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Immunologic Outcomes of Antiretroviral Therapy among HIV-Infected Nigerian Children and its Association with Early Infant Feeding and Nutritional Status at Treatment Initiation

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Abstract

Objectives: To evaluate immunologic response to ART among HIV-infected Nigerian children (<36 months old) and to assess its association with early infant feeding pattern and nutritional status at treatment initiation

Design: Mixed prospective and retrospective cohort study

Methods: 150 HIV-infected children were followed for 12 months from initiation of ART. CD4 count/CD4% was assessed at baseline and every 4–6 months. Nutritional status was assessed by height-for-age (HAZ), weight-for-age (WAZ) and weight-for-height (WHZ) z-scores using the 2006 WHO growth reference. Children were classified into 4 feeding groups - exclusively breast fed, predominantly breastfed, mixed fed and exclusively formula fed. Logistic regression was used to model odds of failure to reach CD4% of ≥25% at the 12 month follow-up. Linear random effects models were used to model the longitudinal change in CD4%.

Results: There was a significant increase in CD4% for all children from 13.8% at baseline to 28.5% after 12 months (ΔCD4%=14.7%, 95% CI: 12.1%−17.4%). There was no association of feeding pattern with immunologic outcomes. In adjusted analyses, children who were underweight (WAZ<−2.0) or with CD4% <15% at baseline were 4.30 (95% CI: 1.16, 15.87; p<0.05) times and 3.41 (95% CI: 1.10, 10.52; p<0.05) times, respectively, more likely not to attain CD4% of ≥25% at 12 months.

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Conclusion: Baseline nutritional status and CD4% were independently associated with failure to reach CD4% ≥25% at 12-months among HIV-infected Nigerian children on ART. These results emphasize the importance of early screening and initiation of ART among children in resource-poor settings before malnutrition and severe immuno-suppression sets in.

Keywords

Immunologic outcomes; antiretroviral therapy; HIV-infected children; early infant feeding; nutritional status

In the absence of antiretroviral treatment (ART), there is a progressive decline in CD4 cells of HIV-infected individuals [1], and the immunodeficiency that results leads to increased morbidity from susceptibility to opportunistic infections [2]. In adults and older children, the CD4 cell count (and CD4 percentage in children < 5 years) is used to assess disease progression, the timing of treatment initiation, and for monitoring response to ART [3, 4]. The goal of ART is to slow down or stop disease progression by suppressing HIV replication and reversing immunodeficiency [5], thus immune reconstitution is an important outcome of successful treatment programs.

The vast majority (over 90%) of the world's HIV-infected children live in resource-poor Sub-Saharan Africa [6], where access to pediatric HIV treatment is relatively new [7]. Despite severe immune suppression and advanced disease stage at treatment initiation common in these resource-poor settings [8], immunologic responses to ART that have been reported among African children are encouraging [9–17] and comparable to those obtained among children in developed countries [1, 5, 18–21]. Most of the children in previous African studies started ART treatment malnourished [11, 13–16], but there is little information on the impact of nutritional status at treatment initiation on immunologic treatment outcomes. Furthermore, an important determinant of nutritional status among children in resource-poor settings is feeding practice during the first six months of life, a factor which has been a dilemma for HIV-positive mothers with respect to prevention of mother-to-child transmission of HIV [22]. The challenge has been how to balance the benefits of breastfeeding with the risk of transmitting HIV through their milk to the infant [22]. The recently revised WHO HIV and infant feeding guidelines [23] recommend exclusive breastfeeding for the first 6 months of life and continued breastfeeding for the first 12 months of life for infants who are HIV uninfected or of unknown HIV status born to mothers known to be HIV-infected. For already infected infants, exclusive breastfeeding for the first six months of life and continued breastfeeding up to two years or beyond is strongly encouraged [23]. With ART now being provided earlier to these infected children [24], the impact of early feeding practice on immunologic treatment outcomes remains to be known.

In the present study, we sought to evaluate the immunologic response to ART over 12 months among HIV-infected Nigerian children under 36 months of age, and assess the association between early infant feeding practice, nutritional status at treatment initiation and immunologic outcomes.

METHODS

HIV-infected children below 36 months of age on ART were recruited from the pediatric HIV clinic at two hospitals in Nigeria - University of Benin Teaching Hospital, Benin City and University of Abuja Teaching Hospital, Abuja. Both sites are part of the AIDS Care and Treatment in Nigeria (ACTION) Project in Nigeria. The ACTION Project is funded by the United States' President's Emergency Plan for AIDS Relief (PEPFAR) and implemented by the Institute of Human Virology, Nigeria (IHVN), an affiliate of the University of Maryland's Institute of Human Virology, Baltimore, Maryland.

