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# Effect of Age at Antiretroviral Therapy Initiation on Catch-up Growth Within the First 24 Months Among HIV-infected Children in the IeDEA West African Pediatric Cohort

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**Background:** We described malnutrition and the effect of age at antiretroviral therapy (ART) initiation on catch-up growth over 24 months among HIV-infected children enrolled in the International epidemiologic Databases to Evaluate Aids West African paediatric cohort.

**Methods:** Malnutrition was defined at ART initiation (baseline) by a Z score <−2 standard deviations, according to 3 anthropometric indicators: weight-for-age (WAZ) for underweight, height-for-age (HAZ) for stunting and weight-for-height/BMI-for-age (WHZ/BAZ) for wasting. Kaplan–Meier estimates for catch-up growth (Z score ≥−2 standard deviations) on ART, adjusted for gender, immunodeficiency and malnutrition at ART initiation, ART regimen, time period and country, were compared by age at ART initiation. Cox proportional hazards regression models determined predictors of catch-up growth on ART over 24 months.

**Results:** Between 2001 and 2012, 2004 HIV-infected children <10 years of age were included. At ART initiation, 51% were underweight, 48% were stunted and 33% were wasted. The 24-month adjusted estimates for catch-up growth were 69% [95% confidence interval (CI): 57–80], 61% (95% CI: 47–70) and 90% (95% CI: 76–95) for WAZ, HAZ and WHZ/BAZ, respectively. Adjusted catch-up growth was more likely for children <5 years of age at ART initiation compared with children ≥5 years for WAZ, HAZ ( $P < 0.001$ ) and WHZ/BAZ ( $P = 0.026$ ).

**Conclusions:** Malnutrition among these children is an additional burden that has to be urgently managed. Despite a significant growth improvement after 24 months on ART, especially in children <5 years, a substantial proportion of children still never achieved catch-up growth. Nutritional care should be part of the global healthcare of HIV-infected children in sub-Saharan Africa.

**Key Words:** HIV, children, antiretroviral therapy, growth, malnutrition, Africa

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In 2011, 3.3 million children aged <15 years were living with HIV worldwide, with more than 90% living in sub-Saharan Africa.<sup>1</sup> Growth faltering has been reported in up to 50% of untreated HIV-infected children in resource-limited settings,<sup>2–4</sup> and several studies have shown that HIV-related growth faltering can be reversed with antiretroviral therapy (ART).<sup>3–11</sup> ART reduces the risk of HIV-infection progression and reduces mortality in children.<sup>12,13</sup> ART also has an impact on the child's nutritional status, by reducing proinflammatory cytokine concentration and improving immune system functions.<sup>14</sup> Improvements in growth may in turn help toward a slower HIV disease progression and reduce pediatric HIV-related morbidity and mortality.<sup>15,16</sup> Several factors at ART initiation could influence treatment response and therefore growth reconstitution. Data suggest that children starting ART at an early age have a greater chance for catch-up growth and reaching the reference growth standards for their age and gender.<sup>17,18</sup> Although a better growth response is found among younger children at ART initiation compared with older ones in some studies,<sup>5,6,17,19</sup> others report that growth response after ART initiation is not associated with age.<sup>4,20</sup> In addition, despite an improvement of weight and height after ART initiation, restoration to a normal nutritional status is often not reached for a high proportion of children, even after 2 years of follow-up.<sup>3–5,18</sup> Most of these studies have been conducted in Eastern and Southern Africa. Few data are available on malnutrition in West-African HIV-infected children,<sup>21</sup> and none have been described in the post-ART era.

We hypothesized that children who start ART at a younger age will have a better growth recovery than children who start ART at a later age. Our main objective was to describe malnutrition at ART initiation and study the association between age at ART initiation and time to catch-up growth within 24 months post-ART initiation among HIV-infected children enrolled in the International epidemiologic Databases to Evaluate Aids (IeDEA) West African pediatric cohort.

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## METHODS

### Study Population

The IeDEA network is an international consortium collecting data on HIV infection and AIDS. The West African Database on Antiretroviral therapy (WADA) collaboration is in charge of the IeDEA program in West Africa. The pediatric WADA (pWADA) cohort is a multicenter observational prospective cohort including children from 11 pediatric clinical centers from 7 countries (Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, Senegal and Togo) of the WADA collaboration.<sup>22,23</sup> Eligible criteria for the pWADA cohort are the following: all HIV-infected children <16 years with a confirmed HIV-infection (positive serology in children >18 months, or positive polymerase chain reaction, whatever the age), receiving ART or not and all HIV-exposed children born to HIV-infected mothers until their definite HIV diagnosis.

Children included in this study were those in the pWADA cohort, HIV-infected, naïve of any ART before inclusion other than prevention of mother to child transmission, with a documented date of birth and ART regimen, who initiated ART during follow-up in pWADA, and aged <10 years, with at least 2 anthropometric measurements during follow-up, including 1 in the first 3 months of ART and 1 after 6 months of ART. We excluded children who were enrolled in centers with a very small sample size (<50 children).

