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Association between age at antiretroviral therapy initiation and 24-month immune response in HIV-infected children in West Africa

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Abstract

Objective—We describe the association between age at antiretroviral therapy (ART) initiation and 24-month CD4⁺ cell response in West African HIV-infected children.

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Methods—All HIV-infected children from the IeDEA paediatric West African cohort, initiating ART, with at least two CD4⁺ cell count measurements, including one at ART initiation (baseline) were included. CD4⁺ cell gain on ART was estimated using a multivariable linear mixed model adjusted for baseline variables: age, CD4⁺ cell count, sex, first-line ART regimen. Kaplan-Meier survival curves and a Cox proportional hazards regression model compared immune recovery for age within 24 months post-ART.

Results—Of the 4808 children initiated on ART, 3014 were enrolled at a median age of 5.6 years; 61.2% were immunodeficient. After 12 months, children at least 4 years at baseline had significantly lower CD4⁺ cell gains compared with children less than 2 years, the reference group ($P < 0.001$). However, by 24 months, we observed higher CD4⁺ cell gain in children who initiated ART between 3 and 4 years compared with those less than 2 years ($P < 0.001$). The 24-month CD4⁺ cell gain was also strongest in immunodeficient children at baseline. Among these children, 75% reached immune recovery: 12-month rates were significantly highest in all those aged 2–5 years at ART initiation compared with those less than 2 years. Beyond 12 months on ART, immune recovery was significantly lower in children initiated more than 5 years (adjusted hazard ratio: 0.69, 95% confidence interval: 0.56–0.86).

Conclusion—These results suggest that both the initiation of ART at the earliest age less than 5 years and before any severe immunodeficiency is needed for improving 24-month immune recovery on ART.

Keywords

antiretroviral therapy; CD4⁺ cell; children; HIV; immune reconstitution; west Africa

Introduction

Worldwide, in 2011, more than 3 million children lived with HIV, 90% of whom lived in sub-Saharan Africa [1]. When untreated, HIV-infected children experience increased risks of severe morbidity and mortality, through immunodeficiency [2–5]. Antiretroviral therapy (ART) is the standard treatment of HIV [6]. Since the introduction of ART in resource-limited settings in 2004, we have observed significant reductions in mortality and morbidity rates, as CD4⁺ cell counts increase in ART-treated children [7–9].

Until 2008, the optimal timing for ART initiation was based on clinical and immunological criteria for age groups according to the WHO [3]. In 2008, following the Children with HIV Early antiretroviral therapy (CHER) trial [10], showing that early ART before 12 months of age reduced infant mortality and morbidity by 76 and 75% respectively, compared with deferred ART until reaching the WHO criteria, WHO recommended ART initiation in all children aged less than 12 months, irrespective of their immune status [11]. These recommendations were extended to all HIV-infected children less than 24 months in 2010 [6]. In 2013, WHO guidelines recommended treating all children less than 5 years of age, irrespective of their immune status [12]; the rationale of new guidelines was mainly based on programmatic simplification. However, there is still limited evidence on the optimal timing of ART initiation in children aged more than 2 years.

Pediatric Randomized to Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) trial enrolled children aged 1–12 years, but detected no difference in mortality and morbidity between those who initiated immediate ART and those on deferred ART [13]; the authors concluded that the study was underpowered. Although early ART may improve survival, it can also lead to earlier cumulative toxicity or failure of the ART regimen, with drug resistance, if adherence is poor. Understanding treatment response is especially important in children, given the limited alternative regimen choice available in resource-limited settings.

The current access to ART is delayed in children with a median age of 5 years at ART initiation in lower income countries in 2008–2012 [14]. Younger children are faced with a still-developing immune system that could interfere with response to treatment. The effects of earlier ART initiation in HIV-infected children, including immune recovery for age remain, therefore, to be explored to guide both clinicians and healthcare policy makers and bring evidence to the recent WHO recommendations.

We hypothesize that earlier ART initiation is associated with a better immune response associated with immune recovery, defined as a return to normal CD4⁺ cell counts for age above the WHO thresholds for immunodeficiency. The objective of this study was first to investigate the association between age at ART initiation and the 24-month immune response to ART in a large paediatric cohort in West Africa, IeDEA paediatric West African Cohort (pWADA). Second, we determined rates and predictors of 24-month immune recovery on ART.