This study was mixed prospective and retrospective cohort in design. The inclusion criteria for enrollment into the study were documented HIV infection, age less than 36 months, and mother/caregiver willing to give informed consent. Enrollment of study subjects was from August 2008 to June 2009. All children attending the pediatric HIV clinic at both sites during this time period who met the inclusion criteria were enrolled in the study. Study subjects were recruited from among those just initiating treatment and were followed-up for 12 months; and from among those already on treatment who were then followed from the point of enrollment up to 12 months post-treatment initiation. For children already on treatment, previously collected data at treatment initiation (baseline) and subsequent clinic visits were abstracted from medical records. Informed consent was obtained from the child's mother or primary caregiver prior to enrollment into the study. Follow-up of study subjects was completed in June 2010.

Before initiation of treatment, children at the pediatric HIV clinic underwent a comprehensive clinical evaluation by a physician and were classified into a disease stage using the WHO staging criteria [3]. Children with advanced disease (stages 3 & 4) were eligible for treatment regardless of age according to the Nigerian national guideline at the time of this study. Age-specific recommendations for initiating treatment based on immunological markers were according to the WHO guidelines [3] in place at the time of data collection. Children <12 months of age with CD4% <25% or CD4 count <1500 cells/mm^3 and children ages 12–35 months with CD4% <20% or CD4 count <750 cells/mm^3 were eligible for treatment. Following initiation of treatment, children were routinely monitored at monthly or bimonthly clinic visits. All children in the treatment program received cotrimoxazole prophylaxis as part of routine HIV care.

Weight and height/length measurements were taken at treatment initiation (baseline) and during monthly/bimonthly clinic visits by trained staff as part of routine clinical examination. Weight measurements were taken using a Salter baby weighing scale (Model 180, Made in England) and recorded to the nearest 0.1 kg. Older children were weighed using a Seca Digital scale (Model 872). Recumbent length was measured in children <24 months in the supine position using an infant length measuring board/infantometer (Seca Model 416). Standing height was measured in children ≥ 24 months old using a Shorr stadiometer (Irwin Shorr, Olney, MD, USA). Measurements were recorded to the nearest 0.1 cm. Standardization of anthropometric measurements was achieved by taking multiple measurements on non-study subjects prior to commencement of data collection and repeated twice during follow-up to ensure quality of measurements taken. The reliability of height

and weight measurements was ≥0.99, the total error of measurement for height ranged from 0.1–0.3 cm, while that for weight ranged from 0 – 0.05 kg.

Infant feeding information of study subjects was collected using an interviewer-administered questionnaire (pre-tested in pilot study). Questionnaire administration was conducted by research assistants and administered once to the mother or primary caregiver on the day of enrollment into the study. The questionnaire was designed to collect detailed information on feeding practices during the first 6 months of the child's life. Three children were less than 6 months of age at enrollment [mean (SD) age: 4.9(0.3) months], for whom the questionnaire was re-administered when they became older than 6 months. Additional information collected during questionnaire administration include maternal age, parity, marital status, and socioeconomic status variables including level of education, type of employment, residence (rural vs. urban), and housing (own vs. rent).

CD4 cell count/CD4 percentage was assessed before initiation of treatment and every 4–6 months thereafter and abstracted from the child's medical records. CD4 measurements were done using a Partec CyFlow® Counter (Partec GmbH, Made in Germany). For children already on treatment at enrollment (n=109), previously collected data at treatment initiation and subsequent clinic visits was abstracted from medical records. This included the child's date of treatment initiation, date of birth, disease stage, CD4 cell count/CD4% and anthropometric measurements at initiation of treatment and at subsequent clinic visits. Data abstraction was done by trained research assistants. Data was manually abstracted from medical records and recorded onto data abstraction forms. The data on the abstraction forms were subsequently entered into an electronic database.

Ethical approvals were obtained from the Ethics and Research Committees of the University of Benin Teaching Hospital and University of Abuja Teaching Hospital, and from the Institutional Review Board of the University of Maryland, Baltimore MD, to which the Institute of Human Virology, Baltimore and Institute of Human Virology, Nigeria are affiliated.

Statistical methods

Height and weight measurements for each child were converted to age- and gender-specific z-scores to obtain height-for-age, weight-for-age and weight-for-height z-scores (HAZ, WAZ & WHZ) using the 2006 WHO Child Growth Standards [25]. Children with HAZ, WAZ and WHZ <−2 at baseline were classified as stunted, underweight and wasted, respectively. Extreme or biologically implausible z-scores at baseline [HAZ <−6 (13/129), WAZ <−6 (6/144) and WHZ <−5 (4/129)] were excluded from the analysis according to the WHO recommendation for data exclusion [25].

