ART initiation. Even though growth improved on ART, some children remained malnourished even after 2 years of ART, highlighting the need for more active nutritional support.

Key Words: children, HIV infection, growth, antiretroviral therapy, West Africa

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In 2016, 2.1 million children were infected by HIV, with more than 90% of them living in sub-Saharan Africa, and only 43% of them on antiretroviral therapy (ART).¹ Malnutrition affects 15% of children <5 years (99 million) worldwide,² and is responsible for nearly half of less than 5 deaths globally, resulting in 3.1 million deaths each year.^{3,4} Malnutrition can also lead to poor development, with cognitive and psychomotor retardation.⁵ Nutrition care within the first 2 years of life is especially important to reduce further detrimental consequences on adult health.⁶ Malnutrition is a frequent comorbidity among HIV-infected children and is associated with a high risk of morbidity and mortality.^{7,8} More than 50% of children were underweight or stunted at ART initiation in several studies in sub-Saharan Africa.^{9–15}

Early ART initiation reduces morbidity and mortality risk in HIV-infected infants.¹⁶ Despite the World Health Organization (WHO) guidelines promoting early ART in resource-limited settings, ART initiation is still delayed, occurring at a median age of 5 years often when HIV disease is already advanced.¹⁷ Even among ART-treated children, malnutrition rates remained still high, reaching 42% in a multicenter study conducted in West and Central Africa.¹⁸ ART initiation can help to resolve malnutrition, but improvement is greater for children initiated early on ART compared with those initiated at older ages.^{9,13,15,19–22}

Earlier ART initiation seems associated with greater growth restitution.^{16,23} However, few studies have focused on growth restitution among infant initiated early on ART.¹⁴ No such study has been conducted in West Africa, where the context of both HIV and malnutrition epidemics differs from that in Southern Africa.^{1,2} In Burkina Faso (BF) and Côte d'Ivoire (CI), respectively, 10,000 and 36,000 children <15 years were estimated to be HIV infected in 2016 according to United Nations Programme on HIV and AIDS (UNAIDS) estimates.²⁴ Prevalence of underweight, stunting and wasting among children <5 years in 2012 were, respectively, 24%, 33% and 11% in BF and 16%, 30% and 8% in CI.²⁵

Furthermore, metabolic problems are common among HIV-infected children, depending on ART drug regimen, with important changes in lipid profiles for example, and increasing risk of long-term comorbidity.^{26–28}

The objective of this study was to analyze malnutrition at ART initiation, growth evolution and the metabolic changes over the first 2 years on ART among HIV-infected children initiated on ART before 2 years of age in West Africa.

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MATERIALS AND METHODS

Study Design and Study Population

This study was part of the MONOD ANRS-12026 study which aimed to evaluate the implementation of early ART based on lopinavir before 2 years of age, and to conduct a phase 3 noninferiority open-label randomized clinical trial in Abidjan (CI) and Ouagadougou (BF; ClinicalTrials.gov registry: NCT01127204). Between 2011 and 2013, all children diagnosed with confirmed HIV infection (DNA-PCR) before 2 years of age and ART-naïve except for drugs used for prevention of mother-to-child transmission were enrolled if both parents consented. Participants were followed in the University Hospital Centers Charles de Gaulle and Yalgado Ouedraogo in Ouagadougou, Centre de Prise en charge et de Formation (CePREF) and Formations Sanitaires Urbaines (FSU) Abobo Avocatier in Abidjan. All participants were initiated on a twice-daily Lopinavir/ritonavir (LPV/r)-based-ART (with lamivudine and either abacavir or zidovudine) combined with cotrimoxazole prophylaxis and therapeutic education for 12 months, except for those with tuberculosis at inclusion who received an Efavirenz (EFV)-based therapy (abacavir-lamivudine-efavirenz). Those on LPV/r with virologic suppression [HIV-1-RNA viral load (VL) <500 copies/mL] confirmed after 12–15 months were randomized to once-daily ABC-3TC-EFV (EFV Arm) versus continuation of the twice-daily Zidovudine (AZT) or ABC-3TC-LPV/r (LPV Arm) for another 12 months, while those with virologic failure remained on LPV/r. Details on the main outcomes of the trial are published elsewhere.²⁹

For this substudy, all children initiated on ART in the above project, with available data on weight and height at ART initiation, were included. There was no routine nutritional support during the study in any participating center, except for those children diagnosed with severe malnutrition who were managed in nutrition rehabilitation units according to the national guidelines.