Methods

Study population and design

The IeDEA paediatric West African Database to evaluate AIDS is aimed at addressing research questions in the field of HIV/AIDS care using data from multicentric HIV/AIDS adults and children cohorts in West Africa [8,15]. This collaboration, initiated in 2006, currently involves 11 paediatric HIV/AIDS clinics in seven countries: Benin ($n = 1$), Côte d'Ivoire ($n = 5$), Ghana ($n = 1$), Mali ($n = 1$), Senegal ($n = 1$), Togo ($n = 1$), and Burkina Faso ($n = 1$). HIV-infected children are typically seen in these clinics at least 3-monthly

All HIV-infected children (with a confirmed positive PCR test < 18 months or positive serology ≥ 18 months) aged 16 years or less who initiated ART were included irrespective of first-line ART regimens in the prospective pWADA cohort. Treatment initiation was based on international guidelines [6,16]. Clinical staging, anthropometric indicators, and CD4⁺ cell count were monitored at ART initiation (± 3 months), and then every 6 months (± 3 months) during follow-up. The following data were recorded in the database: age, gender, weight and height, WHO clinical staging, date of ART initiation, absolute CD4 cell count and percentage, haemoglobin, cotrimoxazole, initiation, and type of ART regimens.

All children included in the pWADA cohort, with at least two CD4⁺ cell count measurements, including one at ART initiation (baseline) were included in the present study. We describe children and compare baseline characteristics between children included and

those not. For all analyses, we used absolute CD4⁺ cell counts, which have been shown to have greater prognostic value compared with CD4% [17] and also more adequate to measure immune status in children more than 5 years of age. Definitions for severe and moderate immunodeficiency for age at time of CD4⁺ cell measurement were derived from the 2006 WHO definitions for immunodeficiency. Severe immunodeficiency was defined as CD4⁺ cell count less than 1500 cells/ μ l, less than 750 cells/ μ l, less than 350 cells/ μ l, and less than 200 cells/ μ l in children aged less than 1 year, 1–3 years, 3–5 years, and at least 5 years, respectively. Moderate immunodeficiency was defined as CD4⁺ cell count between 1500 and 2000 cells/ μ l in children aged less than 1 year, 750 and 1500 cells/ μ l in children aged 1–3 years, 350 and 750 cells/ μ l in children aged 3–5 years, and 200 and 350 cells/ μ l in children at least 5 years. Immune recovery was defined as the return to normal CD4⁺ cell count for age, above these thresholds. We defined underweight at baseline as weight-for-age z-score (WAZ) less than -2 standard deviations (SD), and stunting as height-for-age z-score (HAZ) less than -2 SD [18].

Loss-to-follow-up (LTFU) was defined as any patient with last clinical contact more than 3 months before the database closing date.

Statistical analysis

The 24-month evolution of CD4⁺ cell count since ART initiation was described according to age and immunodeficiency at baseline. Since 2010, the WHO recommends treating all HIV-infected children aged less than 2 years; we, therefore, selected this group as the reference group for all analyses.

We modelled the CD4⁺ cell change at 6, 12, and 24 months after ART initiation using a repeated-measures linear regression model adjusted for the following baseline variables: age, immunodeficiency, gender, and first-line ART regimen. There was a change in slope intensity at 6 months, which we computed and random effects were used on both slopes (before and after 6 months) to account for within-subject correlation caused by repeated measures.

Fixed effects on CD4⁺ cell change were estimated using Wald tests. Residual homoscedasticity and normality were checked graphically. Results from primary analysis were confirmed by performing a sensitivity analysis excluding patients who died or were LTFU within the 24-month follow-up period.

Kaplan–Meier survival curves were used to compare time to immune recovery for age at 24 months on ART in immunodeficient children at baseline and a Cox proportional hazard regression model allowed identifying associated factors. Immune recovery was defined as reaching a CD4⁺ cell count above WHO threshold for age at time of measurement. Analyses were adjusted for baseline age, gender, ART regimen, and severity of baseline immunodeficiency (moderate vs. severe). The Cox proportional hazards assumption was checked graphically for all variables. We could not confirm this assumption for age at ART initiation and consequently computed the interaction with time: adjusted hazard ratios (aHRs) are expressed for the two main follow-up periods, within the first 12 months on

ART, and then between 12 and 24 months. For other variables, the risks were constant over time.