Children were grouped into feeding categories based on how they were fed during the first 6 months of life as follows - exclusively breast fed (EBF), predominantly breast fed (PBF), mixed-fed (MF) and exclusively formula fed (EFF). The exclusively breastfed children were those who received breast milk only and no other liquids or solids during the first 6 months of life. The predominantly breastfed children were those whose predominant source of nourishment during the first 6 months was breast milk, but also received non-milk liquids,

e.g., water, juice. The mixed-fed group comprised the mixed breast fed (i.e. given breast milk + infant formula or cows' milk or solids/semi-solids) and mixed formula fed children (i.e. not breastfed but given infant formula + other solids/semi-solids). The exclusively formula fed children received only infant formula during the first 6 months and represents those in line with the WHO replacement feeding recommendation (in avoidance of all breastfeeding) at the time the data for this study was collected [26]. Feeding pattern was coded as an indicator variable with EBF as the reference category.

Baseline characteristics of all children (n=150) were compared between feeding groups using one-way analysis of variance for continuous variables and chi-square tests for categorical variables. There were 2 main outcomes examined – change in CD4 percentage from baseline to 12 months and failure to reach CD4% of 25% or more by 12 months of ART. Only those children with both baseline and 12-month CD4% were included in this analysis (n=88). The mean change in CD4% from baseline to12 months was tested using the paired t-test. Differences in CD4% at baseline and at 12 months between groups were tested by one-way ANOVA. Univariate and multivariable logistic regression was used to model odds of failure to reach CD4% ≥25% at 12-months. Linear random effects modeling which takes into account the correlation between repeated measurements on the same child [27], was used to assess the association between feeding pattern, baseline nutritional status and longitudinal change in CD4% in univariate and multivariable regression analyses. Models were fit with a time interaction for each covariate to assess the rate of change in CD4% from baseline to 6 months, and from 6 months to 12 months. All adjusted analyses included potential confounders including age, gender, disease stage and baseline CD4% and variables that were associated univariately at $p<0.10$ level. Socioeconomic status variables and maternal demographics did not have any significant effect on the outcomes and were excluded from the regression models. Statistical analyses were conducted using STATA Version 11.1 (StataCorp, College Station, TX).

RESULTS

Baseline characteristics

A total of 150 children were enrolled in the study whose baseline characteristics are summarized overall and by feeding pattern categories in Table, Supplemental Digital Content 1, http://links.lww.com/INF/B480. The mean (SD) age at treatment initiation among children was 14.3 (8.3) months, with 44.7% commencing treatment at less than 12 months of age. Children commenced treatment mostly severely immuno-compromised and malnourished. Their mean (SD) CD4 count at baseline was 778 (532) cells/μL, while mean (SD) CD4% at baseline was 13.7 (6.7) %. About 56% of the children had CD4% < 15%, and 66%, 57% and 27% were stunted, underweight and wasted, respectively. More than half (58%) had advanced disease (Stages 3&4) at treatment initiation. Those with advanced disease were 2.7 (95% CI: 1.1, 6.3; $p<0.05$), 4.9 (95% CI: 2.2, 10.7; $p<0.001$) and 6.6 (95% CI: 2.3, 18.9; $p<0.001$) times more likely to be stunted, underweight and wasted respectively, compared to those with mild disease (data not shown). There were no significant differences in baseline characteristics between feeding groups, except in age at treatment initiation (Table, Supplemental Digital Content 1, http://links.lww.com/INF/

B480). In the course of the study, 2 children were transferred to other treatment sites at the request of their mothers, 4 died, and 11 others were lost to follow-up. Thus the attrition rate was 11% (17/150).

Change in CD4 percentage

Mean CD4% increased from 13.8% at baseline to 28.5% at 12 months for all children included in the main analysis (n=88), an increase of 14.7% (p<0.001, Table 2). The mean change in CD4% from baseline to 12 months for EBF, PBF, MF and EFF children was 13.1% (p=0.023), 15.3% (p<0.001), 14.8% (p<0.001) and 14.6% (p=0.004), respectively, but there was no difference between feeding categories (p=0.984). Children who had CD4% <15% at baseline had an increase of 15.8%, while those with CD4% ≥15% at baseline had an increase of 13.3% (p<0.001). Children who were underweight at treatment initiation increased in CD4% from 11.9% at baseline to 24.3% at 12 months (p<0.001). Those who were stunted at baseline increased in CD4% from 13.9% at baseline to 28.2% at 12 months (p<0.001), while those who were wasted at baseline increased in CD4% from 14.1% to 23.5% (p<0.01). The increase in CD4% did not differ between groups. However, there was a significant difference in 12-month CD4% by baseline underweight status (p=0.006) and by baseline CD4% category (p=0.02) (Table 2).

