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Effect of HAART on growth parameters and absolute CD4 count among HIV-infected children in a rural community of central Nigeria

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Abstract *Background:* Monitoring response to highly active antiretroviral therapy (HAART) in HIV infected children using both laboratory and physical growth parameter is important. But monitoring laboratory parameters could sometimes be challenging in resource-poor settings as the machines used for these measurements may not always be functional or the required technical expertise be available especially in rural areas. Hence, changes in weight-for-age (WAZ), height-for-age (HAZ) and body mass index-for age (BAZ) Z scores during clinic follow-up visits with or without changes in absolute CD4 count, could be used instead of viral load measurements as indicators of response to HAART in children.

Objectives: To determine the effect in children of treatment with HAART - on changes in physical growth using WAZ, HAZ and BAZ and on changes in CD4 count using absolute CD4 count.

Methods: Data on demographic/ clinical variables, viral load, absolute CD4 count, and weight and height measurements done at enrolment and at follow-up visits for 72 eligible children < 15 years who were consecutively enrolled into HAART were analysed

Results: After nine months of HAART, the median absolute CD4 count increased by 28.2% and median WAZ increased by 28.6%. The reduction in the proportion of children with moderate malnutrition (WAZ ≤ -2) from time of HAART commencement to nine months after HAART, was by 61.5% in those without severe immune suppression (SIS) and by 50% in those with SIS

Conclusion: This study showed that WAZ and absolute CD4 count changes could be useful for monitoring response to HAART in resource –limited settings.

Key words: Growth, Absolute CD4 count, Z score, HAART

Introduction

Human immunodeficiency virus (HIV) infection/ Acquired immunodeficiency syndrome (AIDS) continues to be a major health problem with a 2011 estimate showing that 23.5 million people living with HIV resided in sub-Saharan Africa, representing 69% of the global HIV burden .[1] In 2011 it was estimated that about 3.4 million children were living with HIV/AIDs with 91% of them living in sub-Saharan Africa but only 28% of them were receiving anti-retroviral treatment (ART).[2] A 2010 estimate showed that Nigeria had 440,000 children below the age of 15 years living with HIV/AIDS [3] and of which 280,000 need ART but only 7% were getting it.[4] Monitoring response to highly active anti-retroviral therapy (HAART) in these few children receiving HAART using laboratory (HIV RNA viral load and CD4 percentage / absolute CD4 counts) and clinical parameters of physical growth is important.[5]

Monitoring using viral load and CD4 percentage/ absolute counts could sometimes be challenging in resource poor settings as the machines used for these measurements may not always be functional or the required technical expertise be available especially in rural areas.[6] Also, viral load measurements are usually more expensive and take a longer time to get the results. [7] Measuring physical growth indices such as weight and height, which can be used to determine weight-for-age (WAZ),

height-for-age (HAZ) and body mass index-for age (BAZ) Z scores, would be easier to do in routine clinical settings during clinic follow-up visits for children on HAART than measuring viral load and CD4 percentage/ absolute counts. Changes in Z scores during follow-up visits with or without changes in absolute CD4 count, especially increases in WAZ and HAZ, could be used as indicators of response to HAART.[5] Very low Z scores ($Z \leq -2$) in children are indicative of moderate malnutrition which could be wasting ($WAZ \leq -2$ or $BAZ \leq -2$) or stunting ($HAZ < -2$).[8] Children with HIV who have low Z scores are expected to improve/ increase their scores over time while on HAART as clinical evidence of response to HAART .[9-11] Similarly, children with low absolute CD4 counts including severe immune suppression are also expected to improve/ increase their count as evidence of improved immune response to HAART.[12, 13]

This study therefore aims to determine the effect in children of treatment with HAART: on changes in physical growth (weight, height, and body mass index) using Z scores (weight-for- age, height- for- age and body mass index- for- age z scores) and on CD4 count changes using absolute CD4 count.

Methods

The study site was the Aids Preventive Initiative Nigeria (APIN) satellite site at the General Hospital in Shendam. Shendam town with a population of 16, 731[14] is a rural area by definition.[15] This satellite site offers HIV care/ services to children and adults, predominantly from the surrounding villages. Data on clinical and laboratory parameters collected over a 2 ½ year period from Nov 2009 –June 2012 for eligible children < 15 years who were consecutively enrolled into treatment with HAART were used for the analysis. Eligibility criteria included diagnosis for HIV/ AIDS and fulfilment of the criteria for commencement of HAART in children, based on the Nigeria's National Guidelines for Paediatric HIV and AIDS Treatment and Care.[16] The data included: demographic and clinical variables, viral load, CD4 count and anthropometric measurements done at enrolment into HAART and at six and nine months follow-up visits.

