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Predictors of Sub-Optimal CD4 Recovery during the First Six Months of Anti-Retroviral Treatment (ART) in HIV Infected Children: A Retrospective Cross Sectional Study from Tikur Anbessa Tertiary Hospital, Addis Ababa, Ethiopia

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Abstract

Background: Highly active anti-retroviral therapy (HAART) has brought significant change in reducing morbidity and mortality among children living with HIV/AIDS. Decisions concerning initiation and/or shifting of antiretroviral therapy (ART) are guided by monitoring the laboratory parameters of plasma HIV RNA (viral load) and CD4+ T cell count in addition to the patient's over all clinical response. The demonstrations of the prognostic value of the CD4 cell count was of major importance in the development of therapeutic strategies. Therefore, the objective of this study was to assess factors predicting suboptimal CD4 cell recovery during first six months of ART.

Methods: The study is retrospective cross sectional study to assess factors predicting suboptimal CD4 cell recovery. Medical records of patients' were retrieved and important variables are captured to standard questionnaire tool. T-test is used to assess changes in CD4 cell count after initiation of ART. Binary logistic and multiple regressions were used to assess factors predicting CD4 cell recovery.

Results: Data of 360 children were analyzed. CD4 cell count at the start of HAART ranged from 3-2003 cell/mL with an interquartile range of 231-317 cell/mL. After 6 months of HAART, the CD4 cell count has increased ranging from 71-2300 cell/mL with inter quartile range of 458-612 cell/mL and mean CD4 cell count difference of 230, 95%CI (199.414-260.613); P<0.001. Advanced clinical stage of the disease, severe degree of immunosupression, presence of anemia, presence of chronic diarrhea at base line, poor weight gain during first six months of HAART adversely affect the trends of CD4 recovery.

Conclusion: Our study demonstrated that advanced clinical stage of the disease, severe degree of immunosupression, presence of anemia at baseline and presence of chronic diarrhea, poor weight gain during first six months of HAART were factors adversely affect the trends of CD4 recovery.

Keywords: HIV/AIDS; HAART/ART; Suboptimal CD4 recovery; Predictors; CD4 cell count recovery

Abbreviations: AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral Treatment; ARV: Antiretroviral Drug; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immune-Virus; MTCT: Mother to Child Transmission; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; NRTI: Nucleoside Reverse Transcriptase Inhibitors; PMTCT: Prevention of Mother to Child Transmission; SD: Standard Deviation; TB: Tuberculosis; WHO: World Health Organization

Introduction

More than 2 million children are living with HIV/AIDS worldwide and more than 90% of them are living in sub-Saharan Africa [1]. More than 90% of children acquire the infection through mother to child HIV transmission (MTCT). Despite this, only 10% of HIV-infected pregnant ladies are offered any form of prevention of mother to child HIV transmission (PMTCT) in sub-Saharan countries [1,2]. Ethiopia has an estimated population of close 100 million people, of whom 44% are under 15years of age [2]. Currently 367,000 patients including 23,400 children under the age of 15 are taking ART. Based on the 2014 estimate, the 2014 ART need is 542, 121 for adults and 178,500 for children under 15 years of age. On the basis of the 2010-2014 strategic plan, ART coverage for adults has reached 76% but the coverage remains low (23.5%) for children. If HAART is not started promptly, a third of children infected prenatally will not survive to their first birthday, and more than half will succumb to death by their second birthday [3-5]. Highly active anti-retroviral therapy (HAART) has brought significant change in reducing morbidity and mortality among children living with HIV/AIDS. Decisions concerning initiation and/or shifting of antiretroviral therapy (ART) are guided by monitoring the laboratory parameters of plasma HIV RNA (viral load) and CD4+ T cell count in addition to the patient's overall clinical status. Monitoring clinical and diagnostic progression of patients on anti-retroviral treatment (ART) is important to examine responses to the treatment and for clinical decision-making. The demonstrations of the prognostic value of the CD4 cell count was of major importance in the development of therapeutic strategies. Children's immune response to ART differs based on age at ART initiation and degree

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of viral levels. As shown in recent adult studies, there are likely other baseline factors contributing to differential immunological responses. Baseline clinical and demographic factors have been used to predict mortality in HIV-infected children on ART [2]. However, few baseline clinical characteristics other than age, CD4% and viral response have been examined as potential predictors of weight and immune response in HIV-infected children. Children in the lower percentile of weight, CD4 cell count, and CD4 cell per cent gain at 6 months of HAART were likely to have unsatisfactory immune response [6-13]. Studies are, however, scarce in assessing these potential clinical parameters such as the presence of baseline underweight, chronic diarrhea, tuberculosis, opportunistic infections or anemia as predictors of early immunologic response. Clinicians could possibly use these factors as an early alarming sign to identify children at higher risk of poor immune response to ART and target them for more intense monitoring and closer follow-up. Patients with insufficient CD4 cell recovery at six months of ART should undergo extensive clinical and laboratory assessments, as it could indicate poor adherence, which is believed to be the key element for the acquisition of antiretroviral drug resistance and finally lead to treatment failure [10,11]. In resource-limited settings, in which the number of drugs available is limited, maximizing the duration of existing lines of treatment, and identifying and addressing the reasons for poor response worth emphasized [11,12]. In this study, we mainly focused on factors predicting poor CD4 cell recovery during the first six months of ART.