Failure to attain CD4% ≥25% at 12 months

Overall, 37% of the children did not attain CD4% ≥25% in the first 12 months of ART. There was no significant association of feeding pattern with failure to attain CD4% ≥25% at 12 months in both unadjusted and adjusted analysis (Table 3). Those with CD4% <15% at baseline were 3.41 (95% CI: 1.10, 10.52; p<0.05) times more likely not to attain CD4% ≥25% compared to those with CD4% ≥15%, while those who were underweight (WAZ <−2) at baseline were 4.3 (95% CI: 1.16, 15.87; p<0.05) times more likely to experience failure to reach CD4% ≥25% compared to those not underweight, after adjusting for confounders (Table 3).

Factors associated with change in CD4 percentage

The pattern of change in CD4% by feeding pattern and by baseline underweight, stunting and wasting status is shown in Fig. 1. The pattern observed is a rapid increase in CD4% within the first 6 months of ART (overall mean rate of change of 2.02% per month, followed by a slower increase from 6 to 12 months (overall mean rate of change of 0.51% per month. There was no significant association of feeding pattern with change in CD4% from baseline to 6 months, and from 6 to 12 months in both univariate and multivariable analysis (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B481). Being underweight at baseline was associated with a significant 1.12% lower monthly change in CD4% (95% CI: −2.11,−0.14; p<0.05) from baseline to 6 months in the adjusted analysis. Age at treatment initiation and gender were independently associated with change in CD4% from 0–6 months, but not from 6–12 months. Initiating treatment at ≥12 months of age was associated with a 1.30% (95% CI: 0.28, 2.32; p<0.05) greater change in CD4% per month from 0–6 months, after adjusting for confounders (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B481). Compared to male children, females had a 1.56% lower change in CD4% per month (95% CI: −2.52,−0.61; p<0.01) from 0–6 months.

Socioeconomic status variables and maternal demographics did not have any significant effect on change in CD4% and were excluded from the analysis.

DISCUSSION

This study describes the immunological response to ART among HIV-infected Nigerian children, and our results confirm the positive impact of ART on immune reconstitution among children in a resource-constrained setting. Significant improvements in CD4% were observed for all children and occurred in all subgroups of feeding pattern, age at treatment initiation, gender, baseline disease stage, CD4% and nutritional status. The overall increase in CD4% among all children in our study and stratified by baseline immunological status are comparable to those reported in pooled analyses of results from other pediatric cohorts in similar resource-constrained settings [28, 29].

We observed that children with severe immuno-suppression (CD4% <15%) at baseline had more than 3 times the odds of failure to attain CD4% ≥25% at 12-months compared to those not severely immuno-suppressed, and only half of these children attained CD4% values above 25% after 12 months of ART. These results emphasize the importance of early initiation of ART prior to severe immuno-suppression [24]. A longer duration of follow-up may be required to determine whether children who commenced treatment with low CD4% are able to normalize their CD4 values, since children have an active thymus [18, 30, 31] and compared to adults have a greater recovery of naïve CD4+ T cells which promotes immune reconstitution when HIV replication is suppressed [32]. However, there is evidence to suggest that even from a long-term perspective, only about one-third of children with the most severe immuno-suppression at baseline will reach normal CD4 percentages, i.e. above 25% [33]. Thus, early initiation of ART is of utmost importance in achieving immune recovery.

The nutritional status of HIV-infected children has been shown to be associated with HIV disease progression [34]. Generally as disease progresses, nutritional status becomes impaired due to increased nutrient requirements, insufficient dietary intake, malabsorption and diarrhea, altered metabolism and impaired nutrient storage [35, 36]. While the beneficial impact of ART on nutritional status and growth of children is well documented [37–39], there is little information on the impact of nutritional status prior to treatment commencement on immunologic response to ART. One South African study reported significant improvements in CD4% among children who commenced treatment moderately and severely underweight, not significantly different from that of their better nourished peers after 24 months of treatment [40]. In our study, we observed a significant increase in CD4% for all children from baseline to 12 months whether or not they were underweight, wasted or stunted at baseline. However, while we found no association of baseline stunting and wasting status with 12-month immunologic outcomes, those who were underweight at baseline had a significantly lower CD4% at 12 months and ~4 times the odds of failure to attain CD4% ≥25% at 12-months compared to those not underweight and independent of CD% at baseline. Although it is possible that the observed association between baseline underweight status and CD4 response at 12 months may be due to under-dosing effect since physicians are trained on weight-based dosing for antiretrovirals,

this effect may be greater in the early months following treatment initiation and diminish over time. It is also known that pathophysiological changes in the gut associated with malnutrition can alter pharmacokinetic processes but the exact mechanisms involved are unclear and deserves further study since a large proportion of children initiating treatment in resource-limited settings are underweight (57% in our study), and is likely to be an important risk factor for CD4 response. Thus our finding underscores the need to increase case finding of undernourished children in general and especially among pediatric ART patients. Furthermore, HIV testing and treatment should be integrated into programs treating both moderate and severe malnutrition. Nutrition counseling, including anthropometric and dietary assessment should be integrated into all HIV programs.