Results

Cohort characteristics

Overall, 4808 children initiated ART within the pWADA cohort, of whom 3014 (62%) met inclusion criteria. The selection process of the study population is described in Fig. 1. Baseline characteristics by age at ART initiation of included children are described in Table 1. Median age at ART initiation was 5.6 years [interquartile range (IQR): 2.6–9.0]. At baseline, 20.2% of the children had already reached WHO clinical stage 3 and 11.1% WHO clinical stage 4: this was more frequent among children aged less than 3 years at baseline ($P < 0.001$). Anthropometric and clinical data were limited, available in 65.4% of cases. When data were available, both median baseline WAZ and HAZ were below average; 37.8% of the children were known to be underweight and 38% stunted; this proportion was significantly higher in children less than 3 years ($P < 0.001$). Overall, 1846 children (61.2%) initiated ART while already presenting signs of immunodeficiency; 1272 (42.2%) were severely immunodeficient; and the proportion of these children was highest in children aged less than 3 years old ($P < 0.001$). We had cotrimoxazole data only for 46.5% of children, among whom 72.4% were following cotrimoxazole prophylaxis. There was no significant difference in the age distribution of these children ($P=0.39$). Most patients (77.1%) initiated a nonnucleoside reverse transcriptase inhibitor (NNRTI) ART-based regimen, mostly children aged more than 2 years ($P < 0.001$). The most common ART combinations for these children were zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV) (35%) and AZT + 3TC + nevirapine (30%). The remaining children initiated protease inhibitor-based ART (25%), including AZT+3TC+nelfinavir (NFV), stavudine+3TC+ NFV. Most protease inhibitor-based regimens included NFV before withdrawing this drug in 2007; 24% of the protease inhibitor group was on lopinavir/ritonavir (LPV/r).

We compared these characteristics to those of the 1794 excluded children (Supplemental Content 1, <http://links.lww.com/QAD/A508>). Excluded children were significantly younger ($P < 0.001$), (24% <2-year-olds vs. 17%) and sicker (31% had reached WHO Stage 4 vs. 18%, $P < 0.001$). We also noted higher rates of loss-to-programme in excluded children: 10% died and 40% were LTFU compared with those included (1.6% died and 9.1% were LTFU by 24 months). There was no significant difference in the loss-to-programme rate (death or LTFU) based on age groups at ART initiation ($P = 0.18$).

Twenty-four-month immune response on antiretroviral therapy

The median number of CD4⁺ cell count measurements during the 24-month follow-up period was 5 (IQR: 3–8). The median baseline CD4⁺ cell count was 431 cells/ μ l (197–762) and reached 735 cells/ μ l (455–1135) and 784 cells/ μ l (494–1159) after 12 and 24 months on ART, respectively. Figure 2a illustrates the observed mean CD4⁺ cell count evolution since ART initiation according to the different age groups at ART initiation. We observe on this graph that the younger the age at ART initiation, the stronger the CD4⁺ cell gain. In all age groups, there was a significant increase of CD4⁺ cell counts over the 24-month period.

CD4⁺ cell gain by 6 months post-ART was strongest, particularly in the younger children at baseline, aged less than 3 years. CD4⁺ cell counts then continue to increase, at a slower pace, and in a nonsignificant manner among children less than 5 years; the observed CD4⁺ cell change in children aged at least 5 years was much lower. When observing mean CD4⁺ cell gain by immunodeficiency status at baseline, we observed a stronger increase in CD4⁺ cell counts in those who presented moderate or severe immunodeficiency at baseline, particularly in the first 6 months of ART. However, these children do not seem to reach normal CD4⁺ cell counts for age by 24 months (Fig. 2b).

Table 2 presents adjusted estimates of mean CD4⁺ cell gain at specific time points. The reference group was boys aged less than 2 years at baseline, who initiated an NNRTI-based ART regimen, without baseline immunodeficiency for age. In this group, CD4⁺ cell count increased at 6 months and then declined slightly at 12 and 24 months, but remained significantly higher than baseline (+152 cells, 95% confidence interval, CI: +89 to +216). In adjusted multivariate analyses, age at ART initiation remained significantly associated with CD4⁺ cell gain at 6 and 12 months, but this tended to fade by 24 months. After 6 months on ART, compared to children aged less than 2 years, the mean CD4⁺ cell gain was significantly lower in all children at least 2 years ($P < 0.001$). After 12 months on ART, the mean CD4⁺ cell gain was significantly lower in children aged at least 4 years at baseline compared with those aged less than 2 years. After 24 months on ART, and compared with children aged less than 2 years at ART initiation, the mean CD4⁺ cell gain was not significantly different within age groups, except for those initiated ART aged 3–4 years compared with those aged less than 2 years (+88 cells/ μ l, 95% CI: +2 to +173).