Statistical methods

The independent variables were age, sex, WHO clinical stage, HIV-1 RNA viral load, absolute CD4 count and z scores (WAZ, HAZ and BAZ). The z scores were obtained from the weight and height of the children, adjusted for age and sex, using the WHO AnthroPlus software[17] by importing the variables - weight, height, age and sex in the form of a text file into the software. We then categorised the Z scores into a binary variable using the WHO cut-off of $Z \leq -2$ for moderate malnutrition: wasting ($WAZ \leq -2$) or stunting ($HAZ < -2$) or wasting ($BAZ \leq -2$).[8] The dependent variable was used in two forms – as a continuous variable and as a categorical variable in the analysis. As a categorical variable the immune status of the child was obtained from the absolute CD4 count using the Centers for Disease Control and Prevention (CDC) definition[18], where counts of $<750/mm^3$ for children < 1year, $500/mm^3$ for those one to five years and, $<200/mm^3$ for those > 5 years were considered as severe immune suppression (SIS). As a continuous variable it was the absolute CD4 count. Only children with follow-up visits of at least 9 months and have received at least 9 months of HAART during the study period were included in the analysis. Analysis was done using Stata software version 10 (Stata Corporation, College Station, Texas, USA). The association of each independent variable with both SIS and absolute CD4 count was examined in a univariate analysis using the Chi-squared test for the association between categorical variables and the analysis of variance (ANOVA), respectively. Paired t test was used to examine the difference between the means of two z scores and the Kruskal Wallis test for the difference between the medians of two z scores. Multivariate logistic regression was used to examine the association between Z score categories and SIS. Pvalues of <0.05 were considered statistically significant.

Results

A total of 72 HIV-1 positive children were enrolled into the ARV treatment programme with 49% being males. The median age of the children was 3.8 years (IQR, 1.7-9.0) with only 11% below the age of one year. At enrolment into HAART, majority (89.9%) of the children were in WHO clinical stage 1 and 74% (51/69) did not have SIS but 66% had a HIV-1 RNA viral load of >400 copies /ml. The median viral load at enrolment was higher in those who had SIS (127,691 copies/ml) compared to those who did not (2,616 copies/ml). Majority of the children were stunted ($HAZ \leq -2$) both at commencement (76%) and after 9 months of HAART (82%) but in contrast, only 40% of them still remained moderately malnourished ($WAZ \leq -2$) after nine months of HAART compared to 59% at commencement of HAART and only 2.5% of them were wasted ($BAZ \leq -2$) after nine months of HAART compared to 18.2% at commencement of HAART. Four out of the 72 children died (case fatality rate of 5%) within the 2 ½ years period of study while two were lost to follow-up; with two dying before completing nine months of HAART and these deaths occurred in those with severe immune suppression (Table1).

Table 1: Characteristics of children at enrolment into HAART and at 9 months of commencing HAART according to severe immune suppression status