### Variables and Data Management

Malnutrition is defined by several anthropometric indicators according to the Waterlow definition used by the World Health Organization (WHO).<sup>24</sup> In this study, we defined standardized malnutrition using Z scores, which quantify how many standard deviations (SD) child's weight and height are from the median value of a child of the same age and gender, in a reference population. Malnutrition is defined by a Z score <-2 SD, with moderate malnutrition between -3 and -2 SD and severe malnutrition <-3 SD. The 2006 WHO growth charts were used for children <5 years,<sup>25</sup> and the 2007 WHO growth charts for children ≥5 years.<sup>26</sup> We defined 3 anthropometric indicators: weight-for-age (WAZ) for underweight, height-for-age (HAZ) for stunting and weight-for-height/BMI-for-Age (WHZ/BAZ) for wasting. The latter indicator was combined using weight-for-height for children until 5 years of age and BMI-for-age for older children.

The Z scores were calculated with WHO Anthro Software (version 3.2.2, January 2011) and WHO AnthroPlus. Z scores <-10 and Z scores >+10 SD were viewed as outliers and were not included in the catch-up growth analysis, as representing less than 2% of data.

The principal covariables were age at ART initiation (in classes: 0-2, 2-3, 3-4, 4-5 and 5-10 years), gender, ART regimen, cotrimoxazole prophylaxis, clinical centers and immunodeficiency for age according to the 2006 WHO guidelines.<sup>27</sup> CD4 was expressed in percentage for children <5 years and in cells per microliter for children ≥5 years. Severe immunodeficiency was defined as CD4% <15% or CD4 count <350 cells/μL, and moderate immunodeficiency as CD4% between 15% and 25% or CD4 count between 350 and 499 cells/μL.

All children on ART were seen monthly and had unrestricted free access to antiretroviral drugs. Weight and height were measured at each visit, using standardized procedures.<sup>28</sup> Absolute CD4 cell count and CD4% were measured every 6 months. Nutritional supplementation was not part of the standard HIV healthcare. Children detected with severe wasting were hospitalized.

Data from each center were collected prospectively from 1998 to 2012 with the formal approval of each participating clinic of pWADA, with local Institutional Review Board and U.S. National Institutes of Health approval.

### Statistical Analysis

We first measured the prevalence of malnutrition at ART initiation (baseline) according to the 3 anthropometric indicators above. Baseline characteristics at ART initiation were compared according to malnutrition using the Pearson  $\chi^2$  test for categorical variables and the Kruskal-Wallis test for continuous variables. To investigate the factors associated with malnutrition at ART initiation, we ran logistic regression models for each indicator. The variables with a *P* value <0.25 in univariate analysis were selected for multivariate analysis and then kept in a full model. Results were adjusted for age, immunodeficiency, gender, countries and time period of ART initiation.

The database closing date was October 30, 2012. Children were lost to follow-up (LTFU) when the last clinical contact was more than 6 months. Catch-up growth was defined by transition from a Z score <-2 SD to a Z score ≥-2 SD. A sensitivity analysis was then conducted defining catch-up growth by transition to a Z score ≥-1 SD. Among children malnourished at ART initiation, the probability for catch-up growth, for each growth outcome separately, within the first 24 months on ART, was described using an adjusted Kaplan-Meier estimator. Children were followed up from ART initiation to time of first growth recovery, or death, date of last clinical contact, transfer out or the database closing date, whichever came first. Additionally, because wasting is defined only until 10 years, children were censored on their 10th birthday. A Cox proportional hazards regression model was used to study predictors associated with time to catch-up growth. Analyses were adjusted for age, gender, immunodeficiency status at ART initiation, ART regimen, time period of ART initiation, countries and severity of baseline malnutrition (moderate vs. severe).