The trial was approved by ethical review boards of BF and CI, and the caregivers of participating children signed an informed consent form before the start of the study.

Variables and Data Management

Data collected at baseline included sociodemographic data, such as age, sex, main caregiver, orphanhood, access to electricity, safe water and refrigerator; current and past breastfeeding practices; weight and height measurements; WHO stage; laboratory results, including hemoglobin, CD4 percentage, VL and metabolic measures (lipase, cholesterol, triglyceride, albumin and blood glucose). Weight and height were measured at monthly visits. VL was measured every 3 months and other laboratory tests were collected every 6 months. Immunodeficiency was defined as severe if CD4% < 15 and as moderate if CD4% = 15 to <25.³⁰ Malnutrition was defined by anthropometric indicators, expressed in Z scores, and constructed with the 2006 WHO growth charts³¹: Weight-for-age (WAZ) for underweight, height-for-age (HAZ) for stunting and weight-for-height (WHZ) for wasting. Head circumference-for-age and mid-upper arm circumference-for-age were also assessed. A Z score less than -2 standard deviations (SDs) was considered malnutrition, with severe malnutrition defined as Z score less than -3 SD. Z scores were calculated using WHO Anthro Software (version 3.2.2, January 2011). The Division of AIDS table for grading the severity of adult and pediatric adverse events³² was used to grade abnormal metabolic test results.

Statistical Analyses

Baseline characteristics at ART initiation were compared by country using the Pearson χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. All these baseline characteristics were then tested as potential covariates in the following statistical models.

Prevalence of malnutrition at ART initiation was determined for each anthropometric indicator, and factors associated with malnutrition were investigated with logistic regression models. Variables with a *P* value <0.25 in univariate analysis were selected in a step-down procedure multivariate analysis. All results were automatically adjusted for age, sex, country, immunodeficiency category and VL at ART initiation.

Growth evolution within the first 24 months was assessed running linear mixed models, with random intercept, slope for time and unstructured variance–covariance matrix. The goodness of fit of the models was assessed using residual analysis and looking at the trajectories predicted by the model. Thus, for WAZ and WHZ evolution, a spline term was added to the final models at the 6-month time point, taking into account the change of slope at this period. Variables were selected as for the logistic regression models. The effect of treatment arm on growth evolution was also assessed. No difference between arms was seen for any of the growth parameters. Thus, the results for growth evolution are presented without adjusting for the ART regimen arm. Interaction with time was taken into account for each variable. All results were adjusted on sex, age, country, immunodeficiency category, VL, breastfeeding practices and severity of malnutrition at ART initiation.

Metabolic parameters were measured every 6 months and compared with the value at ART initiation using McNemar test for categorical variables and Student *t* test for paired samples for continuous variables. Furthermore, the effect of randomization to the EFV Arm on metabolic changes was assessed with these statistical tests, comparing values between the start of postrandomized phase (12–15 months) and its end, 12 months after. Metabolic measurements at ART initiation and every 6 months were also compared by nutritional status and country, using Pearson χ^2 and Kruskal–Wallis tests.

All analyses were conducted using SAS V 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics at ART Initiation, Prevalence of Malnutrition and Associated Factors

From May 2011 to January 2013, 226 children screened for HIV infection met the inclusion criteria. Among them, 161 (71.2%) children were enrolled in the initial cohort and in this subanalysis. Main reasons for not being enrolled were refusal (12.4%), death (9.7%) and false positive test (4.4%). During the 24 months of follow-up, 14 infants died (8.7%; 6 resulting from severe malnutrition, 3 from malaria; other causes were septicemia, anemia, acidosis, pulmonary disease and infectious syndrome); 2 were lost-to-follow-up (1.2%) and 3 withdrew their consent (1.9%). Five children had a diagnosis of tuberculosis and were initiated on EFV; and 32 (19.9%) were in virologic failure before randomization. Of the 106 remaining children, 54 were randomized to the LPV Arm and 52 to the EFV Arm.