Furthermore, after 24 months on ART, the mean CD4⁺ cell gain was the highest in children with signs of moderate and severe immunodeficiency for age compared with those with no signs ($P < 0.001$). When studying other covariates, the mean CD4⁺ cell gain was consistent and significantly lower over the first 24 months of ART in children initiating a protease inhibitor-based regimen compared with those on NNRTIs ($P < 0.001$). In addition, it was significantly higher in girls compared with boys ($P < 0.001$).

Twenty-four-month immune recovery for age for children immunodeficient at antiretroviral therapy initiation

Of the 1846 (61.2%) children who were either severely or moderately immunodeficient at ART initiation, 1393 (75.4%) experienced immune recovery for age by 24 months on ART. The observed overall median time to immune recovery for age was 9.4 months (IQR: 6.1–15.8). The overall 12-month and 24-month cumulative probabilities for immune recovery were 53.7% (95% CI: 51.3–56.1) and 84.7% (95% CI: 82.7–86.6), respectively. The 24-month cumulative probability for immune recovery on ART was more than 85% in all children aged less than 5 years at baseline, whereas for older children, immune recovery was significantly lower reaching only 79.3% (95% CI: 76.1–82.3), ($P_{\text{logrank}} < 0.001$) (Supplemental Content 2, <http://links.lww.com/QAD/A509>).

When examining predictors of the rate of immune recovery over the 24 months on ART and adjusted for the degree of immunodeficiency (moderate or severe), ART regimen, and gender, the association with age at ART initiation differed significantly over time (Table 3).

Indeed, we identify two main periods in the immune recovery: before and after 12 months (Supplemental Content 2, <http://links.lww.com/QAD/A509>). Table 3 describes associations between baseline covariates and immune recovery on ART by 24 months on ART. Within the first 12 months of ART, children aged 2–5 years at baseline were more likely to achieve immune recovery for age compared with those who initiated ART aged less than 2 years with aHRs reaching 1.51 (95% CI: 1.18–1.93) in children aged 4–5 years (Table 3). During this first period, there was no significant difference between children aged less than 2 years and those aged at least 5 years. However, between 12 and 24 months post-ART initiation, we observed a change in trends as children aged at least 5 years who had not yet experienced immune recovery were significantly less likely to reach immune recovery for age compared with children aged less than 2 years at ART initiation (aHR: 0.69, 95% CI: 0.56–0.86). There were no differences among other age groups.

For the other covariables, the risks of immune recovery for age were constant over the first 24 months on ART. Children who were severely immunodeficient at baseline were less likely to achieve immune recovery for age compared with those who were moderately immunodeficient (aHR: 0.47, 95% CI: 0.42–0.53). ART regimen and gender were not predictors of immune recovery for age in this analysis.

Discussion

This collaboration of prospective cohorts of HIV-infected children provides for the first time an estimate of the 24-month immune response in West African ART programmes. We first observed a high prevalence of severe immunodeficiency at ART initiation. Second, we found a significant association between age at ART initiation and immune response; in the first 12 months on ART, children aged less than 4 years at ART initiation had a significant and substantially higher gain of mean CD4⁺ cell count compared with those at least 4 years, a trend which then faded over time. Third, among immunodeficient children at ART initiation, children aged at least 5 years who had not yet experienced immune recovery in the first 12 months of ART were significantly less likely to do so afterwards, compared with children initiating ART before 2 years of age.

