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Pattern and predictors of cluster of differentiation 4 (CD_4) cell count recovery among cohorts of human immunodeficiency virus (HIV)-infected patients on antiretroviral therapy in Hawassa University Referral Hospital

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Cluster of differentiation 4 (CD_4) cell count recovery is used in determining disease progression and outcome monitoring. This study was conducted to determine the trends of CD_4 cell count recovery, and its determinants in Hawassa university referral hospital, Ethiopia. Retrospective cohort study design was employed to gather relevant data among human immunodeficiency virus (HIV) positive-patients visiting Hawassa University referral hospital. Data were collected from December 1, 2014 to May 15, 2015. A total of 2400 medical records of adult patients aged above 15 years were examined. Of these, 1479 were evaluated and analyzed. Multivariate logistic regression was constructed to determine predictors of change in CD cell count. The median change in CD_4 cell count from baseline to six months was 124 cells/µl. 19.3% of patients were at risk of immunologic non-response at 12 months of treatment. Patients with a baseline CD_4 cell count of less than 100 cells/ml were 5 times more likely to exhibit immunologic non-response compared to those with a baseline CD_4 cell count > 350 cells/µl. Baseline body mass index (BMI) and sex were associated with failure to attain ≥200 cells/µl at 12 months of treatment. Rapid recovery of CD_4 cell count occurred during the first six months of treatment in this study. However, significant proportions of patients were at risk of immunologic non-response. Low baseline CD_4 cell counts were predictive of non-response in this setting. The findings suggest that initiation of antiretroviral therapy (ART) at a CD_4 cell count greater than 500 cells/µl is associated with better immune recovery.

Key words: Antiretroviral therapy, CD4 cell count, HIV/AIDS, Ethiopia.

INTRODUCTION

Antiretroviral therapy (ART) began in Ethiopia in 2003, and was made freely available in 2005. An estimated 769,500 Ethiopians are currently living with human immunodeficiency virus (HIV), of whom 542600 require ART and 367 000 are currently taking the treatment (FDRE, 2014).

Recognizing the need for ART, the government of Ethiopia issued the first ART guidelines in 2003. Revisions were issued in 2005, 2008 and 2014 to facilitate a rapid scale-up of the service (FDRE, 2014; FMOE, 2008; MoH, 2005). These guidelines recommended measurement of CD4 cell count every six months as a major tool for monitoring treatment outcome.

In a resource limited setting like Ethiopia, where viral load determination is expensive, CD_4 cell count will remain an important tool for monitoring response (FDRE, 2014). ART is celebrated for its reduction of mortality. The mortality rate was 15.4 per 100 person-years of observation (PYO) in the highly active antiretroviral therapy (HAART) group, and in the pre-HAART group it was 58.1 per 100 PYO in an early study conducted in Ethiopia (Jerene et al., 2006b). However, mortality is higher in Ethiopian cohorts than in patients in developed world (Jerene et al., 2006b; Jerene et al., 2006a; Johansson et al., 2008). Higher mortality is partly attributed to delay in the initiation of treatment, at a time when the disease has progressed to a state of severe immune depletion (Jerene et al., 2006b; Berhe et al., 2012).

Studies examining the association between baseline CD_4 cell count and immune recovery following ART report conflicting results. It has been reported that higher baseline CD_4 count is associated with reduced early mortality (Stephen et al., 2008), and counts of less than 50cells/µl is associated with high mortality in both experienced and naive patients on HARRT (Zachariah et al., 2006; Evan et al., 2003).

Some studies have revealed that a significant percentage of HIV-infected patients who initiate therapy with a low baseline CD_4 cell count do not achieve a normal CD_4 cell count, even after a decade of effective treatment (Lange et al., 2002; García et al., 2004; Lederman et al., 2003; Kaufmann et al., 2002). Other studies indicate patients with low baseline CD_4 cell count achieve better CD_4 cell recovery compared to those with high baseline CD_4 level (Lawn et al., 2006). In another study, researchers report no association between baseline CD_4 cell count or viral load, and immunologic or virologic response after commencement of ART (Kilaru et al., 2006).

The survival rates of human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) patients in Ethiopia can be improved given the factors responsible for death in Ethiopian cohort of patients initiating ART are well explored. One possible explanation for high mortality in Ethiopia is that treatment in Ethiopia begins after sever immunosuppression. There are, however, conflicting results in the literature about advantage of early initiation before sever immune damage. Given that, factors affecting CD_4 cell count recovery after ART is unclear in Ethiopia setting, this paper explores such factors. Furthermore, there are few large-scale studies examining immunological correlates, with long-term follow-up, of Ethiopian patients.

We present the overview of the trends of CD_4 cell count recovery and its determinants in an Ethiopian patient population using routinely available clinical data.

METHODOLOGY

Study area

The study was conducted in Hawassa University Referral Hospital, a major referral hospital serving over 15 million people in a region located 270 kilometers south west of Addis Ababa, Ethiopia. The hospital provides general service including HIV/AIDS comprehensive care and treatment.

