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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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Abstract

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 IeDEA West African paediatric cohort (pWADA).

Methods—Malnutrition was defined at ART initiation (baseline) by a Z-score <-2 SD, according to three 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 SD) on ART, adjusted for gender, immunodeficiency

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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 to children ≥5 years for WAZ, HAZ (P<0.001), and for 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.

Keywords

HIV; children; antiretroviral therapy; growth; malnutrition; Africa

Introduction

In 2011, 3.3 million children aged <15 years were living with Human Immunodeficiency Virus (HIV) worldwide, with more than 90% living in Sub-Saharan Africa [1]. Growth faltering has been reported in up to 50% of untreated HIV-infected children in resource-limited settings [2-4], and several studies have shown that HIV-related growth faltering can be reversed with antiretroviral therapy (ART) [3-11]. ART reduces the risk of HIV-infection progression and reduces mortality in children [12,13]. ART also has an impact on the child's nutritional status, by reducing pro-inflammatory cytokine concentration, and improving immune system functions [14]. Improvements in growth may in turn help towards a slower HIV disease progression and reduce pediatric HIV-related morbidity and mortality [15,16]. 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 [17,18]. While a better growth response is found among younger children at ART initiation compared to older ones in some studies [5,6,17,19], others report that growth response after ART initiation is not associated with age [4,20]. 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 two years of follow-up [3-5,18]. Most of these studies have been conducted in Eastern and Southern Africa. Few data are available on malnutrition in West-African HIV-infected children [21], 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

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time to catch-up growth within 24 months post-ART initiation among HIV-infected children enrolled in the IeDEA West African pediatric cohort.

Methods

Study population

The IeDEA network (International epidemiologic Databases to Evaluate Aids) is an international consortium collecting data on HIV infection and AIDS. The WADA collaboration (West African Database on Antiretroviral therapy) 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 seven countries (Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, Senegal and Togo) of the WADA collaboration [22,23]. 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 (PCR), 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 (PMTCT), with a documented date of birth and ART regimen, who initiated ART during follow-up in pWADA, and aged <10 years, with at least two anthropometric measurements during follow-up, including one in the first 3 months of ART and one 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 WHO [24]. In this study, we defined standardized malnutrition using Z-scores, which quantify how many Standard Deviations (SD) child's weight and height is 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 [25], and the 2007 WHO growth charts for children ≥5 years [26]. We defined three 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 Anthro Plus. 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 [27]. CD4 was expressed

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in percentage for children < 5 years and in cells per μL for children ≥ 5 years. Severe immunodeficiency was defined as CD4% <15% or CD4 cells/μL <350 cells/μL, and moderate immunodeficiency as CD4% between 15-25% or CD4 count between 350-499 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 [28]. 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 NIH approval.

Statistical analysis

We first measured the prevalence of malnutrition at ART initiation (baseline) according to the three 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 30th 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 (Figure 1). Among them, 2004 (56%) fitted the inclusion criteria. At ART initiation, the median age was 4.1 years (interquartile range

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(IQR)=[2.1;6.7]), and 46% were girls. Median baseline WAZ, HAZ and WHZ/BAZ were -2.05 (IQR=[-3.27,-1.08]), -1.98 (IQR=[-2.98;-0.97]), and -1.31 (IQR=[-2.58;-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 immunedeficient 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]), (Figure 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 14766 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 4per child (IQR=[3;7]).

Compared with the selected population, children excluded for missing anthropometric data did not differ in age 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% vs. 2% and 34% vs. 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 to children >5 years (adjusted Odds Ratio (aOR)=2.09, 95%CI=[1.62; 2.71]). Furthermore, severely immunedeficient children had higher odds of being underweight at ART initiation compared with non immunedeficient 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]), while the adjusted rate was 69% (95%CI=[57-80]) (Figure 2). Children aged 0 to 2 years and 2 to 3 years at ART initiation had the highest probability for catch-up growth for WAZ 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 ≥5 years ($p <0.001$) (Figure 2). In Cox analysis, catch-up growth was more likely in all children <5 years compared to older children. Boys were more likely to catchup growth for WAZ than girls (aHR=0.80, 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 to moderate malnutrition (Table 3).

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Stunting (Height-for-Age Z-score)

Adjusted for all co-variables, 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 immunedeficient children compared to 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).