Our study presents several limitations that need to be discussed. First, as children initiate ART at a late age, the youngest and most vulnerable children have died before any chance of inclusion in our cohort [19], leading to a left-truncation bias leaving a population of survivors. The few children aged less than 2 years included in this cohort are those who accessed care following symptomatic conditions and are probably the sickest. Thus, the effect of early age at ART initiation could have been underestimated compared with a more representative live-birth cohort, as CD4⁺ cell gain and immune recovery in children less than 2 years was compared with that of older and stronger children, who have already survived many HIV-related diseases. Second, we faced missing CD4⁺ cell data, the main study outcome, leading to a selection bias: a large proportion of children (37%) were excluded because of this, mostly LTFU children soon after ART initiation. As these children were younger and sicker than those included, we hypothesize that they probably died also contributing to minimizing the association between young age at ART initiation and immune response. Third, the rate of LTFU reached 9% at 24 months, but is comparable to

other cohort studies in Africa [7–9]. Fourth, there were many missing data, such as weight and height, cotrimoxazole prophylaxis for which we could not adjust our estimates. Other studies have accounted for this information bias using methods such as longitudinal multiple imputations [20,21]. Multiple imputation may be a solution; however, we feel that this may not be effective in our study, in which percentage of missing data is high and reasons for missing are unclear. These issues are a methodological drawback encountered in many cohort studies that need to be addressed. Interventions such as provider-based electronic medical records could help improve data completeness as well as retention in care [22,23]. Fifth, the methodology of our study is subject to discussion. Indeed, long-term evolution of CD4⁺ cell count has been described as asymptotic in European children on ART [24]. We feel, however, that in a 24-month time frame, a linear mixed model fits our data. Last, we assumed that all children follow the same immune response pattern, whereas a previous study has identified qualitatively different CD4⁺ cell recovery patterns on ART [25]. In the context of a large and heterogeneous cohort, analysing the overall immune response to ART accounting for different recovery patterns, including those excluded for missing CD4⁺ data will be an important complementary analysis to account for this informative selection bias.

Nevertheless, this study is one of the first to describe immune response to ART in West African HIV-infected children. Our results confirm the association between age at ART initiation and the 24-month immune response to ART, as reported by other studies in both high-income and low-income contexts [24–29]. Children experienced substantial improvements in CD4⁺ cell count after ART initiation; CD4⁺ cell gain was highest in the younger children, particularly in the first year on ART. Children aged less than 2 years had significantly higher CD4⁺ cell gains within the first 6 months of ART and by 12 months, children aged more than 4 years had a significantly lower CD4⁺ cell gain compared with children less than 2 years. The immune reconstitution in children is mainly via the production of naive CD4⁺ T cells by the thymus [30]; slower recovery in older children could be linked to an age-related decrease in the thymic activity [30,31]. This could explain the fading of the association with age by 24 months. Thymic activity may be compromised by malnutrition and other AIDS-related infections; considering that 38% of children were growth-impaired at ART initiation, this may have played a key role in the immune response to ART. Further investigations on the combined growth and immune response to ART are necessary in order to improve the care of HIV-infected children initiating ART.

We report poor immune status at treatment initiation associated with a stronger CD4⁺ cell gain, comparable to other cohorts [27], but data on time to immune recovery are scarce. In the Pediatric AIDS Clinical Trials Group (PACTG 219/219C), only 36% of children initiating ART with baseline severe immunodeficiency reached normal CD4⁺ cell levels by 5 years [27]. In a cohort of HIV-infected children in Ghana, 76% of children achieved immune recovery at 24 months on ART, similarly to our results [32]. Within the first year, we observed higher chances for immune recovery in children aged 2–5 years. We explain this by the survival bias described in the limitations above; the younger children included in this cohort were most likely the sickest. Children aged at least 5 years showed no difference in the immune recovery in the first year of ART compared with children aged less than 2 years. However, those who did not experience immune recovery within the first year on ART are significantly less likely to recover afterwards, between 12 and 24 months compared

with those children aged less than 2 years. Indeed, older children, at least 5 years, have been infected longer and therefore are subject to more advanced disease, which could have caused permanent changes to the immune system, contributing to poorer long-term status.