Study design

We used a retrospective cohort study design to gather relevant data from the records of HIV positive-patients who visited the hospital between 2005 and 2014.

Study period

Data was collected from December 1, 2014 to May 15, 2015.

Inclusion and exclusion criteria

Patients older than fifteen years old during the initiation of the treatment and initiated treatment at Hawassa University hospital, and whose patient record included the information necessary for the current study were included. Patients with competing causes of death (cause of death other than HIV, those with immune compromising chronic diseases such as diabetes, thyroid disease, or any non-AIDS malignancies) were excluded.

Sample size

A total of 2400 medical records met the age requirement from a total 2,950 medical records. About 550 medical records of pediatric (ages less than 15) were excluded. Data collected from 921 medical records were excluded because they have missing baseline and six month CD_4 cell count. Therefore, 1479 medical records included sufficient information for inclusion in the current study, were evaluated and analyzed. Secondary data were extracted from the ART register database, and unique identities were assigned to these records.

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Data collection tool

We used a data collection tool that was previously described, and that was developed using the federal ministry of health HIV care/ART entry and follow-up forms used in the ART clinic of the Hospital (Naftalin et al., 2015; Mutimura et al., 2015; Luz et al., 2014; Kanters et al., 2014; Calmy et al., 2012; Boulassel et al., 2012; Wright et al., 2011; Waters et al., 2011; Okulicz et al., 2010; McKinnon et al., 2010; Lok et al., 2010). Data sources included the pre-ART registration, lab requests, monthly cohort and follow up forms, the ART intake form, the patients' card, and the death certificate. We additionally examined the home visitors' registration, and records of phone calls made by drug adherence professionals, or that revealed death of a patient following inquiries about missed appointment. Where baseline CD4 levels were not measured we relied on tests performed within one month before ART was initiated.

Study variables

The data extraction form includes the following variables: socio-demographic characteristics (age, sex, height, religion, marital status, educational status), baseline laboratory values (CD4 cell count)**,** world health organization (WHO) clinical staging**,** duration on ART**,** and **r**egimen type)

Data quality assurance

Data was collected by counselor nurses trained in comprehensive ART, working in an ART clinic. Data quality was assured with the help of the data collection tool through routine cross-checking of data on a daily basis. Data collection forms were examined for completeness and consistency during data management, storage, and analysis by investigators. A pilot study was conducted in order to test consistency of the tool, and to ensure data quality. The tool was revised using feedback from the pilot study. Data encoded and edited by the principal investigator was checked by co-investigators.

Operational definitions

Change in CD_4 cell count

A general term used to quantify immunologic recovery. In this paper it is measured as: baseline-to-six-month median change in CD4 cell count, the median six-month-to-12-month change, immunologic non-response, and failure to attain 200 cells/µl

Baseline-to-six-month median change in CD4 cell count

The difference between the median of six months measurement and baseline measurement was recoreded.

The median six-month-to-12-month change

The difference between the median of 12th month measurement and 6th month measurement was recorded

Immunologic non-response

An increase of <50 cells/µl, following 12 months of treatment and was calculated using data from records that included a CD^4 cell count at baseline, and at 12 months of treatment (n=1140).

Failure to attain ≥200 cells/µl following 12 months of treatment

This response measure used to quantify non-response in subsample of those who had baseline CD_4 cell count of < 200 cells/µl was calculated using data from records that included a CD4 cell count at baseline, and at 12 months of treatment (n=681)

Baseline CD_4 cell count

The CD4 cell count was measured just during the initiation of treatment in treatment of naïve-patients.

Ethical statement

Ethical clearance was obtained from Hawassa University Medicine and Health Science College Institutional Review Board. Written consent could not be obtained for this retrospective study so the investigators were authorized by the institutional review board (IRB) to use the data after de-identification prior to collection.

Statistical analysis

Data were entered and analyzed using statistical package for social sciences (SPSS) for Windows, version 20. Patient cohort characteristics were described in terms of mean/median value for continuous data and percentage for categorical data. Multivariate logistic regression was constructed to determine predictors of change in CD cell count, factors determining non-response, and failure to attain a CD_4 count of 200 cells/µlfollowing12 months of treatment. All statistical tests were considered significant if the two-sided P-value was<0.05.

RESULTS

Socio-demographic profile of the study participants

Routinely collected data from a total of 1479 medical records of HIV-infected patients on HAART were reviewed and analyzed. At baseline, 90% of the cohort where under the age of 45 years with a mean (SE) age of 33.3(0.23). 62.4% were female, 54.4% were married and 9.5% were pregnant. 37.1% had attained secondary-level education and 14.4% were illiterate. Complete socio-demographic profiles of the study population are listed in Table 1.

Clinical profiles of the patients

More than one-third of the patients (38.7%) initiated treatment with a TDF+3TC+EFV regimen. At baseline, more than half of the study participants (53.7%) were in clinical stage III. 694 (46.9%) patients had a normal BMI at baseline and 258 (17.4%) were underweight. Clinical

Table 1. Socio-demographic characteristics of the HIV positive-patients (n=1479).