## RESULTS

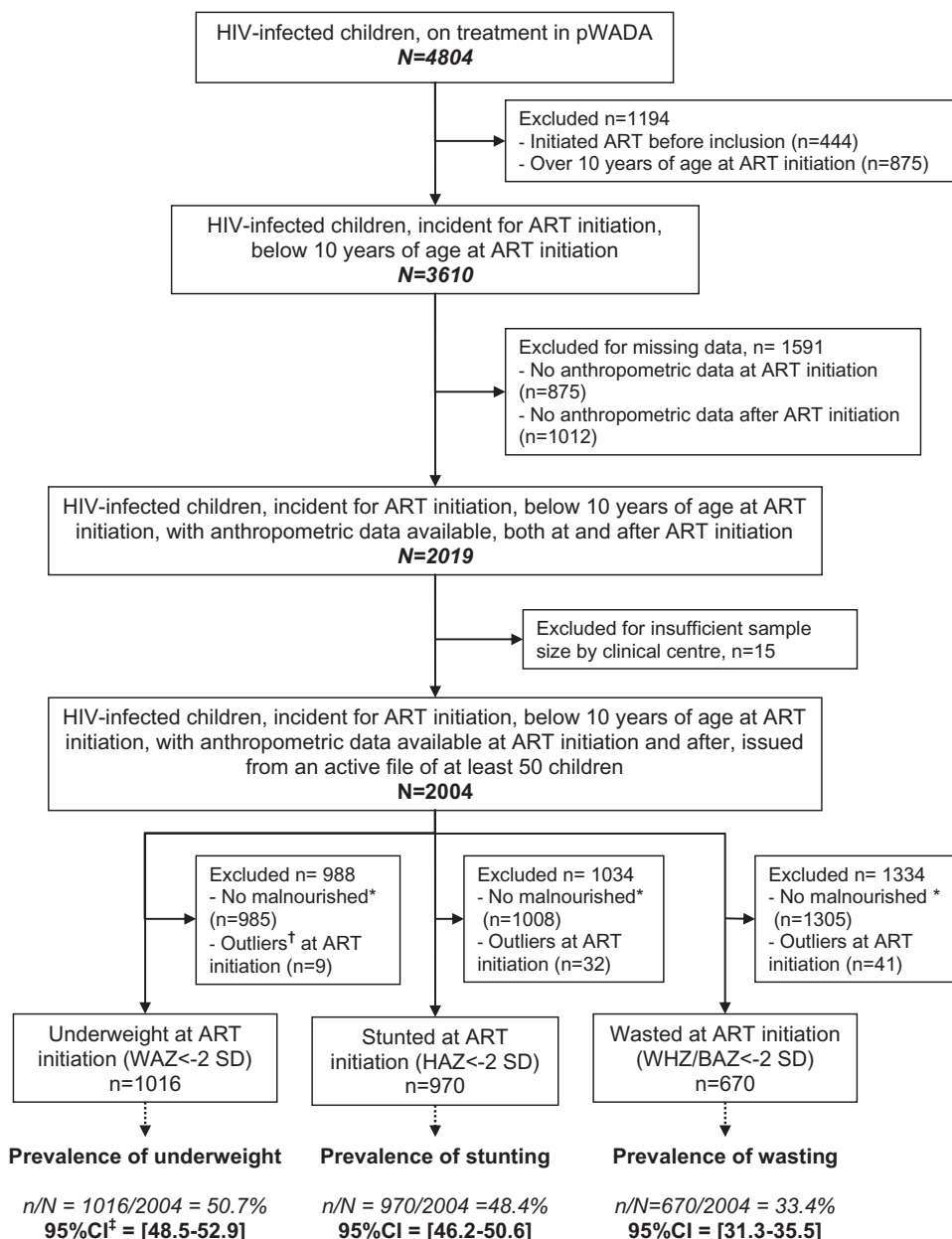
### Baseline and Follow-up Characteristics of the Study Population

Among the 4804 HIV-infected children on ART included in the pWADA cohort, 3610 initiated ART <10 years between 2001 and 2012 (Fig. 1). Among them, 2004 (56%) fitted the inclusion criteria. At ART initiation, the median age was 4.1 years [interquartile range (IQR): 2.1-6.7], and 46% were girls. Median baseline WAZ, HAZ and WHZ/BAZ were -2.05 (IQR: -3.27 to -1.08), -1.98 (IQR: -2.98 to -0.97) and -1.31 (IQR: -2.58 to -0.32), respectively. The first-line ART regimen was based on protease inhibitors (PI) for 17% of children. Data on cotrimoxazole use were missing for most children, slightly more for malnourished children. Forty-one percent were classified at WHO clinical stage III or IV, and 37% were severely immunodeficient for age. Fifty-three percent of children initiated ART between 2005 and 2008 (Table 1). Overall, 50.7% were underweight [95% confidence interval (95% CI): 48.5-52.9], 48.4% were stunted (95% CI: 46.2-50.6) and 33.4% were wasted (95% CI: 31.3-35.5) (Fig. 1). Among malnourished children, according to each type of malnutrition, 58.8% were severely underweight, 50.1% were severely stunted and 57.0% were severely wasted.

The median follow-up time on ART for the 2004 children was 25 months (IQR: 12-47). Thirteen percent of children were LTFU, and 3% were deceased before 24 months of ART.

The 2004 children contributed 14,766 available anthropometric measurements during the first 24 months of treatment, which represents >75% of the overall available anthropometric data during the entire follow-up. The median number of observations was 4 per child (IQR: 3-7).

Compared with the selected population, children excluded for missing anthropometric data did not differ in age



**FIGURE 1.** Cohort profile of the study sample selection and prevalence of malnutrition with their 95% CI according to WAZ, HAZ and WHZ/BMI. \*, Z score  $\geq -2$  SD; †, Z score  $< -10$  or  $> 10$  SD. leDEA West African paediatric cohort.

or gender but differed in terms of follow-up quality. Clinical variables were more often missing ( $P < 0.001$ ), and the proportion of death and LTFU during the entire follow-up was highest in excluded children: 11% versus 2% and 34% versus 24%, respectively ( $P < 0.001$ ).

**Factors Associated at ART Initiation, Probabilities and Predictors of Catch-Up Growth at 24-Month Underweight (Weight-for-Age Z score)**

In multivariate analyses, children  $< 2$  years had significantly higher odds of being underweight at ART initiation compared with children  $> 5$  years [adjusted odds ratio (aOR): 2.09; 95% CI: 1.62–2.71]. Furthermore, severely immunodeficient children had higher odds of being underweight at ART initiation compared with

nonimmunodeficient children (aOR: 1.81; 95% CI: 1.36–2.40) (Table 2).