Among these 161 children, 103 (64.0%) were from CI, and 58.0% were girls. At ART initiation, median age was 13.7 months (interquartile range = 7.7–18.4), 30.4% were severely immunodeficient and 62.1% were at an advanced WHO clinical stage (3 or 4). Mean log VL was 6.1 copies/mL (SD, 1.1). Some characteristics differed by country: children from BF were more severely ill and more severely immunodeficient (*P* = 0.008), and they had higher VL (*P* < 0.001) and more advanced WHO clinical stage (*P* < 0.001) compared with those from CI. They also had less access to electricity, tap water and refrigerator at home (*P* < 0.001; Table 1).

At ART initiation, 53.4% were underweight (95% confidence interval: 46%–61%) and 36.0% were severely underweight; 51.6% were stunted (95% confidence interval: 44%–59%) and 30.4% were severely stunted; 36.0% were wasted (95% confidence interval:

TABLE 1. Characteristics at ART Initiation of Children Included in the MONOD Cohort, According to the Country, N = 161

Variables at Baseline	Total (N = 161)	Burkina Faso (N = 58)	Côte d'Ivoire (N = 103)	P*
	N (%)	N (%)	N (%)	
Age groups (mo)				0.227
<6	25 (15.5)	5 (8.6)	20 (19.4)	
6–12	45 (28.0)	15 (25.9)	30 (29.1)	
12–18	45 (28.0)	18 (31.0)	27 (26.2)	
18–24	46 (28.6)	20 (34.5)	26 (25.2)	
Girls	87 (54.0)	34 (58.6)	53 (51.5)	0.381
Immunodeficiency category				0.008
No	50 (31.1)	12 (20.7)	38 (36.9)	
Moderate (CD4% = 15 to <25)	61 (37.9)	19 (32.8)	42 (40.8)	
Severe (CD4% < 15)	49 (30.4)	26 (44.8)	23 (22.3)	
Missing	1 (0.6)	1 (1.7)	0 (0.0)	
Viral load > 6 log cp/mL (n = 160/58/102)	102 (63.7)	45 (77.6)	57 (55.8)	<0.001
WHO clinical stage 3–4	100 (62.1)	51 (87.9)	49 (47.6)	<0.001
Mother main caregiver	132 (82.0)	39 (67.2)	93 (90.3)	<0.001
Orphan	14 (8.7)	2 (3.4)	12 (11.7)	0.076
PMTCT prophylaxis (maternal)	95 (59.0)	33 (56.9)	62 (60.2)	0.683
PMTCT prophylaxis (neonatal)	95 (59.0)	35 (60.3)	60 (58.3)	0.796
Breastfeeding				<0.001
No breastfed	22 (13.7)	5 (8.6)	17 (16.5)	
<12 mo	53 (32.9)	10 (17.2)	43 (41.7)	
≥12 mo	86 (53.4)	43 (74.1)	43 (41.7)	
Low birth weight (<2500 g) (n = 151/54/97)	35 (23.2)	12 (22.2)	23 (23.7)	0.835
Electricity at home	120 (74.5)	22 (37.9)	98 (95.1)	<0.001
Tap water at home	108 (67.1)	21 (36.2)	87 (84.5)	<0.001
Refrigerator at home	36 (22.4)	7 (12.1)	29 (28.2)	<0.001
Randomization arm				0.543
LPV	54 (33.5)	18 (31.0)	36 (34.9)	
EFV switch	52 (32.3)	17 (29.3)	35 (34.0)	
Not randomized	55 (34.1)	23 (39.7)	32 (31.1)	
Malnutrition				
WAZ < -2 SD	86 (53.4)	44 (75.9)	42 (40.8)	<0.001
HAZ < -2 SD	83 (51.6)	41 (70.7)	42 (40.8)	<0.001
WHZ < -2 SD	58 (36.0)	32 (55.2)	26 (25.2)	<0.001
MUACZ < -2 SD (n = 159/57/102)	71 (44.7)	33 (57.9)	38 (37.2)	0.012
HCZ < -2 SD (n = 158/56/102)	50 (31.6)	20 (35.7)	30 (29.4)	0.415

* χ^2 test.