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]), while the adjusted rate was 61% (95%CI=[47-70]) (Figure 2). Children aged ≥5 years had a significantly lower 24-month probability for catch-up growth (40% (95%CI=[28;49]) compared to younger children, where this probability reached 58% (95%CI=[44;68])(p<0.001) (Figure 2).In Cox analysis, catch-up growth was more likely in children <5 years, and less likely in children with severe compared to 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 to 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 to 4 years (aOR=0.64, 95%CI=[0.44;0.93]). For other age groups, there was no significant difference, though there was trend towards lower risks in 4-5 years as well (Table 1). 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]), while the adjusted rate was 90% (95%CI=[76-95]) (Figure 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 to children ≥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 catchup 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 ≥ -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 previously: 28% (95%CI=[16;38]), 31% (95%CI=[14-44]), 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, for each anthropometric indicator, younger children were more likely to catch up growth.

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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 three indicators (51% underweight, 48% stunted, and 33% wasted, with a higher prevalence in the younger children and those severely immunedeficient). 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 catchup growth compared to older children. Furthermore, children aged 3-4 years were more likely to catch-up growth according to Weight-for-Height / BMI-for-age compared to children ≥5 years.

Growth reconstitution on ART was more effective and occurred sooner in wasted children compared to 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 ≥ 0 SD [17]. 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 [18].

Children <5 years at ART initiation presented a better growth reconstitution than older children. This is consistent with other studies [5,6,17,29], but not all [4]. 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 to 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 [30] 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 two 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.

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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 two years [31,32]. 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 currents 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 [33]. 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) [34], 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 [35]. However, it has been previously reported that height is correlated with CD4% at baseline in children on ART [36].For wasted and underweight children, some studies also observed an association with immunodeficiency at ART initiation [18,29]. Among malnourished children at ART initiation, those who were severely immunedeficient could have nutritional problems directly due to 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 [37].

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 [38,39].

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 [31,33]. Initiation of ART before children develop growth failure, especially stunting, should be encouraged. The present 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

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growth failure, independently of baseline immunodeficiency. This is in line with the revised WHO guidelines recommending ART initiation in all children aged <5 years [40]. Despite a significant growth improvement after ART initiation, a substantial proportion of children still did not achieve catch-up growth after two 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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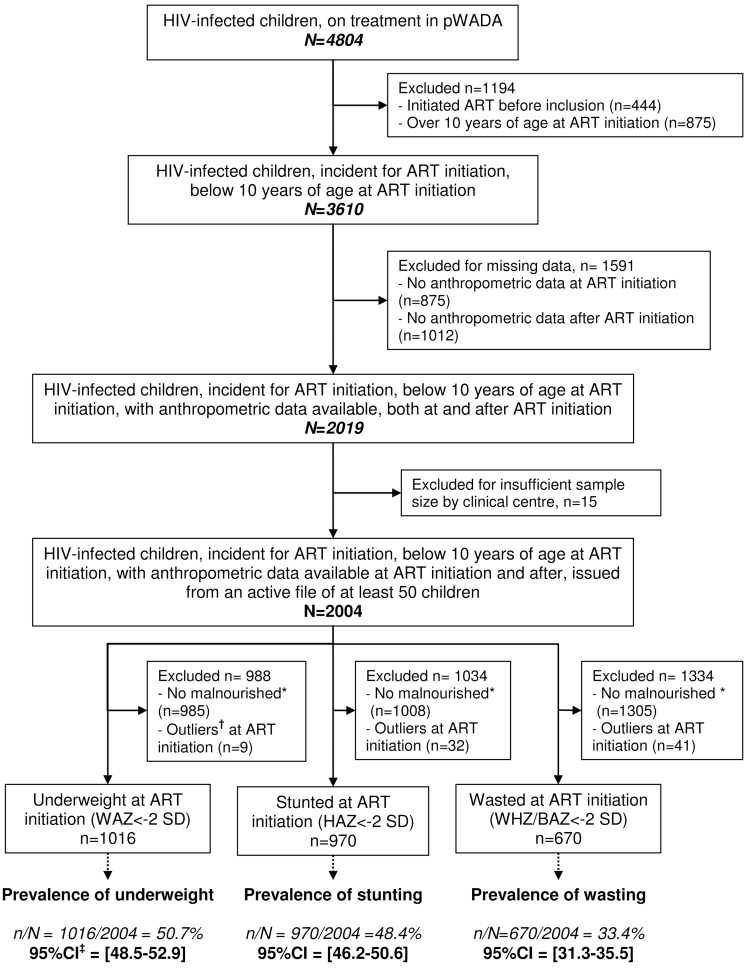

Figure 1.