For the 1016 children underweight at baseline, the median time to catch-up growth was 11.7 months (95% CI: 9.8–12.2). Their crude 24-month cumulative probability for catch-up growth was 70% (95% CI: 67–74), whereas the adjusted rate was 69% (95% CI: 57–80) (Fig. 2). Children aged 0–2 and 2–3 years at ART initiation had the highest probability for catch-up growth before 24 months: the adjusted cumulative probabilities by 24 months were both 81% (95% CI: 69–88 and 67–89, respectively), whereas it was 53% (95% CI: 40–63) for children  $\geq 5$  years ( $P < 0.001$ ) (Fig. 2). In Cox analysis, catch-up growth was more likely in all children  $< 5$  years compared with older children. Boys were more likely to catch up growth for WAZ than girls [adjusted hazard ratio (aHR): 0.80;

**TABLE 1.** Socio-demographic and Clinical Characteristics at ART Initiation According to the Prevalence of Malnutrition (Z score <-2 SD) for Each Anthropometric Indicator in HIV-infected Children

Variables	Underweight: WAZ<-2 SD						
	Yes (N = 1016)		No (N = 988)		P Value*	Yes (N = 970)	
	Median	IQR	Median	IQR		Median	IQR
Age (yrs)	3.5	1.7–6.5	4.5	2.6–6.8	<0.001	3.4	1.9–5.9
CD4 % for children under 5 yrs (n = 623)	14	8.4–19.1	14.2	11.0–20.0	0.033	13.7	9.0–18.0
CD4 cell count/mL for children upper 5 yrs (n = 721)	233	37–456	383	203–652	<0.001	255	64–466
	N	%	N	%		N	%
Age groups (yrs)					<0.001		
0–2	306	30.1	158	16		264	27.2
2–3	152	15	133	13.5		175	18
3–4	89	8.8	128	13		115	11.9
4–5	86	8.5	126	12.8		98	10.1
5–10	383	37.7	443	44.8		318	32.8
Gender					0.049		
Boy	570	56.1	511	51.7		560	57.7
Girl	446	43.9	477	48.3		410	42.3
WHO clinical stage					<0.001		
I	80	7.9	170	17.2		75	7.7
II	131	12.9	230	23.3		137	14.1
III	318	31.3	209	21.2		283	29.2
IV	233	22.9	54	5.5		195	20.1
Missing	254	25	325	32.9		280	28.9
Immunodeficiency status†					<0.001		
No immunodeficient	122	12	185	18.7		110	11.3
Moderate	131	12.9	166	16.8		133	13.7
Severe	414	40.7	324	32.8		388	40
Missing	349	34.4	313	31.7		339	34.9
First line regimen					0.002		
2 NRTIs + 1 NNRTI	789	77.7	824	83.4		745	76.8
2 NRTIs + 1 PI	199	19.6	151	15.3		202	20.8
3 NRTIs	28	2.8	13	1.3		23	2.4
Cotrimoxazole prophylaxis					<0.001		
Yes	184	18.1	208	21		179	18.5
No	170	16.7	217	22		170	17.5
Missing	662	65.2	563	57		621	64
Time period of ART initiation					0.041		
2001–2004	114	11.2	88	8.9		114	11.8
2005–2008	551	54.2	511	51.7		538	55.5
2009–2012	351	34.5	389	39.4		318	32.8
Countries and centers					<0.001		
Benin	68	6.7	32	3.2		67	6.9
Burkina Faso	70	6.9	59	6		58	6
Côte d’Ivoire	289	28.4	396	40.1		316	32.6
Site 1	125	12.3	177	17.9		154	15.9
Site 2	20	2	39	3.9		19	2
Site 3	84	8.3	96	9.7		92	9.5
Site 4	38	3.7	49	5		35	3.6
Site 5	22	2.2	35	3.5		16	1.6
Ghana	140	13.8	196	19.8		153	15.8
Mali	369	36.3	241	24.4		303	31.2
Senegal	80	7.9	64	6.5		73	7.5

IeDEA West African paediatric cohort (n = 2004)

\*The  $\chi^2$  test for qualitative variables; Kruskal–Wallis test for quantitative variables.

†Defined by age according to WHO 2006 guidelines.

NRTI indicates nucleoside reverse-transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor.

95% CI: 0.68–0.95), as well as children with severe malnutrition at baseline (aHR: 0.42, 95% CI: 0.36–0.50) compared with moderate malnutrition (Table 3).

**Stunting (Height-for-Age Z score)**

Adjusted for all covariables, children <5 years suffered more from stunting at ART initiation than children ≥5 years (P < 0.001).

Boys had higher odds of being stunted at ART initiation than girls (aOR: 1.32; 95% CI: 1.10–1.58), as well as severely immunodeficient children compared with those not (aOR: 1.71; 95% CI: 1.28–2.27), and children initiating ART in the 2001–2004 and the 2005–2008 periods, compared with children initiating ART between 2009 and 2012 (aOR: 1.67; 95% CI: 1.19–2.36 and aOR: 1.30; 95% CI: 1.07–1.59, respectively) (Table 2).