HCZ indicates head circumference Z score; MUACZ, mid-upper arm circumference Z score; PMTCT, prevention of mother-to-child transmission.

29%–43%) and 16.8% were severely wasted. Rates of malnutrition were much higher in BF than in CI ($P < 0.001$), affecting up to 3 quarters of children in BF compared with 40.8% in CI (Table 1).

At ART initiation, children from BF had higher odds of malnutrition compared with children from CI, adjusted for covariables [adjusted odds ratio (aOR) = 4.63, 95% confidence interval: 1.79–10.65 for WAZ; aOR = 2.71, 95% confidence interval: 1.11–6.64 for HAZ; aOR = 3.08, 95% confidence interval: 1.46–6.53 for WHZ]. Overall, children 12–24 months of age had higher odds of malnutrition compared with children <6 months of age at ART initiation. A high VL at ART initiation (>6 log) and low birth weight (<2500 g) were associated with a higher odd of underweight or stunting. Children who had not been breastfed were at higher odds of underweight compared with children breastfed <12 months (aOR = 6.76, 95% confidence interval: 1.71–26.77). Sex and immunodeficiency were not associated with any type of malnutrition (Table 2).

24-month Evolution of Growth and Associated Factors

Weight-for-age Evolution

WAZ improved during the first 2 years of ART, resulting in a reduction of the prevalence of underweight from 53.4% at ART initiation to 20.2% at 24 months (Fig. 1). Improvement was greater in

the first 6 months of ART, with an estimated monthly mean increase of 0.12 SD, than for the 6- to 24-month period, when the estimated monthly mean increase was 0.02 SD. Adjusted for covariables, evolution of WAZ within the first 6 months differed by country and severity of malnutrition, with significantly better increase for children from BF (+0.06 SD, P value = 0.029) and for those severely underweight at ART initiation (severely vs. not underweight: +0.24 SD by month, $P < 0.001$; moderately versus not underweight: +0.13 SD by month, $P < 0.001$). After 6 months of ART, evolution of WAZ was greater only for severely underweight children compared with those not underweight at ART initiation (+0.03 SD; $P < 0.001$; Supplemental Digital Content 1a, <http://links.lww.com/INF/C979>).

Height-for-age Evolution

HAZ improved linearly during the first 2 years of ART, with an estimated monthly mean increase of 0.03 SD ($P < 0.001$). After 24 months on ART, 31.8% of children were still stunted, versus 51.6% at baseline (Fig. 1). Adjusted for covariables, evolution of HAZ differed according to the severity of malnutrition, with a greater increase for children stunted at ART initiation (severely vs. not stunted: +0.07 SD by month, $P < 0.001$; moderately vs. not stunted: +0.02 SD by month, $P = 0.013$; Supplemental Digital Content 1b, <http://links.lww.com/INF/C979>).

TABLE 2. Associated Factors to Malnutrition (Z Scores Less Than -2 SD) at ART Initiation (Adjusted Logistic Regression Model), MONOD Project, N = 161