Cohort profile of the study sample selection and prevalence of malnutrition with their 95% confidence Intervals according to Weight-for-Age, Height-for-Age and Weight-for-Height/ Body Mass Index-for-Age Z-scores (WAZ, HAZ, WHZ/BMI). * Z-score ≥ -2 Standard Deviations (SD) † Z-score < -10 or >10 SD, ‡CI = Confidence Intervals. IeDEA West African paediatric cohort

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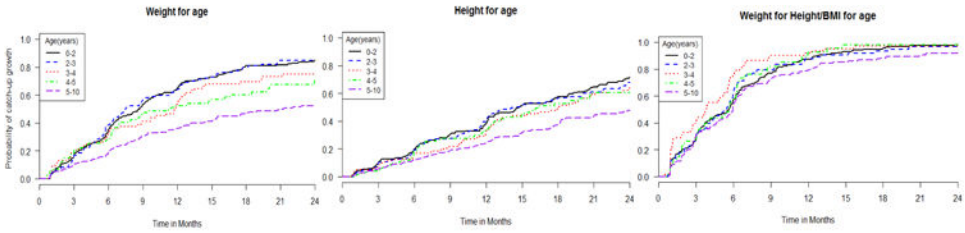

Number at risk,*probability% (95%CI)*

Age groups	M0	M6	M12	M18	M24	M0	M6	M12	M18	M24	M0	M6	M12	M18	M24
0-2	306	189	86	45	29	264	192	119	71	39	241	100	30	15	7
		37	*64*	*78*	*81*		*22*	*41*	*58*	*70*		*57*	*84*	*92*	*96*
		(26-46)	*(51-73)*	*(66-85)*	*(69-88)*		*(14-30)*	*(29-51)*	*(44-68)*	*(55-78)*		*(43-67)*	*(71-90)*	*(82-96)*	*(87-98)*
2-3	152	87	41	23	15	175	131	73	46	30	90	33	11	6	3
		40	*63*	*77*	*81*		*22*	*43*	*58*	*67*		*62*	*84*	*90*	*94*
		(27-50)	*(49-73)*	*(62-85)*	*(67-89)*		*(13-30)*	*(29-53)*	*(43-67)*	*(51-76)*		*(44-73)*	*(69-91)*	*(75-95)*	*(81-98)*
3-4	89	57	31	18	15	115	91	60	39	27	48	13	4	1	1
		35	*54*	*68*	*73*		*19*	*35*	*51*	*63*		*75*	*88*	*95*	*95*
		(21-45)	*(38-66)*	*(51-79)*	*(55-83)*		*(10-26)*	*(22-46)*	*(35-62)*	*(47-74)*		*(53-85)*	*(71-95)*	*(77-98)*	*(77-98)*
4-5	89	56	29	19	10	98	74	52	31	22	48	16	3	1	1
		31	*53*	*60*	*69*		*22*	*37*	*54*	*61*		*58*	*90*	*95*	*95*
		(18-41)	*(37-64)*	*(43-71)*	*(50-80)*		*(11-30)*	*(23-48)*	*(37-66)*	*(43-72)*		*(37-71)*	*(67-96)*	*(73-99)*	*(73-99)*
5-10	383	270	146	85	51	318	243	163	110	70	243	104	40	19	8
		20	*38*	*48*	*53*		*14*	*27*	*40*	*49*		*55*	*77*	*85*	*90*
		(14-27)	*(27-46)*	*(36-57)*	*(40-63)*		*(09-19)*	*(18-35)*	*(28-49)*	*(36-59)*		*(38-62)*	*(64-85)*	*(73-92)*	*(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) respectively, according to age at ART initiation. IeDEA West African paediatric cohort

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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. IeDEA West African paediatric cohort (n=2004)