In summary, we show that the initiation of ART at both an early age and before any immunodeficiency is a necessity for a recovery of normal CD4⁺ cell counts for age, sustainable beyond 12 months of ART. These results have public health policy implications that are in line with the 2013 WHO guidelines that recommended ART initiation in all children aged less than 5 years, irrespective of clinical or immunological disease severity [12]. Our results on immune recovery on ART in these surviving children show that treating all children less than 5 years is associated with a significantly higher immune recovery. However, the short-term CD4⁺ cell gain within 6 months was the best in those who initiated ART before the age of 2 years. Finally, a late initiation more than 5 years does not allow reaching immune recovery. Thus, healthcare programmes in West Africa must continue to concentrate on identifying HIV-exposed infants born to HIV-infected mothers to offer them the earliest appropriate HIV diagnosis and care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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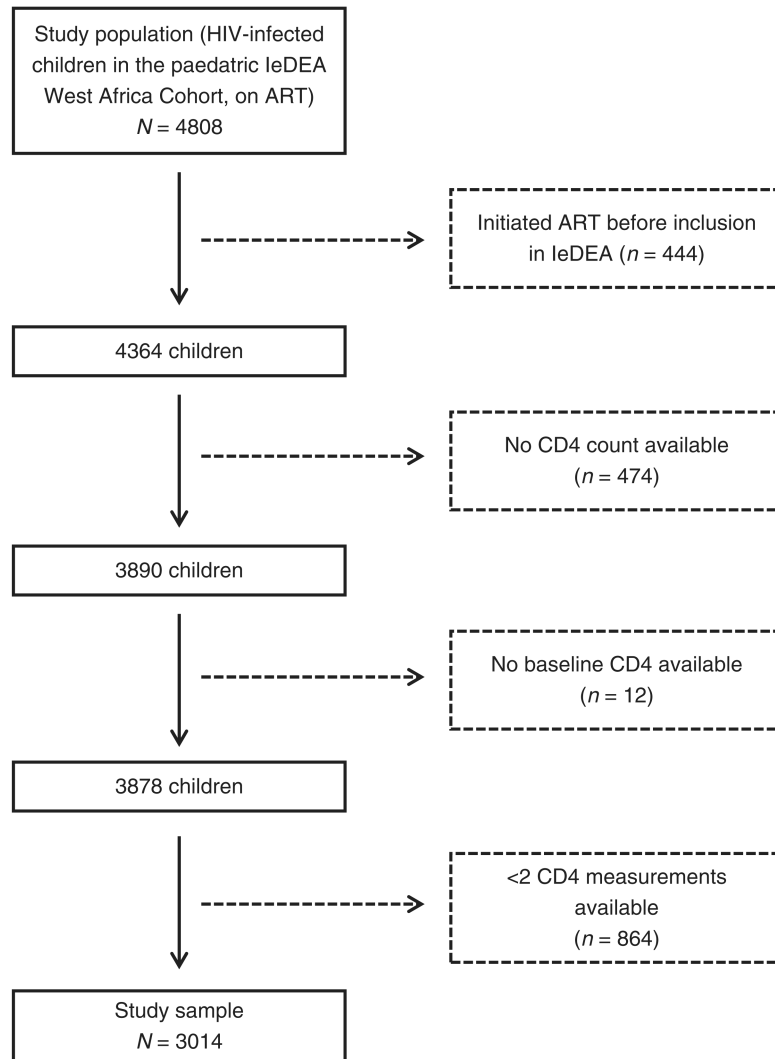


Fig. 1. Flow diagram of the selection of the study sample
Paediatric IeDEA West Africa Cohort.