Stunting: HAZ<-2 SD			Wasting: WHZ/BAZ<-2 SD					Total Study Population	
No (N = 1034)			Yes (N = 670)		No (N = 1334)				
Median	IQR	P Value*	Median	IQR	Median	IQR	P Value*	Median	IQR
4.9	2.5–7.2	<0.001	3.1	1.6–6.6	4.4	2.5–6.7	<0.001	4.1	2.1–6.7
15	10.0–21.0	0.011	14	8.0–20.0	14	10.0–19.0	0.397	14	9.2–19.9
357	139–620	<0.001	200	26–468	335	175–595	<0.001	309	113–561
N	%		N	%	N	%		N	%
		<0.001					<0.001		
200	19.3		241	36	223	16.7		464	23.2
110	10.6		90	13.4	195	14.6		285	14.2
102	9.9		48	7.2	169	12.7		217	10.8
114	11		48	7.2	164	12.3		212	10.6
508	49.1		243	36.3	583	43.7		826	41.2
		0.001					0.115		
521	50.4		378	56.4	703	52.7		1081	53.9
513	49.6		292	43.6	631	47.3		923	46.1
		<0.001					<0.001		
175	16.9		56	8.4	194	14.5		250	12.5
224	21.7		88	13.1	273	20.5		361	18
244	23.6		207	30.9	320	24		527	26.3
92	8.9		173	25.8	114	8.5		287	14.3
299	28.9		146	21.8	433	32.5		579	28.9
		<0.001					0.117		
197	19.1		87	13	220	16.5		307	15.3
164	15.9		98	14.6	199	14.9		297	14.8
350	33.8		266	39.7	472	35.4		738	36.8
323	31.2		219	32.7	443	33.2		662	33
		<0.001					0.082		
868	83.9		524	78.2	1089	81.6		1613	80.5
148	14.3		127	19	223	16.7		350	17.5
18	1.7		19	2.8	22	1.6		41	2
		0.033					<0.001		
213	20.6		124	18.5	268	20.1		392	19.6
217	21		100	14.9	287	21.5		387	19.3
604	58.4		446	66.6	779	58.4		1225	61.1
		<0.001					0.924		
88	8.5		69	10.3	133	10		202	10
524	50.7		351	52.4	711	53.3		1062	53
422	40.8		250	37.3	490	36.7		740	37
		<0.001					<0.001		
33	3.2		30	4.5	70	5.2		100	5
71	6.9		52	7.8	77	5.8		129	6.4
369	35.7		171	25.5	514	38.5		685	34.2
148	14.3		58	8.7	244	18.3		302	15.1
40	3.9		17	2.5	42	3.1		59	2.9
88	8.5		50	7.5	130	9.7		180	9
52	5		30	4.5	57	4.3		87	4.3
41	4		16	2.4	41	3.1		57	2.8
183	17.7		76	11.3	260	19.5		336	16.8
307	29.7		285	42.5	325	24.4		610	30.4
71	6.9		56	8.4	88	6.6		144	7.2

For the 970 children stunted at baseline, the median time to catch-up growth was 17.7 months (95% CI: 15.4–19.3). Their crude 24-month cumulative probability for catch-up was 61% (95% CI: 58–65), whereas the adjusted rate was 61% (95% CI: 47–70) (Fig. 2). Children aged ≥5 years had a significantly lower 24-month probability for catch-up growth [40% (95% CI: 28–49)] compared with younger children, where this probability reached 58% (95% CI: 44–68;  $P < 0.001$ ) (Fig. 2). In Cox analysis, catch-up growth was more likely in children <5 years and less likely in children with severe compared with moderate malnutrition at ART initiation

(0.33, 95% CI: 0.27–0.39). The time period of ART initiation did not have an effect on catch-up growth for HAZ (Table 3).

### Wasting (Weight-for-Height/BMI-for-Age Z score)

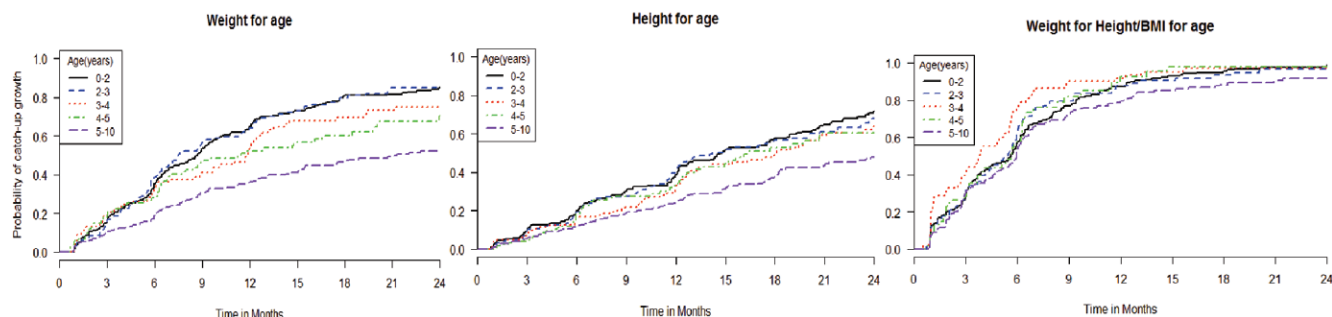
Compared with children ≥5 years, children <2 years had higher odds of being wasted at ART initiation (aOR: 2.45; 95% CI: 1.89–3.17), whereas we observed an opposite trend in children aged 3–4 years (aOR: 0.64; 95% CI: 0.44–0.93). For other age groups, there was no significant difference, although there was trend toward lower risks in 4–5 years as well (Table 1).