Variables	Underweight: WAZ< -2 SD*					Stunting: HAZ< -2 SD*					Wasting: WHZ/BAZ< -2 SD*					Total study population	
	Yes (N=1016)		No (N=988)		P-value†	Yes (N=970)		No (N=1034)		P-value†	Yes (N=670)		No (N=1334)		P-value†		
	Median	*(IQR)*	Median	*(IQR)*		Median	*(IQR)*	Median	*(IQR)*		Median	*(IQR)*	Median	*(IQR)*		Median	*(IQR)*
Age (years)	3.5	*(1.7-6.5)*	4.5	*(2.6-6.8)*	<0.001	3.4	*(1.9-5.9)*	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)*
CD4 % for children under 5 years (n=623)	14.0	*(8.4-19.1)*	14.2	*(11.0-20.0)*	0.033	13.7	*(9.0-18.0)*	15.0	*(10.0-21.0)*	0.011	14.0	*(8.0-20.0)*	14.0	*(10.0-19.0)*	0.397	14	*(9.2-19.9)*
CD4 cell count/mL for children upper 5 years (n=721)	233	*(37-456)*	383	*(203-652)*	<0.001	255	*(64-466)*	357	*(139-620)*	<0.001	200	*(26-468)*	335	*(175-595)*	<0.001	309	*(113-561)*
	N	*%*	N	*%*		N	*%*	N	*%*		N	*%*	N	*%*		N	*%*
Age groups (years)					<0.001					<0.001					<0.001		
[0-2]	306	*30.1*	158	*16.0*		264	*27.2*	200	*19.3*		241	*36.0*	223	*16.7*		464	*23.2*
[2-3]	152	*15.0*	133	*13.5*		175	*18.0*	110	*10.6*		90	*13.4*	195	*14.6*		285	*14.2*
[3-4]	89	*8.8*	128	*13.0*		115	*11.9*	102	*9.9*		48	*7.2*	169	*12.7*		217	*10.8*
[4-5]	86	*8.5*	126	*12.8*		98	*10.1*	114	*11.0*		48	*7.2*	164	*12.3*		212	*10.6*
[5-10]	383	*37.7*	443	*44.8*		318	*32.8*	508	*49.1*		243	*36.3*	583	*43.7*		826	*41.2*
Gender					0.049					0.001					0.115		
Boy	570	*56.1*	511	*51.7*		560	*57.7*	521	*50.4*		378	*56.4*	703	*52.7*		1081	*53.9*
Girl	446	*43.9*	477	*48.3*		410	*42.3*	513	*49.6*		292	*43.6*	631	*47.3*		923	*46.1*
WHO clinical stage					<0.001					<0.001					<0.001		
I	80	*7.9*	170	*17.2*		75	*7.7*	175	*16.9*		56	*8.4*	194	*14.5*		250	*12.5*
II	131	*12.9*	230	*23.3*		137	*14.1*	224	*21.7*		88	*13.1*	273	*20.5*		361	*18.0*
III	318	*31.3*	209	*21.2*		283	*29.2*	244	*23.6*		207	*30.9*	320	*24.0*		527	*26.3*
IV	233	*22.9*	54	*5.5*		195	*20.1*	92	*8.9*		173	*25.8*	114	*8.5*		287	*14.3*
Missing	254	*25.0*	325	*32.9*		280	*28.9*	299	*28.9*		146	*21.8*	433	*32.5*		579	*28.9*
Immunodeficiency status ‡					<0.001					<0.001					0.117		
No immunodeficient	122	*12.0*	185	*18.7*		110	*11.3*	197	*19.1*		87	*13.0*	220	*16.5*		307	*15.3*
Moderate	131	*12.9*	166	*16.8*		133	*13.7*	164	*15.9*		98	*14.6*	199	*14.9*		297	*14.8*