Objective

To assess factors predicting suboptimal CD4 cell recovery during the first six months of ART in HIV infected children.

Methods

A retrospective cross sectional study was conducted by reviewing medical records of children living with HIV who are on ART at Tikur Anbessa Specialized Tertiary Hospital. The hospital is a teaching specialized and national tertiary hospital. Pediatric and child health department is one of the major departments delivering patient caring service, teaching and research activities under different unit categories. Pediatric infectious clinic is one of the functioning units of the department and highly overburden subspecialty clinics mainly delivering pediatric HIV/AIDS care and treatment.

Sample

There were a total of 1145 children living with HIV registered in pediatric HAART clinic at pediatric infectious Clinic at the time of data collection. About 503 patients have already been on HAART and around 405 patients were taking HAART for six months and above. Of factors affecting CD4 cell recovery, baseline under weight is one of the most important clinical variables occurring in about 50% of the cases as shown in most studies [5,6]. So, using single proportion formula, the sample size found to be 384. Only 360 medical records with complete clinical and laboratory parameters were accessed for data extraction.

Definition of suboptimal CD4 cell recovery

Different literatures and guidelines define suboptimal CD4 recovery using different values. However, most guide lines including national guideline define suboptimal CD4 recovery as CD4 increment of less than 20% or 50 cell/mL of baseline [2,3].

Data Extraction and Statistical Analysis

Data were extracted from the patients' medical records and enumerated to data retrieval form, and then were entered to EPI info software for clean-up and pre and post-HAART anthropometric interpretation and directly transferred to SPSS version 17 for further analysis of important variables, significance testing. Paired-t-test was used to compare pre and post-HAART CD4 cell count differences. Using logistic regression, we first determined univariate associations between demographic and clinical variables, which, based upon clinical observations and prior studies. The independent variables included: baseline CD4%/count, baseline hemoglobin, Weight at baseline, at three and six months of and WHO clinical staging, presence of chronic diarrhea, ART regimen. We disaggregate age into two categories (under 5 and 5-14 years old) to control for the age-related difference in CD4 count/proportion. Multivariate logistic regression was used to assess factors possibly contributing for poor CD4 recovery. P value of less than 0.05 considered statistically significant.

Results

Medical records of 360 patients which were eligible for the study were retrieved from medical record office and data extracted. Males constitute 51% (183/360) while females were 49% (177/360). The minimum age at the start of ART was 4 months and the highest being 168 months (Interquartile age range 87-120 months).

Those who started on ART at the age of less than 12 months constitute the least number, 4.1% (15/360) and those who started treatment between 60-120 months were by far the largest 54.6% (197/360). Baseline anthropometric interpretation showed that total patients with wasting were 42.6% with moderate and severe wasting being 20.4% and 1.5%, respectively. Anemia was detected in 16.3% (61/360) of patients at the start of HAART with the majority of the cases having a mild degree of anemia accounting for 81% (49/61) of the cases of anemia (Table 1).

About 206 (57.1%) of patients were started on AZT-based nucleoside reverse transcriptase inhibitors (NRTI) while 132 (36.7%) patients were taking d4T based regimen. There is no difference in degree of CD4 recovery among patient taking the two regimen (p value is 0.134).

With regards to non-nucleoside reverse transcriptase inhibitors

Base line value	Category	Male	Female	Total
Age category	Under 5 years	60	47	107 (29.7%)
	5-14 years	123	130	253 (70.3%)
Weight-for-age	<3rd centile	88	101	189 (52.5%)
	3rd-97th centile	78	58	136 (37.8%)
	Above 97th centile	17	18	35 (9.7%)
Weight–for-height	<3rd centile	85	100	185 (51.4%)
	3rd-97th centile	92	77	169 (46.9%)
	Above 97th centile	6	0	6 (1.7%)
WHO Clinical Staging of AIDS	I	7	2	9 (2.6%)
	II	59	55	114 (31.6%)
	III	88	95	183 (51%)
	IV	28	26	54 (14.8%)
CD4 cell category	>25% or >500	18	10	28 (7.6%)
	15-25% or 200-500	90	101	191 (53.1%)
	<15% or <200	75	66	141 (39.3%)
Base anemia		29	31	60 (16.7%)

Table 1: Demographic and base line values of some variables at initiation of HAART, Tikur Anbessa Tertiary Hospital, Addis Ababa Ethiopia, 2014.