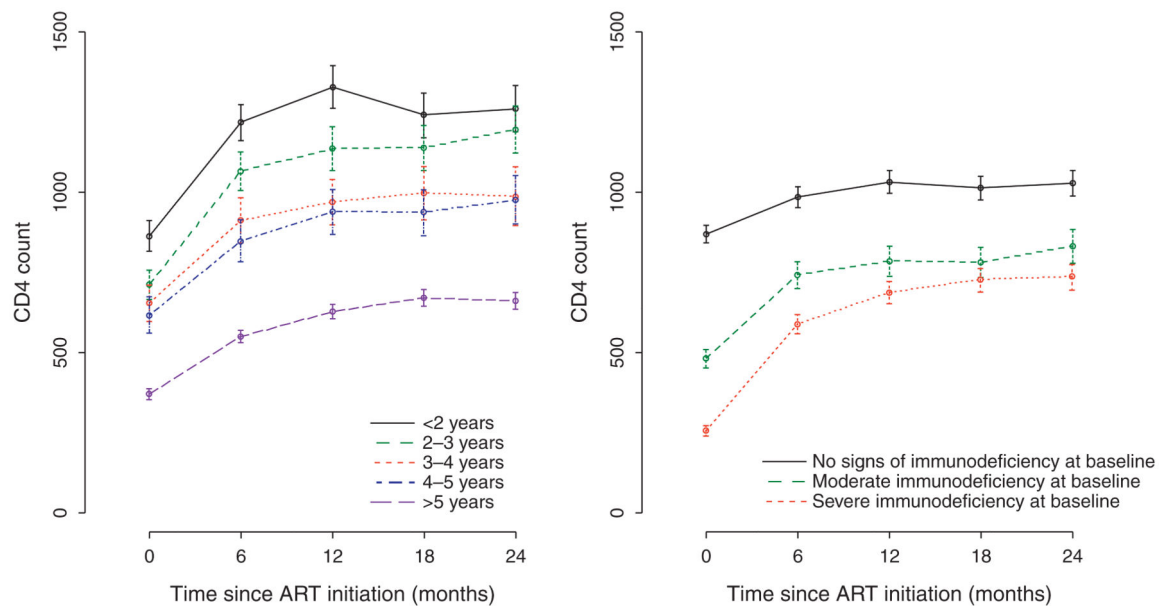


Fig. 2. Mean plot of the observed CD4⁺ cell counts (cells/μl) according to age and immunodeficiency at antiretroviral therapy initiation

Mean plot of the observed CD4⁺ cell counts (cells/μl) at 6, 12, 18, and 24 months postantiretroviral therapy (ART) by age at ART initiation (a) and immunodeficiency status at ART initiation (b) in the 3014 HIV-infected initiating ART in the IeDEA paediatric West Africa Collaboration.

Table 1
Baseline and follow-up characteristics of the 3014 HIV-infected children initiating antiretroviral therapy in the IeDEA paediatric West Africa Cohort (overall and by age group).

	<2 years N = 509	2-3 years N = 350	3-4 years N = 244	4-5 years N = 255	5 years N = 1651
Baseline characteristics (at ART initiation)					
Male sex, n (%)	293(57.6)	185(52.9)	147(60.3)	138(54.1)	843(50.9)
WHO clinical stage 3	128(25.1)	77(22.0)	51(20.9)	44(17.3)	311(18.38)
WHO clinical stage 4	91(17.9)	46(13.1)	14(5.7)	16(6.3)	169(10.2)
WHO stage missing	25 (6.9)	22 (9.4)	12 (7.5)	14 (9.3)	49 (5.4)
Year of ART initiation					
<2006	109 (21.4)	111 (31.7)	84 (34.4)	97 (38.1)	560 (33.8)
2006-2008	143 (28.1)	112 (32.0)	58 (23.8)	51 (20.0)	363 (21.9)
2008-2010	136 (26.7)	62 (17.7)	57 (23.4)	59 (23.1)	390 (23.6)
2010-2012	121 (23.7)	65 (18.6)	45 (18.5)	48 (18.8)	343 (20.7)
CD4 ⁺ cell count at ART initiation	762 (460-1189)	652 (396-951)	573 (331-877)	528 (290-835)	290 (100-523)
Severely immunodeficient	329 (64.6)	204 (58.3)	107 (43.9)	116 (45.5)	963 (58.2)
Moderately immunodeficient	109 (21.4)	68 (19.4)	54 (22.1)	58 (22.8)	256 (15.5)
Weight for age z-score	3.05 (-4.30; -1.47)	2.42 (-3.74; -1.31)	-2.14 (-3.18; -1.11)	1.86 (-3.04; -0.99)	2.38 (-3.61; -1.45)
Underweight (WAZ ^a < -2)	274 (53.8)	173 (49.4)	102 (41.8)	90 (35.3)	499 (30.1)
Missing data	102 (20.4)	62 (17.7)	92 (20.5)	57 (22.3)	811 (49.0)
Height for age z-score	2.48 (-3.76; -1.25)	2.73 (-3.79; -1.79)	-2.50 (-3.56; -1.22)	2.24 (-3.05; -0.97)	2.13 (-3.11; -1.14)
Stunted (HAZ ^b < -2)	202 (39.7)	168 (48.0)	99 (40.6)	93 (36.5)	584 (35.3)
Missing data	172 (33.8)	111 (31.7)	77 (31.6)	91 (35.7)	591 (35.7)
Haemoglobin (g/dl)	9.1 (8.0; 10.2)	9.4 (8.2; 10.2)	9.6 (8.7; 10.6)	10.0 (9.2; 10.9)	10.1 (9.0; 11.0)
Severe anaemia	112 (22.0)	54 (15.4)	27 (11.1)	23 (9.0)	158 (9.6)
Follow-up characteristics within 24 months					
Child deaths	9 (1.8)	3 (0.9)	3 (1.2)	2 (0.8)	30 (1.8)
Children lost to follow-up	46 (9.0)	45 (12.9)	20 (8.2)	17 (6.7)	147 (8.9)
Cotrimoxazole prophylaxis	154 (30.3)	115 (33.1)	73 (29.9)	75 (29.4)	599 (36.3)
NNRTI-based ART regimen	314 (61.7)	235 (67.1)	189 (77.5)	190 (74.5)	1397 (84.4)