In addition to severe immuno-suppression, low WAZ or WHZ has been shown to be associated with poor survival among treated HIV-infected children [41–44]. Another study among untreated HIV-infected children showed rapid declines in CD4 counts after an episode of severe malnutrition [45]. Nutritional status is an important determinant of immune function. Malnutrition is usually a complex syndrome of multiple nutrient deficiencies, and a number of micronutrient deficiencies including vitamin A, B6, iron, copper, selenium and zinc have been shown to impair immune response in malnourished individuals [46]. Micronutrient deficiencies are common in HIV-infected individuals and are associated with a faster rate of disease progression and decline in CD4 counts [47–49]. One randomized placebo-controlled study among 40 HIV-infected adults on HAART reported micronutrient supplementation for 12 weeks significantly increased CD4 cell counts [50]. Possibly macro- and micronutrient supplementation may be beneficial as adjunct to therapy especially among undernourished and immuno-compromised HIV-infected children commencing treatment in resource-poor settings.

We found no association between early feeding pattern and immunologic outcomes suggesting that the significant gain in CD4 was largely driven by ART. It is important to note that the proportion of children exclusively breast or formula fed was small compared to those predominantly breastfed or mixed fed, and thus presents inadequate power to detect differences, if any, in immunologic outcomes between feeding groups. We found that children who initiated treatment when older than 12 months of age had a significantly greater change in CD4% during the first 6 months of treatment compared to those who initiated treatment less than 12 months of age, and that it took the younger children twice as long to achieve the same level of immune reconstitution as the older children, probably due to their more immature immune system [24]. Although the timing of infection for these children could not be ascertained, possibly those who initiated treatment <12 months of age had earlier infection (in utero or intrapartum) and had a faster rate of disease progression compared to the older children and less likely to have survived to one year. An interesting finding was that exclusively breastfed children initiated treatment significantly later compared to predominantly breastfed, mixed breastfed and exclusively formula fed children. This finding suggests that exclusively breastfed children remained healthier longer than those in other feeding groups, underscoring the importance of promoting optimal feeding practices among HIV-positive mothers during their infant’s first 6 months of life.

Our study has a number of limitations. There is the possibility of misclassification of feeding pattern due to recall bias for (mothers of) older children who had a longer time lapse since 6 months of age to enrollment in the study. There is also possible bias from using previously collected data abstracted from medical records in addition to prospective data collection. Furthermore, we did not assess adherence to therapy, an important determinant of treatment response, but difficult to measure in children. Also, given that the treatment regimen for all children in our study included nevirapine, there is the possibility of development of nevirapine-resistant virus and virologic treatment failure as a result of prior exposure to single dose nevirapine as demonstrated in a study among children from several African countries [51]. Nonetheless, the effect of these factors, though not collected, is more likely to be non-differential in relation to nutritional status and feeding pattern. The strength of this study is the younger age of our study population. Most previous studies in similar resource-poor settings have children starting treatment at older ages. Our study thus offers a unique opportunity to evaluate immunologic response to ART among young children in relation to nutritional status and early infant feeding.