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Variables	Underweight: WAZ< -2 SD*					Stunting: HAZ< -2 SD*					Wasting: WHZ/BAZ< -2 SD*					Total study population	
	Yes (N=1016)		No (N=988)		P-value†	Yes (N=970)		No (N=1034)		P-value†	Yes (N=670)		No (N=1334)		P-value†		
	Median	*(IQR)*	Median	*(IQR)*		Median	*(IQR)*	Median	*(IQR)*		Median	*(IQR)*	Median	*(IQR)*		Median	*(IQR)*
Severe	414	*40.7*	324	*32.8*		388	*40.0*	350	*33.8*		266	*39.7*	472	*35.4*		738	*36.8*
Missing	349	*34.4*	313	*31.7*		339	*34.9*	323	*31.2*		219	*32.7*	443	*33.2*		662	*33.0*
First line regimen§					0.002					<0.001					0.082		
2 NRTIs + 1 NNRTI	789	*77.7*	824	*83.4*		745	*76.8*	868	*83.9*		524	*78.2*	1089	*81.6*		1613	*80.5*
2 NRTIs + 1 PI	199	*19.6*	151	*15.3*		202	*20.8*	148	*14.3*		127	*19.0*	223	*16.7*		350	*17.5*
3 NRTIs	28	*2.8*	13	*1.3*		23	*2.4*	18	*1.7*		19	*2.8*	22	*1.6*		41	*2.0*
Cotrimoxazole prophylaxis					<0.001					0.033					<0.001		
Yes	184	*18.1*	208	*21.0*		179	*18.5*	213	*20.6*		124	*18.5*	268	*20.1*		392	*19.6*
No	170	*16.7*	217	*22.0*		170	*17.5*	217	*21.0*		100	*14.9*	287	*21.5*		387	*19.3*
Missing	662	*65.2*	563	*57.0*		621	*64.0*	604	*58.4*		446	*66.6*	779	*58.4*		1225	*61.1*
Time period of ART initiation					0.041					<0.001					0.924		
2001-2004	114	*11.2*	88	*8.9*		114	11.8	88	*8.5*		69	*10.3*	133	*10.0*		202	*10.0*
2005-2008	551	*54.2*	511	*51.7*		538	55.5	524	*50.7*		351	*52.4*	711	*53.3*		1062	*53.0*
2009-2012	351	*34.5*	389	*39.4*		318	32.8	422	*40.8*		250	*37.3*	490	*36.7*		740	*37.0*
Countries and centres					<0.001					<0.001					<0.001		
Benin	68	*6.7*	32	*3.2*		67	*6.9*	33	*3.2*		30	*4.5*	70	*5.2*		100	*5.0*
Burkina Faso	70	*6.9*	59	*6.0*		58	*6.0*	71	*6.9*		52	*7.8*	77	*5.8*		129	*6.4*
Côte d'Ivoire	289	*28.4*	396	*40.1*		316	*32.6*	369	*35.7*		171	*25.5*	514	*38.5*		685	*34.2*
Site 1	125	*12.3*	177	*17.9*		154	*15.9*	148	*14.3*		58	*8.7*	244	*18.3*		302	*15.1*
Site 2	20	*2.0*	39	*3.9*		19	*2.0*	40	*3.9*		17	*2.5*	42	*3.1*		59	*2.9*
Site 3	84	*8.3*	96	*9.7*		92	*9.5*	88	*8.5*		50	*7.5*	130	*9.7*		180	*9.0*
Site 4	38	*3.7*	49	*5.0*		35	*3.6*	52	*5.0*		30	*4.5*	57	*4.3*		87	*4.3*
Site 5	22	*2.2*	35	*3.5*		16	*1.6*	41	*4.0*		16	*2.4*	41	*3.1*		57	*2.8*
Ghana	140	*13.8*	196	*19.8*		153	*15.8*	183	*17.7*		76	*11.3*	260	*19.5*		336	*16.8*
Mali	369	*36.3*	241	*24.4*		303	*31.2*	307	*29.7*		285	*42.5*	325	*24.4*		610	*30.4*
Senegal	80	*7.9*	64	*6.5*		73	*7.5*	71	*6.9*		56	*8.4*	88	*6.6*		144	*7.2*

*WAZ: Weight-for-Age Z-score, HAZ: Height-for-Age Z-score, WHZ/BAZ: Weight-for-Height Z-score or Body Mass Index-for-Age Z-score, SD: Standard Deviations, IQR: InterQuartile Range

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† Khi-square test for qualitative variables, Kruskal-Wallis test for quantitative variables

‡ Defined by age according to WHO 2006 guidelines

§ NRTI: Nucleoside Reverse-Transcriptase Inhibitor, NNRTI : Non-Nucleoside Reverse Transcriptase Inhibitor, PI : Protease Inhibitor

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Table 2

Factors associated with malnutrition (Z-score < -2 SD) at ART initiation, for each anthropometric indicator, adjusted logistic regression analysis (n=2004). IeDEA West African paediatric cohort

Baseline variables	Malnutrition at ART initiation (Zscore< -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 (years)			<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)	

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Baseline variables	Malnutrition at ART initiation (Zscore< -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
Senegal	1.85	(1.27-2.69)		1.22	(0.83-1.77)		2.12	(1.43-3.14)	

*WAZ: Weight-for-Age Z-score, HAZ: Height-for-Age Z-score, WHZ/BAZ: Weight-for-Height Z-score or Body Mass Index-for-Age Z-score.

†aOR: adjusted Odds Ratio, CI: Confidence Interval

‡Defined by age according to WHO 2006 guidelines

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Table 3

Factors associated with catch-up growth (Z-score ≥ -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< -2SD), adjusted Cox model analysis. IeDEA West African paediatric cohort.

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 (years)			<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 ≤ 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

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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
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)	

*WAZ: Weight-for-Age Z-score, HAZ: Height-for-Age Z-score, WHZ/BAZ: Weight-for-Height Z-score or Body Mass Index-for-Age Z-score

†HR: Hazard Ratio, aHR: adjusted Hazard Ratio, CI: Confidence Interval,

‡Defined by age according to WHO 2006 guidelines,

§NRTI: Nucleoside Reverse-Transcriptase Inhibitor, NNRTI : Non-Nucleoside Reverse Transcriptase Inhibitor, PI : Protease Inhibitor.