(NNRTIs) as backbone about 72.4% (261/360) were taking NVP containing regimen while 21.4% (77/360) were on EFV-containing regimen. Still there is no difference in degree of CD4 recovery among patient taking the two regimen (p value is 0.34). There were 57/360 (15.8%) cases had documented chronic illness including new development of tuberculosis and chronic diarrhea, which accounts for the majority of cases and others were seizure disorder and chronic otitis media. About 10.7% (39/360) of patients were treated for tuberculosis during first six months of HAART. Majority of patients (53.1%) were having moderate immune suppression (CD4 cell count of 200-500 or CD4 cell per cent 15-25%) at start of HAART while 39.3% of cases were having severe immunosuppressant (CD4 cell count<200 or <15%) and (7.6%) were having mild immune suppression while baseline WHO clinical stage II, III, and IV were 31.6%, 51% and 18.8% respectively (Table 2 and Figure 1). Baseline CD4 cell count ranged from 3-2003 cell/mL with inter quartile range of 231-317 cell/mL and average CD4 cell count of 261 cell/mL. After six months of HAART, about 85% (306/360) of patients were having CD4 cell increment of greater than 20% or 50 cell/mL of baseline value. Mean of CD4 cell count pre and post-HAART was compared; the mean CD4 cell count difference was 230, 95% CI (199.414-260.613), and count ranged from 71-2300 c/mL with inter quartile range of 458-612 c/mL at six month of initiation of HAART, P-value <0.001. The mean weight gain at three and six months of HAART were found to be 1.00 and 1.50 kg with the mean weight difference of 0.772 and 1.80 kg, 95% CI (0.588-0.957) and (1.60-2.0)P<0.001 respectively. Advanced WHO clinical staging and severe immunosuppression at start of HAART were adversely related CD4 recovery with statistically significant value. Similarly, Low baseline weight, presence of, presence of chronic diarrhea and poor weight gain at three and six months of ART found to have significantly detrimental impact on CD4 cell recovery (Table 3).

Profile after HAART	Category	Male	Female	Total
Rate of weight increment at three months of HAART	<5%	101	110	211 (58.7%)
	6-10%	33	39	72 (19.9%)
	>10%	31	46	77 (21.4%)
Rate of weight increment at six months of HAART	<5%	59	64	123 (34.2%)
	5-10%	51	63	114 (31.6%)
	>10%	68	65	123 (34.2)
CD4 cell count or percent at six month of HAART	>25% or >500	70	72	142 (39.4%)
	15-25% or 200-500	97	88	185 (51.3%)
	<15% or <200	16	17	33 (9.3%)

Table 2: Patterns of weight gain and CD4 cell recovery at three and six month of HAART, Tikur Anbessa Tertiary Hospital, Addis Ababa Ethiopia, 2014.

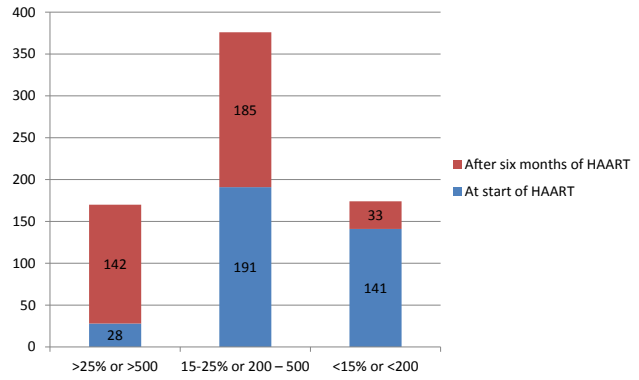

Figure 1: Distribution of CD4 cell category at baseline and after six months of HAART; Tikur Anbessa Tertiary Hospital, Addis Ababa Ethiopia, 2014.