In conclusion, this study adds to the growing body of evidence that demonstrates the effectiveness of ART in improving immune status of children in resource-poor settings, despite severe immune suppression and malnutrition at treatment initiation. However, there is an urgent need to scale up and improve linkages between mother-to-child HIV prevention programs, early infant diagnosis and pediatric ART programs so that HIV-infected children are identified early and initiate treatment before severe immune suppression and malnutrition occurs. Stronger integration between HIV care and nutrition care is also needed. Further studies with a longer duration of follow-up are required in similar resource-poor settings to determine the long-term effects of ART and durability of immunologic response in young children followed into adolescence, particularly among those who commence treatment with poor immune and nutritional status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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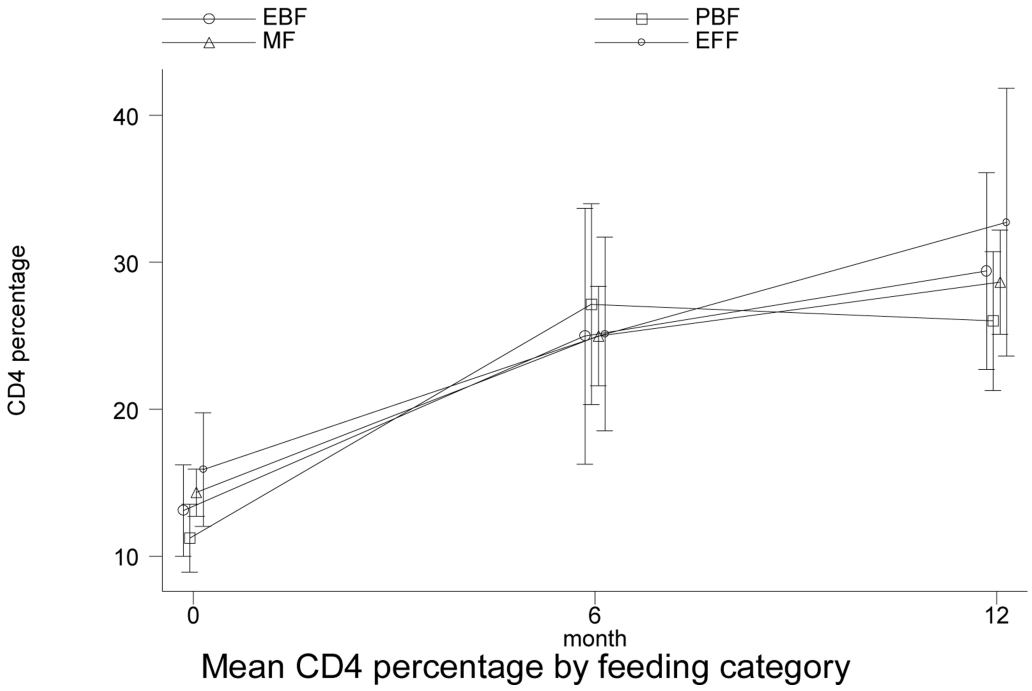
a)



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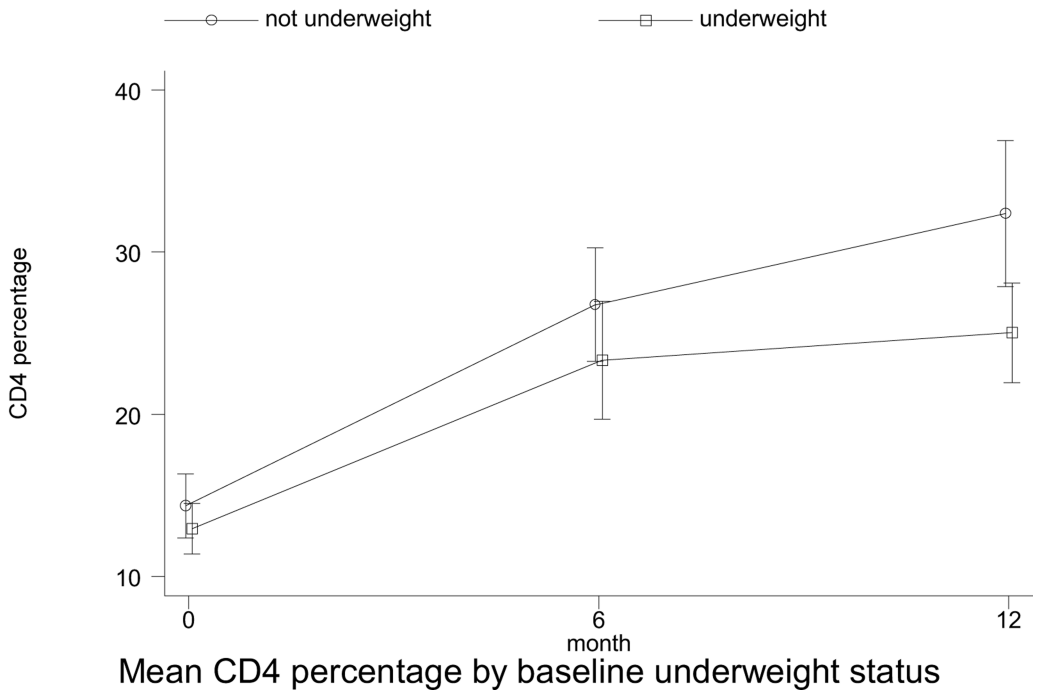
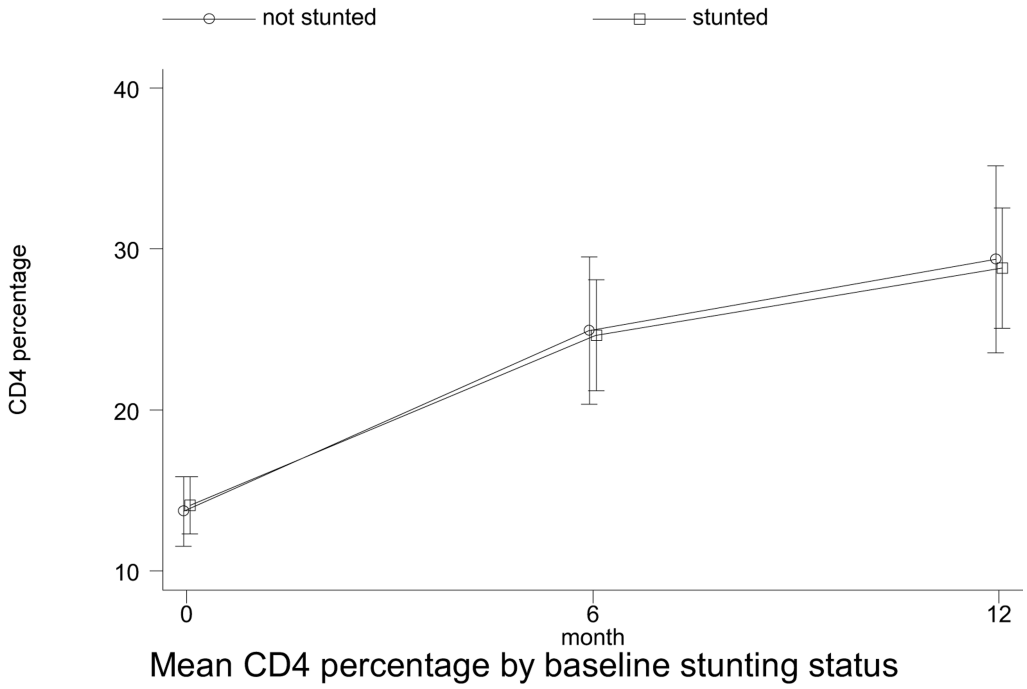