Variables at M0	WAZ		HAZ		WHZ	
	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
Girls vs. boys	0.68 (0.30–1.52)	0.344	1.14 (0.49–2.62)	0.762	0.78 (0.38–1.59)	0.491
Age groups (mo) (ref < 6)		0.012		<0.001		0.061
6–12	1.80 (0.48–6.78)		2.80 (0.65–12.11)		1.66 (0.45–6.17)	
12–24	5.09 (1.48–17.43)		13.11 (3.30–52.05)		3.41 (1.01–11.5)	
Country (BF vs. CI)	4.36 (1.79–10.65)	0.001	2.71 (1.11–6.64)	0.029	3.08 (1.46–6.53)	0.003
Immunodeficiency category (ref no.)		0.106		0.333		
Moderate (CD4% = 15 to <25)	0.40 (0.15–1.08)		0.64 (0.23–1.77)		0.66 (0.28–1.57)	
Severe (CD4% < 15)	0.98 (0.35–2.70)		1.38 (0.45–4.20)		0.72 (0.29–1.80)	
Viral load (>6 log vs. ≤6 log)	2.92 (1.25–6.81)	0.013	4.89 (1.88–12.72)	0.001	2.17 (1.00–4.74)	0.051
Low birth weight (<2500 vs. ≥2500 g)	4.40 (1.58–12.30)	0.005	6.39 (2.01–20.33)	0.002		
Breastfeeding (ref <12 mo)		0.024				
Not breastfed	6.76 (1.71–26.77)		-		-	
≥12 mo	1.49 (0.60–3.70)		-		-	

95% CI indicates 95% confidence interval.