Characteristics	At enrolment to HAART				At 9 months of HAART†			
	Study subjects	Severe immune Suppression		P*	Study subjects	Severe immune suppression		P*
	Total N (%)	Absent N (%)	Present N (%)		Total N (%)	Absent N (%)	Present N (%)	
Age in years				0.024				0.905
<1	11 (16.0)	10 (19.6)	1 (5.6)		1 (2.3)	1 (2.7)	0(0.0)	
1-5	27 (39.1)	23 (45.1)	4 (22.2)		19 (43.2)	16 (43.2)	3 (42.9)	
> 5	31 (44.9)	18 (35.3)	13 (72.2)		24 (54.5)	20 (54.1)	4 (57.1)	
Median (IQR)	3.8(1.7, 9)	2.8(1.4, 7.0)	10(3.5, 12.1)		4.6 (2.4, 9.8)	5.3(2.7, 9.0)	8.9(3.5, 13.0)	
Mean (SD)	5.5 (4.5)	4.4 (3.9)	8.6 (4.6)		6.3(4.5)	6.1 (3.9)	8.4(5.0)	
Sex				0.943				0.778
Male	34 (49.3)	25 (49.0)	9 (50.0)		21 (47.7)	18 (48.6)	3 (42.9)	
Female	35 (50.7)	26 (51.0)	9 (50.0)		23 (52.3)	19 (51.4)	4 (57.1)	
WAZ				0.620				0.135
>-2	22 (40.7)	19 (42.2)	3 (33.3)		19 (59.4)	18 (64.3)	1 (25.0)	
≤ -2	32 (59.3)	26 (57.8)	6 (66.7)		13 (40.6)	10 (35.7)	3 (75.0)	
Median (IQR)	-2.1(-3.1, -1.0)	-2.0(-2.9, -.1)	-3.7(-4.0,-2.0)		-1.5(-2.5, -0.6)	-1.5(-2.4, -0.5)	-2.4(-3.6, -1.2)	
Mean (SD)	-2.1 (1.5)	-2.0 (1.3)	-3.2 (1.6)		-1.5 (1.6)	-1.4 (1.6)	-2.4 (1.7)	
HAZ				0.379				0.805
>-2	16 (24.2)	13 (27.1)	3 (16.7)		7 (17.5)	6 (18.2)	1 (14.3)	
≤ -2	50 (75.8)	35 (72.9)	15 (83.3)		33 (82.5)	27 (81.8)	6 (85.7)	
Median (IQR)	-3.2(-4.2, -2.3)	-3.3(-4.3,-1.7)	-3.1(-4.2, --2.4)		-3.4(-4.6, -2.5)	-3.9(-4.6, -2.3)	-3.5(-3.6, -2.3)	
Mean (SD)	-3.3 (1.8)	-3.2 (1.7)	-3.5 (2.2)		-3.5 (1.7)	-3.4 (1.8)	-3.7 (2.5)	
BAZ				0.008				0.641
>-2	54 (81.8)	43 (89.6)	11 (61.1)		39 (97.5)	32 (97.0)	7 (100)	
≤ -2	12 (18.2)	5 (10.4)	7 (38.9)		1 (2.5)	1 (3.0)	0 (0.00)	
Median (IQR)	0.1(-1.3, -0.9)	0.1(-0.6, 1.4)	-1.5(-2.4, 0.6)		0.4(-0.2, 2.3)	0.8(-0.2, 1.9)	-0.5(-1.8, 0.5)	
Mean (SD)	-3.1 (2.1)	0.1 (1.8)	-1.5 (2.4)		0.9 (2.0)	1.1 (2.0)	0.3 (1.6)	
WHO clinical stage**				0.015				
Stage 1	62 (89.9.0)	49 (96.0)	13 (72.2)					
Stage 2	4 (5.8)	1.0 (2.0)	3 (16.7)					
Stage 3	3 (4.3)	1 (2.0)	2 (11.1)					
HIV-1 RNA (Copies/ml)				0.588				
<400	16 (34.0)	13 (36.1)	3 (27.3)					
> 400	31 (66.0)	23 (63.9)	8 (72.7)					
Median (IQR)	7768 (200, 113938)	2616200, 209832)	127691 (200, 425876)					
HIV-1 RNA (Log_{10} copies /ml)								
Median (IQR)	8.93 (5.30, 11.64)	7.82 (5.30, 10.90)	11.76 (5.30, 12.96)					
Mean (SD)	8.86 (3.10)	8.36 (2.83)	10.49 (3.45)					
CD4 count (cells / μL)								
Median (IQR)	680 (211, 1296)	902(533, 1463)	95 (35, 155)		872 (403, 1407)	1067 (750, 1461)	153 (77, 385)	
Outcome				0.215				0.186
Survived	62 (93.9)	48 (96)	14 (87.5)		41 (95.4)	35 (97.2)	6 (85.7)	
Died	4 (6.1)	2 (4)	2 (12.5)		2 (4.6)	1 (7.8)	1 (14.3)	

Note: Clinical stage, viral load were not assessed at 9 months of commencing HAART **There was no child with clinical stage 4 disease
*P value for chi squared test or Fisher's exact test for the association between categorical variables and severe immune suppression

The median WAZ and BAZ and the median absolute CD4 counts all increased after starting HAART, through six months to nine months of commencing HAART but the HAZ did not (Table 2).