**TABLE 2.** Factors Associated with Malnutrition (Z score < -2 SD) at ART initiation, for Each Anthropometric Indicator, Adjusted Logistic Regression Analysis (n = 2004)

Baseline Variables	Malnutrition at ART Initiation (Z Score < -2 SD), Adjusted Analysis								
	Underweight: WAZ			Stunting: HAZ			Wasting: WHZ/BAZ		
	aOR	95% CI	P Value	aOR	95% CI	P Value	aOR	95% CI	P Value
Age groups (yrs)			<0.001			<0.001			<0.001
5-10	1	—		1	—		1	—	
0-2	2.09	1.62-2.71		2.32	1.80-3.00		2.45	1.89-3.17	
2-3	1.19	0.89-1.59		2.68	1.99-3.60		0.99	0.73-1.36	
3-4	0.72	0.52-1.00		1.87	1.35-2.58		0.64	0.44-0.93	
4-5	0.75	0.54-1.03		1.44	1.05-1.99		0.70	0.48-1.02	
Gender			0.122			0.003			0.320
Girl	1	—		1	—		1	—	
Boy	1.16	0.96-1.39		1.32	1.10-1.58		1.11	0.91-1.35	
Immunodeficiency status*			<0.001			<0.001			0.142
No immunodeficiency	1	—		1	—		1	—	
Moderate	1.02	0.73-1.45		1.11	0.79-1.56		1.06	0.73-1.53	
Severe	1.81	1.36-2.40		1.71	1.28-2.27		1.35	0.99-1.83	
Missing	1.38	0.99-1.91		1.10	0.80-1.53		1.09	0.77-1.55	
Time period of ART initiation			0.484			0.033			
2009-2012	1	—		1	—		—	—	
2001-2004	1.03	0.73-1.45		1.67	1.19-2.36		—	—	
2005-2008	1.13	0.92-1.37		1.30	1.07-1.59		—	—	
Countries			<0.001			0.012			<0.001
Côte d'Ivoire	1	—		1	—		1	—	
Benin	2.85	1.77-4.59		2.20	1.37-3.53		1.30	0.79-2.14	
Burkina Faso	1.59	1.08-2.35		0.89	0.60-1.32		2.05	1.37-3.06	
Ghana	0.99	0.74-1.33		1.06	0.79-1.43		0.95	0.68-1.34	
Mali	1.94	1.53-2.47		0.93	0.73-1.18		2.55	1.99-3.27	
Senegal	1.85	1.27-2.69		1.22	0.83-1.77		2.12	1.43-3.14	

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\*Defined by age according to WHO 2006 guidelines.



Age groups	Number at risk, probability% (95%CI)														
	M0	M6	M12	M18	M24	M0	M6	M12	M18	M24	M0	M6	M12	M18	M24
0-2	306	189 37 (26-46)	86 64 (51-73)	45 78 (66-85)	29 81 (69-88)	264	192 22 (14-30)	119 41 (29-51)	71 58 (44-68)	39 70 (55-78)	241	100 57 (43-67)	30 84 (71-90)	15 92 (82-96)	7 96 (87-98)
2-3	152	87 40 (27-50)	41 63 (49-73)	23 77 (62-85)	15 81 (67-89)	175	131 22 (13-30)	73 43 (29-53)	46 58 (43-67)	30 67 (51-76)	90	33 62 (44-73)	11 84 (69-91)	6 90 (75-95)	3 94 (81-98)
3-4	89	57 35 (21-45)	31 54 (38-66)	18 68 (51-79)	15 73 (55-83)	115	91 19 (10-26)	60 35 (22-46)	39 51 (35-62)	27 63 (47-74)	48	13 75 (53-85)	4 88 (71-95)	1 95 (77-98)	1 95 (77-98)
4-5	89	56 31 (18-41)	29 53 (37-64)	19 60 (43-71)	10 69 (50-80)	98	74 22 (11-30)	52 37 (23-48)	31 54 (37-66)	22 61 (43-72)	48	16 58 (37-71)	3 90 (67-96)	1 95 (73-99)	1 95 (73-99)
5-10	383	270 20 (14-27)	146 38 (27-46)	85 48 (36-57)	51 53 (40-63)	318	243 14 (9-19)	163 27 (18-35)	110 40 (28-49)	70 49 (36-59)	243	104 55 (38-62)	40 77 (64-85)	19 85 (73-92)	8 90 (78-95)

**FIGURE 2.** Estimated probabilities of catch-up growth (Z score ≥ -2 SD) based on adjusted Kaplan-Meier estimates within the first 24 months on ART in HIV-infected children suffering at baseline from underweight (n = 1016), stunting (n = 970) and wasting (n = 670), according to age at ART initiation. leDEA West African paediatric cohort.