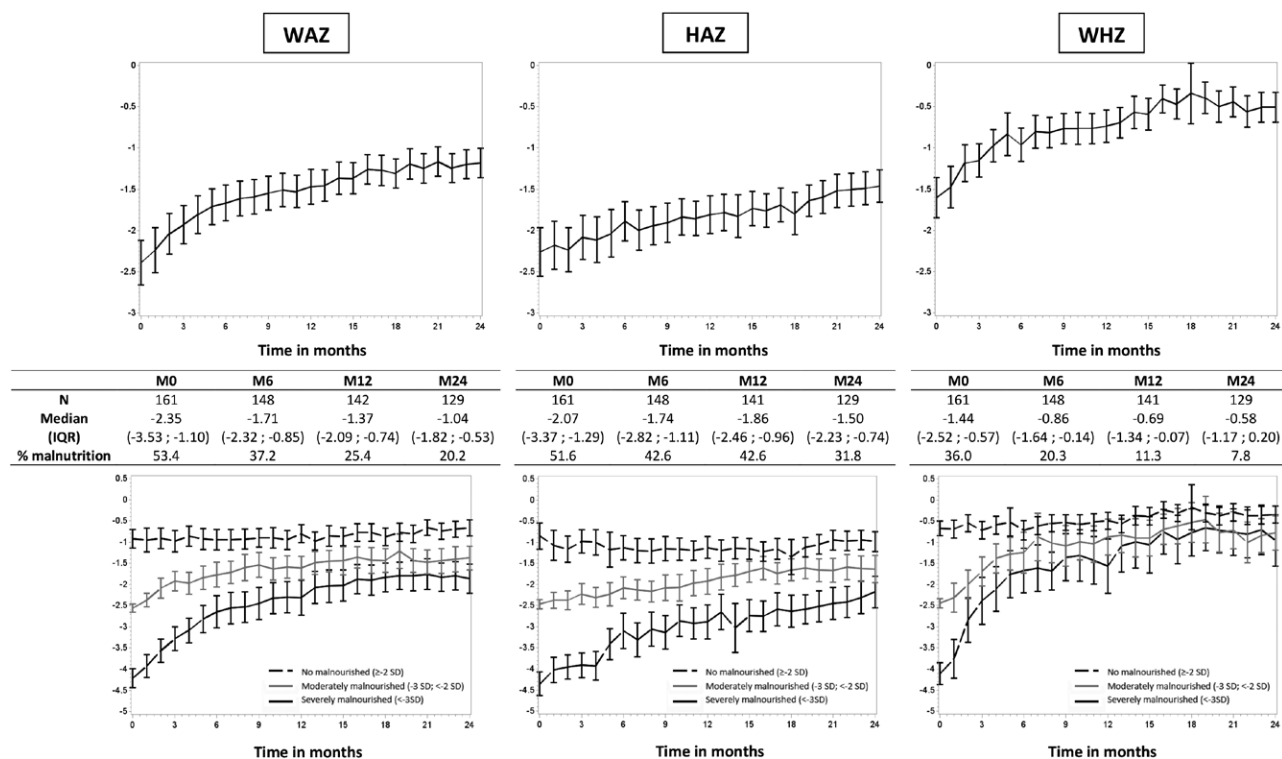


FIGURE 1. Evolution of anthropometric indicators in the first 24 months of ART, expressed in Z scores. Curves represent mean evolution and 95% confidence interval, overall (top), and according to the severity of malnutrition at ART initiation (bottom). Median Z scores and prevalence of malnutrition at M0, M6, M12 and M24 are shown. From left to right, WAZ, HAZ and WHZ.

Weight-for-height Evolution

WHZ improved during the first 2 years of ART, with a high reduction on the prevalence of wasting, from 36.0% at ART initiation to 7.8% at 24 months (Fig. 1). Improvement was greater within the first 6 months of ART, with an estimated monthly mean increase of 0.12 SD, than for the 6–24 months period, when the estimated monthly mean increase was 0.02 SD. Adjusted for covariables, evolution of WHZ in the first 6 months of ART differed by age and severity of malnutrition, with a lower improvement for children <6 months of age at ART initiation compared with those 12–24 months of age (-0.13 SD, P value = 0.006), and a greater

increase for children wasted at ART initiation (severely vs. not wasted: +0.33 SD by month, P < 0.001; moderately vs. not wasted: +0.19 SD by month, P < 0.001). After 6 months of ART, evolution of WHZ was greater for children severely wasted compared with those not wasted at ART initiation (+0.04 SD; P value = 0.008; Supplemental Digital Content 1c, <http://links.lww.com/INF/C979>).

Metabolic Laboratory Abnormalities

At ART initiation, 7.7% of children had hypercholesterolemia, all from CI (Table 3). This rate increased significantly within the 24 months (P < 0.001), reaching 37.6% at 24 months.

By contrast, other rates of metabolic adverse events decreased significantly within the first 24 months on ART: from 49.5% to 0% for hypoalbuminemia; and from 80.7% to 21.1% for anemia (hemoglobin <10 g/mL; $P < 0.001$). Only 3.0% of children had an abnormal high lipase level at ART initiation. Mean triglyceride level was normal at ART initiation for 98.7% of children and decreased during follow-up. Hypoglycemia decreased from 8.6% at baseline to 3.6% at 12 months ($P = 0.046$). Hyperglycemia was stable throughout follow-up, between 2.6% and 5.8% (Table 3). There was no difference in the evolution of metabolic markers according to the randomization arm (data not shown). Children stunted at ART initiation more had hypoglycemia than those not stunted at baseline (7.3% vs. 1.3%; $P = 0.010$); none of the children with wasting at baseline had hypercholesterolemia ($P = 0.004$). There was no difference in metabolic laboratory abnormalities at 24 months between malnourished and nonmalnourished children (data not shown).

DISCUSSION

Malnutrition was highly prevalent among these West-African HIV-infected children <2 years of age at ART initiation. Baseline malnutrition was more likely for children living in BF than in those living in CI, those with a low birth weight and a high VL, those who never breastfed, and in those who were older (12–24 months). Growth measures improved markedly, mainly within the first 6 months on ART, with a greater improvement for those severely malnourished at baseline; however, a substantial proportion of children remained malnourished after 2 years of ART.

Stunting, which results from chronic malnutrition, was the most difficult type of malnutrition to reverse, with more than 30% of children still stunted even after 2 years on ART. In addition, we observed significant rates of lipid abnormalities over the 2 years on ART, with high rates of hypercholesterolemia, whereas we observed an improvement in the proportion who had normal hemoglobin and albumin levels. This evolution was not different according to ART regimen arm or nutritional deficiency at ART initiation.