Table 2: A comparison of the median Z scores and absolute CD counts at enrolment, at 6 months and at 9 months of HAART

Parameter (n)	At enrolment Median (IQR)	At 6 months Median (IQR)	At 9 months Median (IQR)	P value*
WAZ (n=144)	-2.1 (-3.1, -1.0)	-2.1 (-2.7, -1.0)	-1.5 (-2.5, -0.1)	0.088
HAZ (n=169)	-3.2 (-4.2, -2.3)	-3.5 (-4.6, -2.4)	-3.4 (-4.6, -2.5)	0.819
BAZ (n=169)	0.1 (-1.3, 0.9)	0.5 (-1.4, 1.8)	0.4 (-0.2, 2.3)	0.006
CD4 count (n=128)	680 (211, 1296)	725 (262, 1140)	872 (403, 1407)	0.414

*P values for Kruskal Wallis tests for the difference between medians

Thus, the median absolute CD4 count increased by 28.2% from 680/mm^3 (IQR: 211, 1296) at HAART commencement to 872/mm^3 (IQR: 403, 1407) after nine months of HAART. Also, the median WAZ increased by 28.6% from -2.1 (IQR: -3.1, -1.0) at HAART commencement to -1.5 (IQR: -2.5, -0.6) after 9 months of HAART which was significant, p= 0.04 while the median BAZ increased by 300% from 0.1 (IQR: -1.3, 0.9) to 0.4 (IQR: -0.2, 2.3), p=0.001; but there was no significant change (p=0.60) in the median HAZ which decreased by 6% from -3.2 (IQR: -4.2, -2.3) to -3.4 (IQR: -4.6, -2.5) within the same period (Table 3).

Table 3: A comparison of the median Z scores and absolute CD4 counts at enrolment and at 9 months of HAART

Parameter (n)	At enrolment Median (IQR)	At 9 months Median (IQR)	P value*
WAZ (n=103)	-2.1 (-3.1, -1.0)	-1.5 (-2.5, -0.6)	0.043
HAZ (n=123)	-3.2 (-4.2, -2.3	-3.4 (-4.6, -2.5)	0.603
BAZ (n=123)	0.1 (-1.3, 0.9)	0.4 (-0.2, 2.3)	0.001
CD4 count (n=113)	680 (211, 1296)	872 (403, 1407)	0.386

*P values for Kruskal Wallis tests for the difference between medians

A similar pattern was also observed with the mean - WAZ, BAZ and HAZ and log absolute CD4 count; the mean log absolute CD4 count increased by 13.8% from 845 (SD 743) at start of HAART to 962 (SD 618) after nine months of HAART and the increase was significant, p = 0.007 (Table4).

Table 4: A comparison of the mean Z scores and absolute log CD4 counts at enrolment and at 9 months of HAART

Parameter (n)	At enrolment Mean (SD)	At 9 months Mean (SD)	P value*
WAZ (n=47)	-2.1 (1.5)	-1.5 (1.6)	0.012
HAZ (n=53)	-3.3 (1.8)	-3.5 (1.7)	0.283
BAZ (n=53)	-0.3 (2.1)	0.9 (2.0)	0.001
Log CD4 count (n=43)	845 (743)	962 (618)	0.007

*****P values for paired t test for the difference between two means

The median WAZ and BAZ scores were generally higher in those without SIS compared to lower scores in those with SIS whether at commencement of HAART or after 9 months of HAART but there was no such difference observed in the median HAZ scores. Among children without SIS the number with moderate malnutrition (WAZ $\leq$ -2) reduced from 26 before HAART commencement to 10 after 9 months of HAART, a 61.5% reduction; while among those with SIS the number reduced from 6 at HAART commencement to three after nine months of HAART, a 50% reduction (Table 1).

In the association of SIS with moderate malnutrition (WAZ $\leq$ -2), the odds of not having SIS in children who were not malnourished (WAZ > -2) is 1.5 times more at start of HAART compared to those who were malnourished (WAZ $\leq$ -2) (p = 0.622) and this odds increased to 5.8 after 9 months of receiving HAART (p = 0.679); but after adjusting for the confounding effects of age and HAZ in a multivariable logistic regression analysis, these odds became 1.4 (p = 0.167) and 8.7 (p = 0.182) respectively, (Table 5).