**TABLE 3.** Factors Associated with Catch-up Growth (Z score  $\geq -2$  SD) after ART Initiation, According to Weight-for-Age, Height-for-Age, Weight-for-Height/BMI-for-Age Indicators Among Malnourished HIV-infected Children (Z score  $< -2$  SD), adjusted Cox Model Analysis

Baseline Variables	Adjusted Model WAZ			Adjusted Model HAZ			Adjusted Model WHZ/BAZ		
	aHR	95% CI	P Value	aHR	95% CI	P Value	aHR	95% CI	P Value
Age groups (yrs)			<0.001			<0.001			0.026
5–10	1	—		1	—		1	—	
0–2	2.34	1.87–2.94		2.03	1.58–2.60		1.21	0.96–1.51	
2–3	2.35	1.82–3.03		1.98	1.52–2.56		1.25	0.95–1.65	
3–4	1.80	1.33–2.44		1.71	1.29–2.28		1.69	1.21–2.36	
4–5	1.60	1.18–2.18		1.53	1.12–2.09		1.37	0.98–1.91	
Gender			0.008			0.497			0.016
Girl	1	—		1	—		1	—	
Boy	0.80	0.68–0.95		0.94	0.79–1.12		0.81	0.68–0.96	
Immunodeficiency status*			0.005			0.118			0.233
No immunodeficiency	1	—		1	—		1	—	
Moderate	1.18	0.85–1.63		1.00	0.75–1.34		0.97	0.70–1.34	
Severe	1.31	0.99–1.72		1.04	0.75–1.46		1.21	0.92–1.59	
Missing	0.90	0.66–1.23		0.78	0.56–1.08		1.04	0.75–1.43	
Time period of ART initiation			0.940						0.031
2009–2012	1	—		—	—		1	—	
2001–2004	0.95	0.70–1.29		—	—		0.66	0.48–0.91	
2005–2008	1.00	0.83–1.19		—	—		0.87	0.73–1.04	
Malnutrition			<0.001			<0.001			<0.001
Moderate ( $-3 \leq Z$ score $< -2$ )	1	—		1	—		1	—	
Severe (Z score $< -3$ )	0.42	0.36–0.50		0.33	0.27–0.39		0.52	0.44–0.62	
First line regimen			0.851			0.222			
2 NRTIs + 1 NNRTI or 3 NRTIs	1	—		1	—		1	—	0.846
2 NRTIs + 1 PI	1.02	0.83–1.26		0.87	0.70–1.09		1.02	0.81–1.29	
Countries			<0.001			<0.001			<0.001
Côte d'Ivoire	1	—		1	—		1	—	
Benin	0.98	0.65–1.47		0.92	0.53–1.61		0.92	0.59–1.42	
Burkina Faso	1.16	0.82–1.64		1.80	1.26–2.57		0.46	0.32–0.67	
Ghana	1.98	0.96–1.49		1.84	1.36–2.49		2.10	1.51–2.91	
Mali	1.20	0.96–1.49		1.64	1.31–2.06		1.16	0.93–1.46	
Senegal	2.16	1.58–2.97		1.83	1.31–2.06		1.28	0.93–1.78	

IeDEA West African paediatric cohort.

\*Defined by age according to WHO 2006 guidelines.

NRTI indicates nucleoside reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

For the 670 children wasted at baseline, the median time to catch-up growth was 5.5 months (95% CI: 4.8–5.7). The overall crude cumulative probability for catch-up growth by 24 months was 94% (95% CI: 91–96), whereas the adjusted rate was 90% (95% CI: 76–95) (Fig. 2). The probability for catch-up growth for WHZ/BAZ differed according to age at ART initiation ( $P = 0.026$ ). In Cox analysis, there was a significant association between age at ART initiation and catch-up growth; children aged 3–4 years had higher odds compared with children  $\geq 5$  years (aOR: 1.69; 95% CI: 1.21–2.36). As in previous analyses, children with severe malnutrition at baseline were less likely to catch up growth (aHR: 0.52; 95% CI: 0.44–0.62), as were boys (aHR: 0.81; 95% CI: 0.68–0.96). Catch-up growth tended to be more likely in children initiating ART between 2001 and 2004 than in children initiating ART after 2009 (aOR: 0.66; 95% CI: 0.48–0.91) (Table 3).

### Sensitivity Analyses: Catch-up Growth at a Z Score $\geq -1$ SD

Using a higher threshold for the definition of catch-up growth, the adjusted 24-month cumulative probabilities for catch-up growth were much lower than the previous: 28% (95% CI: 16–38), 31% (95% CI: 14–44) and 61% (95% CI: 43–73) for WAZ, HAZ

and WHZ/BAZ, respectively, with significant differences by age group ( $P < 0.001$ ). In Cox analyses, the association with age at ART initiation was more pronounced, and for each anthropometric indicator, younger children were more likely to catch up growth.

## DISCUSSION

This large sample-sized prospective cohort study of 2004 HIV-infected children allows providing an original estimation of the prevalence of malnutrition among children at ART initiation in West Africa and assessing their rates and predictors to catch-up of normal growth for age during the first 24 months on ART. ART was initiated at a late age (median: 4.1 years), and the prevalence of malnutrition at that time was already high according to all 3 indicators (51% underweight, 48% stunted and 33% wasted, with a higher prevalence in the younger children and those severely immunodeficient). After 24 months on ART, malnourished children had a substantial probability of reaching their population age norms, varying from 61% for HAZ, 70% for WAZ, to 94% for WHZ/BAZ. In adjusted analysis, the rates for catch-up growth differed by age at ART initiation for weight-for-age and height-for-age indicators: children  $< 5$  years were more likely to catch up growth compared with older children. Furthermore, children aged 3–4 years were



more likely to catch-up growth according to weight-for-height/BMI-for-age compared with children  $\geq 5$  years.