Mean CD4 percentage by baseline underweight status

C)



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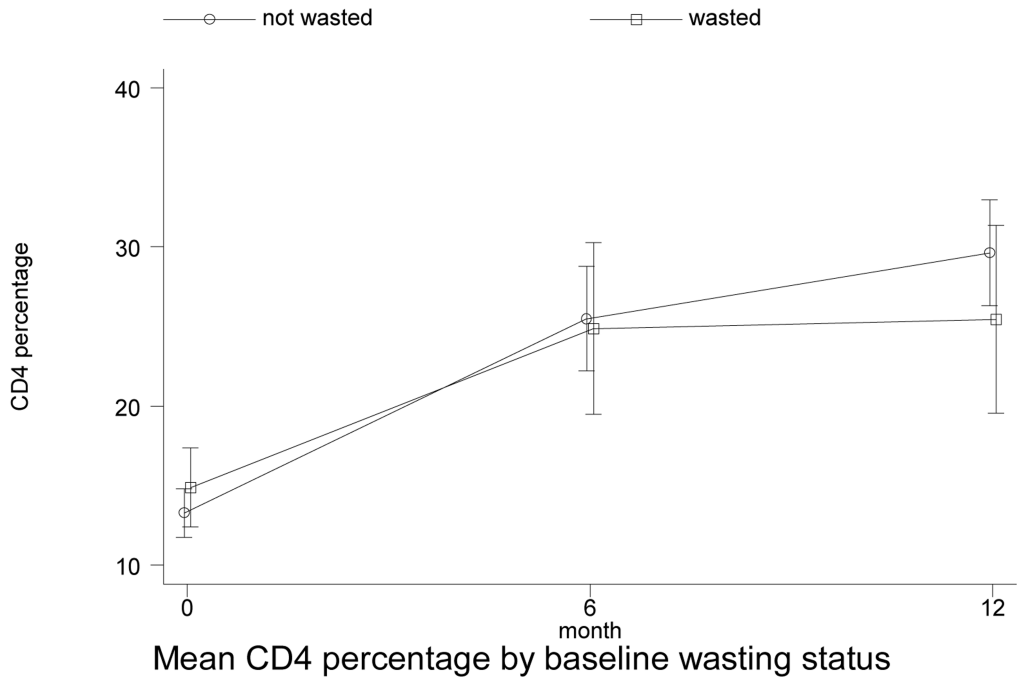

Fig. 1.

Pattern of change in CD4 percentage from baseline to 12 months according to (a) feeding pattern (b) baseline underweight status (c) baseline stunting status (d) baseline wasting status. EBF denoted exclusive breastfed; PBF, predominantly breastfed; MF, mixed-fed; and EFF, exclusively formula fed.

Table 2.