Table 5: Associations of WAZ and HAZ groups with severe immune suppression status at enrolment and at 9 months of HAART

Parameter	N	Crude OR (95% CI)	P value	N	Adjusted OR (95% CI)*	P value
At commencement						
WAZ of HAART (>-2 vs $\leq$ -2)	54	1.5 (0.3-6.5)	0.622	51	1.4 (0.3-6.9)	0.679
HAZ (> -2 vs $\leq$ -2)	66	1.8 (0.5-7.5)	0.384	51	1.3 (0.2-8.2)	0.772
After 9 Months						
WAZ of HAART (>-2 vs $\leq$ -2)	32	5.4 (0.5-59)	0.167	32	8.7 (0.4-207)	0.182
HAZ (>-2 vs $\leq$ -2)	40	1.3 (0.1-13.2)	0.806	32	0.5 (0.02-11.8)	0.665

*Adjusted for age, WAZ and HAZ

Discussion

Overall, the 72 HIV-1 positive children enrolled into HAART had an improvement/ increase in their growth parameters and absolute CD4 counts after 9 months on HAART -the median absolute CD4 count increased by 28.2%, median WAZ increased by 28.6% and median BAZ increased by 300% but with no significant change in the median HAZ. The median WAZ and BAZ were generally higher in those without SIS than in those with SIS but there was no such difference observed in the median HAZ. The reduction in the proportion of children with moderate malnutrition (WAZ $\leq$ -2) from time of HAART commencement to 9 months after HAART, was 61.5% in those without SIS and 50% in those with SIS.

Our finding of an increase of 28.2%, in absolute CD4 count after 9 months of ART is comparable to similar findings in several studies where absolute CD4 count/ CD4 % was noted to increase from after at least 6 months of ART. [9, 12, 13] This is the expected immunological response to ART. For instance in the study by Bolton -Moore et al,[12] the mean CD4 % increased from 12.9% at enrolment into HAART to 23.7% after 6 months of HAART (an increase of 83.7%) among 2,398 children receiving HAART. These studies also agreed with our finding of increase in growth showing as increase in WAZ following ART but contrasts with our observation of no change in HAZ. The lack of a significant change in the median HAZ in our study could be attributed to two factors. Firstly, at the start of HAART, more of the children (76%) were stunted (HAZ $\leq$ -2) compared to fewer (59%) who were wasted (WAZ $\leq$ -2) and increase in height usually lags behind increase in weight over time. Thus, since the follow up time used in our study was only 9 months we may not see a significant increase in height compared to weight. Another possible explanation for the lack of change in HAZ is that our sample size was smaller (72) compared to the larger sizes used in the analyses in the above studies, particularly the one

by Bolton-Moore et al,[12] where the sample size was 2,398. The observed decrease in the proportion of children with moderate malnutrition after 9 months of HAART in our study, is the expected improvement in nutritional status in response to HAART seen in other studies. [5, 9-13] A potent and efficient HAART regimen is usually expected to reverse a poor nutritional status in children with HIV infection.[5]

Despite using absolute CD4 count in our study as against the more commonly used CD4 % in children in most studies[9, 11-13], our result of an overall progressive increase in absolute CD4 with ART after months of ART was similar to the increase in CD4 % seen in these studies. The use of absolute CD4 count as in our study could prove useful in certain situations in rural areas of resource- poor settings were the machines used for these measurements may not always be able to do CD4 % due to the lack of technical expertise[6] or because the machines use cheaper and simpler technologies that are able to do only absolute CD4 count.[19] However, one study supports our use of absolute CD4 count – this study by Boyd K et al which analysed a very large data collected from several multi-centre longitudinal trials and cohort studies showed that absolute CD4 count was more useful than CD % in deciding when to start ART in HIV-1 infected children.[20]

One of the limitations of our study is the small sample size which would explain why we did not find any significant difference between the median HAZ at start of treatment and after 9 months of HAART as seen in most studies.[9, 11, 12] Again the small sample size could explain the lack of statistical significance we noticed in our study in the association of WAZ or HAZ with severe immune suppression despite the very large odds ratios (Table 5). The lack of significance in the association between WAZ and severe immune suppression could be attributed to some unknown confounders in our study which we could not measure, as there was a reduction in the odds ratios following the multivariate analysis.

Conclusion

The growth parameters in children - WAZ and BAZ increased significantly after 9 months of receiving HAART and so was the absolute CD4 count but no change was observed for HAZ. Also, HAART lead to a reduction in the proportion of children with moderate malnutrition (WAZ $\leq$ -2) both in those without SIS and those with SIS. Thus, the WAZ and absolute CD4 count could be useful for monitoring response to ART in resource –limited settings.

Authors contributions

Ebonyi AO: Conception, design, data analysis and manuscript writing
Oguche S and Sagay AS: Revising the manuscript for intellectual content
Dablets E and Sumi B: Patient care and Data collection
Yakubu E: Data management
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