Malnutrition is indeed a significant burden for HIV-infected children, with 2 to 3 times higher rates of malnutrition in our study population than in the general population of children <5 years of ages in the same countries. Similar high rates of malnutrition at ART initiation were already reported in other studies,^{9,13–18} including in the same age group in South Africa¹⁴ and Nigeria.³³ Underweight and stunting at ART initiation were associated with advanced HIV infection, high VL, not having breastfed and low birth weight. Indeed, chronic malnutrition can result from repeated infections and early nutritional deficiency in the first months of life. Wasting, corresponding to acute malnutrition, was higher in BF, where children in our study lived in a worse socioeconomical context, and was not related to HIV disease status at entry or birth characteristics. Growth evolved after ART initiation independently of the HIV disease status and breastfeeding practices. Severely malnourished children had the greater gains for all types of malnutrition. Those who were severely wasted reached the same mean Z scores values at 24 months as those moderately or not wasted at ART initiation. Children severely underweight and stunted at baseline did not reach normal Z scores values after 24 months on ART. Similar evolutions for WAZ and HAZ were found

TABLE 3. Biologic Markers at ART Initiation and Evolution Every 6 Months Until 24 Months on ART

Biologic Data	M0 (N = 161)	M6 (N = 149)	M12 (N = 144)	M24 (N = 142)	P Value Paired Tests*		
					M0 vs. M6	M0 vs. M12	M0 vs. M24
Lipase (IU/L), n	101	91	92	81			
Mean ± SD	34.2 (61.0)	20 (17.1)	21.7 (20.0)	22 (22.8)	0.052	0.070	0.072
Normal (<200), n (%)	98 (97.0)	91 (100)	92 (100)	81 (100)	NA	NA	NA
Grade 1–2 (1.1–3.0 × ULN), n (%)	3 (3.0)	0 (0)	0 (0)	0 (0)			
Cholesterol (mg/dL), n	156	139	139	117			
Mean ± SD	99.4 (47.6)	126 (58.4)	131.9 (63.0)	143.5 (60.7)	<0.001	<0.001	
Normal (<170), n (%)	144 (92.3)	109 (78.4)	97 (69.8)	72 (61.5)	<0.001	<0.001	<0.001
Grade 1–2 (170–300), n (%)	12 (7.7)	29 (20.9)	39 (28.1)	44 (37.6)			
Grade 3 (>300), n (%)	0 (0)	1 (0.7)	3 (2.2)	1 (0.9)			
Triglycerides (mg/dL), n	155	139	139	119			
Mean ± SD	177.5 (102.6)	128.2 (62.1)	128.7 (63.1)	112.7 (56.2)	<0.001	<0.001	<0.001
Normal (<500), n (%)	153 (98.7)	139 (100)	139 (100)	119 (100)	NA	NA	NA
Grade 2 (500–750), n (%)	2 (1.3)	0 (0)	0 (0)	0 (0)			
Albumin (g/dL), n	101	94	91	80			
Mean ± SD	36.9 (6.0)	42.2 (4.2)	42.1 (4.8)	44.9 (3.0)	<0.001	<0.001	<0.001
Normal (>3.0), n (%)	51 (50.5)	83 (88.3)	76 (83.5)	80 (100)	<0.001	<0.001	NA
Grade 1–2 (2.0–3.0), n (%)	50 (49.5)	11 (11.7)	15 (16.5)	0 (0)			
Hemoglobin (g/dL), n	160	149	143	142			
Mean ± SD	9.2 (1.3)	10.3 (1.0)	10.4 (1)	10.8 (1.0)	<0.001	<0.001	<0.001
Normal (>10.0), n (%)	31 (19.4)	91 (61.1)	97 (67.8)	112 (78.9)	<0.001	<0.001	<0.001
Grade 1–2 (7.5–10.0), n (%)	118 (73.8)	57 (38.3)	45 (31.5)	30 (21.1)			
Grade 3–4 (<7.5), n (%)	11 (6.9)	1 (0.7)	1 (0.7)	0 (0)			
Glycemia (mmol/L), n	151	137	139	120			
Mean ± SD	4.6 (1.4)	4.6 (1.2)	4.8 (0.8)	5 (2.1)	0.483	0.095	0.010
Normal (3.56–6.43), n (%)	133 (88.1)	114 (83.2)	131 (94.2)	110 (91.7)			
Hypoglycemia							
Grade 1–2 (2.22–3.55), n (%)	12 (7.9)	14 (10.2)	5 (3.6)	5 (4.2)	0.549	0.046	0.166
Grade 3–4 (<2.22), n (%)	1 (0.7)	1 (0.7)	0 (0)	0 (0)			
Hyperglycemia							
Grade 1–2 (6.44–13.88), n (%)	4 (2.6)	8 (5.8)	3 (2.2)	4 (3.3)	0.405	0.480	0.480
Grade 3 (13.89–27.75), n (%)	1 (0.7)	0 (0)	0 (0)	1 (0.8)			