Variables		CD4 cell recovery by <20% or <50 cell/mL of baseline	
		N=360, Adjusted Odds Ratio (95% CI)	P-value
Base line weight	<3rd centile	0.31 (0.15-0.92)	0.018
	3rd-97th	1	
WHO clinical Staging	II	1.72 (0.61-4.55)	0.014
	II I &IV	4.76 (1.71-10.00)	0.006
	I	1	
Base line CD4 count category	<15% or <200 cell/mL	4.35 (2.89-11.23)	0.025
	15-25% or 200-500 cell/mL	1.78 (0.47-6.25)	0.015
	>25% or >500	1	
Age category	5-14 years	2.11 (0.81-9.11)	0.017
	<5years	1	
Base line hemoglobin level	<10 g/dL	2.94 (1.02-7.14)	0.014
	>10 g/dL	1	
Rate of weight gain at three month of ART	<10%	2.50 (1.05-5.00)	0.012
	>10	1	
Rate of weight gain at six month of ART	<10%	4.34 (1.15-8.33)	0.002
	>10%	1	
Chronic diarrhea	yes	2.56 (0.6-4.45)	0.007
	No	1	

Table 3: Multivariate logistic regression showing predictors CD4 cell recovery by <25% or <50 cell/mL of baseline among patient at six months of HAART, Tikur Anbessa Tertiary Hospital, Addis Ababa Ethiopia, 2014.

Discussion

In our study, the mean CD4 cell count increment is 230 cell/mL with count range of 71-2300 c/mL and inters quartile range of 458-612 c/mL at six month of ART. The probability of having CD4 cell % or count of (>25% or >500) at six month of ART is 40%. This finding is higher than previous studies results with possible explanation that most previous studies were carried out on adult patients where CD4 lymphocytes physiologically decline with increasing age [1-4]. For instance the study conducted in South Africa which involved about 4000 adult patients showed that the probability of having CD4 count of >200 cell/mL at twelve months of ART is about 51%. The association between older age groups and poor immune recovery demonstrated in our study which is in congruence with other previous pediatric and adult reports [5,11]. This might be justified by too depleted thymus and other lymphoid tissues to repopulate the T lymphocytes after initiation of ART in older age groups. On the other hand, in our study there is no relationship between gender of the patient and risk of adverse immune restoration though other studies were with discordant results; some reported male gender is associated with poor immune recovery others showed no gender difference [14-16]. Presence of chronic diarrhea during ART treatment is associated with poor CD4 cell recovery independent of nutritional status of the patient which is in agreement with most previous studies. The reason is not clearly identified so far but could be because of associated mal-absorption and poor adherence during the illness. Our study also showed that the presence of anemia at baseline (Hgb<10 g/dL) is related with poor immune system regeneration which is in concordant with similar studies from other sites [13,15,17,18]. For example, study from South Africa showed that children living with HIV who started on ART with lower baseline hemoglobin had significant risk of adverse CD4 cell recovery (OR=0.87 for each 1 g/dL decrease in hemoglobin; 95%CI 0.75–0.99) [6,7]. This association is scientifically plausible as there is clear interaction between elemental

iron in immune system. Our research findings of lower baseline CD4 cell value predicts poor six month CD4 cell recovery is supported with other cohort studies. A large cohort involving 861 adult patients living with HIV in Spain showed that patients with baseline CD4 count of 200 and of 201 to 350 cells/mm3 had a significantly lower chance of achieving CD4 count of 500 cells/mm^3 compared with patients with baseline CD4 350 cells/mm^3 and above [14,19].

This study also revealed that weight gain of less 10% at three and six months of HAART were independently predicting poor CD4 recovery which is also in compatible with other research findings. The poor weight gain could indicate poor adherence, an advancing disease stage or underlying opportunistic infection implying that the patient should undergo extensive clinical and laboratory evaluation. Similar study in South Africa and elaborated lower percentiles of weight gain after 6 months of ART were associated with poor subsequent treatment outcomes and higher risk of mortality independent of other baseline characteristics [17,20,21]. Likewise, a low baseline weight was an independent predictor of an adverse outcome in our study, which is in agreement with other observational studies where patients with weight less than 3rd centile had a two-fold increased risk of dying [22]. Our study didn't depict association between ART regimen and risk of poor CD4 restoration which could be explained by almost all (94% of the patients) were taking two NRTI and one NNRTI to see the difference between regimens. However, previous studies were reporting discordant results. Some studies reported that AZT or d4T based regimen were associated with adverse immune reconstitution others showed NRTI regimens were associated with poorer recovery of CD4 count [15].

Conclusion

Our study demonstrated that advanced clinical stage of the disease, severe degree of immunosupression, presence of anemia at baseline and presence of chronic diarrhea, poor weight gain during first six months of HAART were factors adversely affect the trends of early CD4 recovery.

Ethical approval and consent to participate

Ethical clearance was obtained from the department of institutional review board of Addis Ababa University College of Health Science. Letter of permission was given from the department of pediatrics and child health to retrieve medical records. The records of patients were kept at safe place and information collected from the record was kept confidential. Patient with possible poor treatment response were traced back and intervened accordingly.

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As we sponsored the research project ourselves for all parts of research work, there is no conflict of interest from anybody.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

As involved in the preparation of the study design, participated in data collection, data entry and data analysis as well as manuscript preparation.

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