Growth reconstitution on ART was more effective and occurred sooner in wasted children compared with those underweight or stunted: it is easier to recover from acute malnutrition than from chronic malnutrition, where damages can be irreversible. Similar results were observed in a Kenyan study where catch-up growth was defined by a Z score  $\geq 0$  SD.<sup>17</sup> In a study in Southern Africa, the percentage of children with a Z score  $>-2$  SD at different times after ART initiation was similar for weight-for-age and weight-for-height, and higher than for height-for-age.<sup>18</sup>

Children  $<5$  years at ART initiation presented a better growth reconstitution than older children. This is consistent with other studies<sup>5,6,17,29</sup> but not all.<sup>4</sup> This could be explained by metabolic and nutritional disorders occurring before ART initiation that obviously would not last as long in the youngest children compared with the older ones, if we assume that all these children were perinatally infected. Indeed, HIV-infected children suffer from opportunistic infections, such as persistent diarrhea, malabsorption and have pro-inflammatory effects, which can cause intestinal dysfunction<sup>30</sup> and affect height and weight. Early ART initiation could prevent these disorders, but its beneficial effects may be too late for older children.

Overall, the population selection process could have led to an underestimation of the prevalence of malnutrition among HIV-infected children initiating ART. Indeed, the children excluded for missing anthropometric data represented 45% of the targeted population and were more often LTFU or deceased, possibly because they suffered from malnutrition. Multiple imputation could be a solution; however, we felt we had 2 very different populations here and chose not to impute for these reasons. More efforts are needed to improve the quality of the follow-up and data collection. In addition, our study is not representative of all children on ART in these regions as most of the data were gathered from urban sites, in which the standard of care may be higher than in rural areas.

Our prospective cohort design allowed controlling the temporality of the events, observing the development of malnutrition in children after ART initiation over 24 months. Unfortunately, we could only include few explanatory variables to study associated factors to malnutrition and catch-up growth for data availability issues. Data on viral load were not collected routinely, neither were data on nutritional supplementation practices during the follow-up period, which could be critical to further explore this question.

All the results observed at and after ART initiation should be interpreted with caution keeping in mind that children were not issued from a representative birth-cohort, with a high risk of death in children before the age of 2 years.<sup>31,32</sup> In this context of difficult access to HIV-care, the younger children are also the more symptomatic, which is what brings them to care, leading to an indication bias. However, this study offers a unique opportunity to describe the problem of malnutrition in this pediatric population in its context and its evolution under ART given the current healthcare practices.

In our study, children started ART late, at an advanced stage of the disease, reflecting the difficulties for early detection of HIV-infected children in resource-limited settings.<sup>33</sup> The prevalence of malnutrition in HIV-infected children at ART initiation in our study was higher than that in the general child population in West Africa (22% of underweight, 36% of stunting and 10% of wasting),<sup>34</sup> underlining the increasing effect of HIV-infection on malnutrition among children in this region.

There was no association between baseline immunodeficiency and growth recovery, as reported in previous studies.<sup>35</sup> However, it has been previously reported that height is correlated with CD4% at baseline in children on ART.<sup>9</sup> For wasted and underweight

children, some studies also observed an association with immunodeficiency at ART initiation.<sup>18,29</sup> Among malnourished children at ART initiation, those who were severely immunodeficient could have nutritional problems directly because of HIV infection. Thus, after ART initiation, immune system disorders can be reversed and associated nutritional problems can be reduced. We report elsewhere in the same population that the initiation of ART at the earliest age before 5 years and before any severe immunodeficiency occurred is needed to optimize the 24-month immune recovery on ART.<sup>36</sup>

Our cohort represents a decade of pediatric HIV care, but we observed little differences in the prevalence of malnutrition and the probabilities of catch-up growth according to the time period of ART initiation. Despite a better access to ART and HIV care, nutritional care does not seem to have evolved. Few studies have investigated nutritional supplementation among HIV-infected children. Despite a trend to beneficial effects of these supplements for the development of HIV-infected children, the level of proof remains low.<sup>37,38</sup>

In conclusion, malnutrition among HIV-infected children in West Africa is highly prevalent at ART initiation, representing an additional burden that needs to be urgently managed. In resource-limited settings, pediatric HIV infection is still detected too late, and ART initiation is delayed.<sup>31,33</sup> Initiation of ART before children develop growth failure, especially stunting, should be encouraged. This study highlights age at ART initiation as a predictor of better catch-up growth, with significantly improved chances for catch-up growth among those starting ART before the age of 5 years. These findings support ART initiation at the earliest convenience before the age of 5 years and the presence of growth failure, independently of baseline immunodeficiency. This is in line with the revised WHO guidelines recommending ART initiation in all children aged  $<5$  years.<sup>39</sup> Despite a significant growth improvement after ART initiation, a substantial proportion of children still did not achieve catch-up growth after 2 years on ART, even in the age groups with the better growth responses, and when defining catch-up growth with the lowest possible threshold. Further research is needed to better understand the growth reconstitution in ART treated children and to investigate nutritional interventions to improve growth on ART. This will lead to the optimization of the ART response of HIV-infected children in West Africa, improving their survival and quality of life.

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