Categorical data are presented as frequencies (%), and continuous data as median [interquartile range, (IQR)].

^aWAZ: Weight-for-age z-score based on the WHO reference population (AnthroPlus).

^bHAZ: Height-for-age z-score based on the WHO reference population (AnthroPlus).

^cNNRTI, nonnucleoside reverse transcriptase inhibitor.

Estimated mean CD4⁺ cell change (cells/ μ l) relatively to baseline level after 6, 12, and 24 months on antiretroviral therapy according to baseline variables in the 3014 HIV-infected children in the IeDEA paediatric West Africa Cohort (adjusted linear mixed model).

Table 2

Characteristics at baseline	Months			0–24 months		
	Estimate ^a	95% CI ^b	P value	Estimate ^a	95% CI ^b	P value
Reference group ^c	+298	[+249; +347]		+152	[+89; +216]	
Age at ART initiation (years)			<0.001			<0.001
2 vs. <2	-59	[-117; -1]		+43	[-33; +119]	
3 vs. <2	-58	[-124; -8]		+88	[+2; +173]	
4 vs. <2	-120	[-185; -55]		+29	[-54; +113]	
5 vs. <2	-199	[-243; -155]		-48	[-105; +10]	
Immunodeficiency for age			<0.001			<0.001
Moderate vs. no signs	+137	[+94; +179]		+205	[+150; +259]	
Severe vs. no signs	+213	[+178; +247]		+337	[+293; +382]	
Gender			0,130			<0.001
Female vs. male	+23	[-7; +54]		+69	[+30; +107]	
ART regimen			0,005			<0.001
Protease inhibitor vs. NNRTI-based ART ^d	-60	[-98; -23]		-61	[-109; -14]	

^aEstimated mean CD4⁺ cell gain at 6, 12, and 24 months since ART initiation.

^b95% confidence interval.

^cReference group: children aged less than 2 years presenting no sign of immunodeficiency for age, of male sex, and initiating NNRTI-based antiretroviral therapy.

^dNNRTI: Nucleoside reverse transcriptase inhibitor.

Table 3

Predictors of time to immune recovery for age in the 1846 immunodeficient children initiating antiretroviral therapy in the IeDEA paediatric West Africa Cohort (adjusted Cox proportional hazard model).

Baseline characteristics at ART initiation	aHR ^a	95% CI ^b	P value
Age			
Within 12 months post-ART			< 0.001
<2 years	1	–	
2–3 years	1.39	[1.16; 1.66]	
3–4 years	1.29	[1.00; 1.67]	
4–5 years	1.51	[1.18; 1.93]	
5 years	0.91	[0.80; 1.10]	
12–24 months post-ART			<0.001
< 2 years	1	–	
2–3 years	1.30	[1.00; 1.54]	
3–4 years	1.12	[0.87; 1.45]	
4–5 years	1.30	[0.94; 1.60]	
5 years	0.69	[0.56; 0.86]	
Immunodeficiency for age			<0.001
Severe vs. moderate	0.47	[0.42; 0.53]	
Sex			0.460
Female vs. male	1.04	[0.94; 1.56]	
ART regimen			0.745
Protease inhibitor vs. NNRTI-based ART ^c	1.02	[0.90; 1.16]	

^a Adjusted hazard ratio.

^b 95% confidence interval.

^c NNRTI, nonnucleoside reverse transcriptase inhibitor.