ULN indicates Upper Limit of Normal.

*MacNemar and Student *t* test for paired samples.

in the South African study¹⁴ and in a recent systematic review.³⁴ In these and other studies,⁹ younger age was associated with greater growth improvements, whereas in our study—probably because of the lack of age variability—age was not associated with WAZ and HAZ evolution, and older children had greater WHZ improvements in the first 6 months on ART. Finally, after 24 months of ART, the prevalence of malnutrition among these HIV-infected children became similar to the prevalence among general population in <5 years old in the same settings.²⁵

ART initiation was also accompanied by significant changes in metabolic profiles, especially with an increase of cholesterol levels, commonly seen among HIV-infected children on ART. Triglyceride levels decreased in our study, unlike what has been reported elsewhere.^{35–37} No differences in the evolution of lipid profiles were observed according to ART regimen arm during the trial period (12–24 months), whereas in other studies Protease Inhibitors (PI)-based regimens were associated with worse lipid profiles, compared with regimens based on efavirenz or nevirapine.^{35,38–41}

High rates of anemia and hypoalbuminemia before ART observed in our study are similar to rates reported in a study of young Nigerian children.³³ Anemia resolved in most children once they were treated with ART. Hypoalbuminemia, an indicator of chronic malnutrition or protein-losing enteropathy or nephrotic syndrome, was entirely reversed over the first 2 years of ART in our study. No hypoalbuminemia among ART-treated children was also found in Nigeria,⁴² whereas persistent hypoalbuminemia was measured in Tanzania.⁴³ Few patients had abnormal glucose levels, as reported elsewhere.^{40,41} Differences in metabolic profiles between countries may be explained by differences in nutritional habits or socioeconomic level. Further investigation is needed about the variation in metabolic profiles across regions on the general population in Africa.

Our study has some limitations. Indeed, children involved in this study all lived in urban areas, where food is more available and the standard of care may be higher than in rural areas. These could have led to an underestimation of the prevalence of malnutrition among HIV-infected children in West Africa. Moreover, even if there was no routine nutritional support provided during the study, the close follow-up required of study participants could have led to improved evolution of anthropometric indicators on ART, compared with children enrolled in standard pediatric HIV care in these settings. Finally, our study sample was quite small, and other specific nutritional data could have been valuable, such as data on daily dietary intake and household food insecurity. Nevertheless, as part of a clinical trial, this substudy provides original data on growth evolution and the metabolic markers on ART usually not collected routinely in the West-African context. Also, there was a regular monitoring with repeated measurements of VL, weight and height, which are often incomplete in routine pediatric HIV care in resource-limited settings. Retention in care during the study was high with only 2 children lost-to-follow-up because they moved from the study area. However, there was a high rate of death related to malnutrition at the beginning of the study, mainly because of HIV disease already being advanced by the time ART was initiated, as reported elsewhere.⁴⁴ Earlier identification and ART initiation for HIV-infected children combined with strengthening of nutritional care services will be essential to reduce the mortality risk for children.

Nutritional care should be optimized, with a regular assessment of anthropometric indicators to screen malnutrition and offer an adapted nutritional support. ART-treated children experience metabolism changes, especially high lipid profiles, which could lead to a higher cardiovascular risk in the long term. Then, growth

and metabolism must be managed regularly to avoid ART adverse events and improve quality of life of HIV-infected children.

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