Mean increase in CD4 percentage from baseline to 12 months according to child characteristics

	CD4 percentage							
	Baseline		12 months		ΔCD4%			
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	p[1]	p[2]	p[3]
All children	88	13.8 (12.4, 15.1)	88	28.5 (25.7, 31.3)	14.7 (12.1, 17.4)	<0.001		
Feeding pattern								
EBF	7	15.6 (12.4, 18.8)	7	28.6 (19.5, 37.8)	13.1 (2.6, 23.6)	0.023	0.984	0.624
PBF	19	10.2 (7.7, 12.8)	19	25.5 (20.6, 30.4)	15.3 (10.8, 19.8)	<0.001		
MF	55	14.2 (12.4, 16.0)	55	29.0 (25.0, 33.0)	14.8 (10.9, 18.7)	<0.001		
EFF	7	18.1 (15.0, 21.3)	7	32.7 (23.6, 41.8)	14.6 (6.9, 22.3)	0.004		
Age at treatment initiation								
<12	33	14.9 (12.3, 17.5)	33	28.9 (24.4, 33.4)	14.0 (9.9, 18.1)	<0.001	0.672	0.823
≥12	55	13.1 (11.5, 14.6)	55	28.3 (24.6, 31.9)	15.2 (11.6, 18.8)	<0.001		
Disease stage								
Stages 1&2	34	14.7 (12.2, 17.2)	34	29.4 (23.7, 35.1)	14.6 (9.1, 20.1)	<0.001	0.771	0.725
Stage 3	38	14.1 (12.2, 16.0)	38	26.8 (23.4, 30.3)	12.7 (9.7, 15.7)	<0.001		
Stage 4	6	12.2 (7.4, 17.1)	6	27.7 (14.2, 41.2)	15.5 (1.1, 29.8)	0.039		
Baseline CD4%								
≥15	38	18.9 (17.2, 20.6)	38	32.2 (28.2, 36.2)	13.3 (9.4, 17.2)	<0.001	0.350	0.020
<15	50	9.8 (8.7, 11.0)	50	25.7 (21.9, 29.5)	15.8 (12.1, 19.6)	<0.001		
Baseline underweight status								
WAZ ≥ −2.00	40	15.2 (13.0, 17.5)	40	32.5 (27.8, 37.3)	17.3 (12.5, 22.0)	<0.001	0.092	0.006
WAZ < −2.00	39	11.9 (10.2, 13.6)	39	24.3 (20.8, 27.7)	12.4 (9.1, 15.7)	<0.001		
Baseline stunting status								
HAZ ≥ −2.00	24	14.7 (12.0, 17.4)	24	30.0 (23.8, 36.1)	15.2 (8.6, 21.9)	0.0001	0.788	0.611
HAZ < −2.00	43	13.9 (11.8, 15.9)	43	28.2 (24.1, 32.2)	14.3 (10.6, 18.0)	<0.001		
Baseline wasting status								
WHZ ≥ −2.00	60	13.5 (11.7, 15.2)	60	29.4 (25.8, 33.0)	15.9 (12.5, 19.4)	<0.001	0.106	0.152
WHZ < −2.00	13	14.1 (10.8, 17.3)	13	23.5 (17.4, 29.6)	9.4 (2.9, 16.0)	0.009		

[1] p-value for mean increase in CD4% from baseline to 12 months post-treatment initiation

[2] p-value for difference in ΔCD4% between groups

[3] p-value for difference in 12-month CD4% between groups

Abbreviations: EBF, exclusively breastfed; PBF, predominantly breastfed; MF, mixed-fed; EFF, exclusively formula fed; WAZ, weight-for-age z-scores; HAZ, height-for-age z-scores; and WHZ, weight-for-height z-scores.

Table 3.

Unadjusted and adjusted odds ratio for failure to attain CD4% ≥25% at 12 months

Factor	Odds Ratio	
Child characteristics	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Feeding		
EBF	1.00	1.00
PBF	1.82 (0.28, 11.86)	1.28 (0.14, 11.52)
MF	1.67 (0.30, 9.37)	1.26 (0.18, 8.60)
EFF	0.42 (0.03, 6.06)	1.03 (0.05, 22.99)
Age at treatment initiation		
<12	1.00	1.00
≥12	1.08 (0.44,2.64)	1.07 (0.28, 4.13)
Gender		
Male	1.00	1.00
Female	0.73 (0.30,1.74)	1.40 (0.43, 4.59)
Baseline CD4%		
≥15	1.00	1.00
<15	3.75** (1.44, 9.76)	3.41* (1.10, 10.52)
Disease stage		
Stages 1&2	1.00	1.00
Stage 3	0.94 (0.36,2.45)	0.79 (0.22, 2.82)
Stage 4	1.62 (0.28,9.23)	0.60 (0.07, 5.01)
Baseline underweight status		
WAZ ≥ −2.00	1.00	1.00
WAZ < −2.00	4.46** (1.68, 11.82)	4.30* (1.16, 15.87)

* p<0.05

** p<0.01

Abbreviations: EBF, exclusively breastfed; PBF, predominantly breastfed; MF, mixed-fed; EFF, exclusively formula fed; WAZ, weight-for-age z-scores.