Variable	Female	Overall Frequency	Valid frequency
Sex	Female	923 (62.4)	62.3
	Male	556 (37.6)	37.7
Age	‹25	166 (11.2)	11.3
	25-45	1169 (79.0)	79.9
	≥45	128 (8.7)	8.7
	Missing	16 (1.1)	
Education status	Illiterate	210 (14.2)	14.4
	Primary	504 (34.1)	34.7
	Secondary	549 (37.1)	37.8
	Tertiary	191 (12.9)	13.1
	Missing data	25 (1.7)	
Marital status	Never married	212 (14.3)	14.5
	Married	805 (54.4)	54.9
	Separated	140 (9.5)	9.5
	Divorced	115 (7.8)	7.8
	Widowed	194 (13.1)	13.2
	Missing data	13 (0.9)	
Pregnancy status at initiation	Pregnant	140 (9.5)	9.9
	Non-pregnant	722 (48.8)	50.8
	Not applicable (male)	558 (37.7)	39.3
	Missing	59 (4.0)	-

profiles of the full patient population are listed in Table 2.

Pattern of CD_4 change

Of the total 1479 patient records, 1460 (98.71%) included measures of CD4 cell count at baseline. The median and mean CD_4 cell count at baseline was 161 and 172 cells/µl, respectively. At six months of treatment measures reached 285 and 311 cells/µl, respectively. The baseline-to-six-month median change in CD_4 cell count was 124, and the median six-month-to-12-month change was 24 cells/µl. The mean increase in CD4 cell count from baseline to six months was 138, and from six months to 12 months was 20 cells/µl. We observed that most CD_4 cell recovery occurs during the first six months (Figure1). Pattern of six monthly changes in CD_4 cell count at and after the commencement of ART are shown in Figure 1. The overall median CD_4 cell count increased continuously for 6.5 years. The CD_4 cell count declines at 78 months (Figure 2).

About 19.3% of study participants exhibited immunological non-response (Table 3). Association between various variables (sex, age, baseline CD_4 count, WHO stage, BMI and baseline regimen type) and non-response were tested. Baseline CD_4 cell count was significantly associated with immunologic non-response after 12 months of treatment: patients with low CD_4 cell count have greater odds of non-response rate than those with high baseline CD_4 cell count. Those with a baseline CD_4 cell count of less than 100 cells/µl had a greater chance of non-response (crude odds ratio (COR) = 6.27, 95% CI: 2.98- 13.16) compared to those with a CD_4 cell count greater than 351 (Table 3).

Multivariate logistic regression analysis revealed that baseline CD_4 cell count is an independent predictor of subsequent CD_4 cell count recovery. Patients with baseline CD_4 cell <100 cells/µl were five times more likely to exhibit immunologic non-response compared to those with a baseline CD_4 cell count>351 cells/µl (adjusted odds ratio (AOR) = 5.17, 95% CI: 2.17-12.32) (Table 3).

We further examined those that failed to reach a CD_4 cell count of >200 cells/ µl at 12 months of treatment in subsample of those who had baseline CD_4 cell count of < 200 cells/µl. Sex, BMI and baseline regimen type were associated with failure to reach 200 cells/µl at 12 month

Table 2. Baseline clinical characteristic of the HIV positive-patient.

Baseline variable	Female	Overall Frequency	Valid frequency
Regimen type	TDF+3TC+EFV	573 (38.7)	38.7
	TDF+3TC+NVP	103 (7.0)	7.0
	AZT+3TC+EFV	194 (13.1)	13.1
	AZT+3TC+NVP	182 (12.3)	12.3
	D4T+3TC+EFV	195 (13.2)	13.2
	D4T+3TC+NVP	232 (15.7)	15.7
WHO stage	I	172 (11.6)	11.7
	II	317 (21.4)	21.7
	III	788 (53.3)	53.7
	IV	191 (12.9)	12.9
	Missing	11 (0.7)	-
Patient status during initiation	Ambulatory	365 (24.7)	25.2
	Bedridden	90 (6.1)	6.2
	Working	994 (67.2)	68.6
	Missing	30 (2.0)	-
BMI category	Underweight (≤ 17)	258 (17.4)	24.3
	Normal (18-25)	694 (46.9)	65.3
	Overweight (26-30)	94 (6.4)	8.9
	Obese ≥ 31	16 (1.1)	1.5
	Missing	417 (28.2)	-
Baseline CD4 category (cells/µl)	<100	426 (28.8)	29.2
	101-250	726 (49.1)	49.7
	251-350	225 (15.2)	15.4
	>351	83 (5.6)	5.7
	Missing data	19 (1.3)	-
CD4 cell count change at 12 months (%)	<50	220 (14.9)	19.3
	≥50	920 (62.2)	80.7
	Missing	339 (22.9)	-
CD4 cell count at 12 months (for baseline CD count less than 200 cells/µl)	Still <200	53	7.8
	>200	628	92.2

of treatment (Table 3). Association with baseline BMI and sex was revealed through multivariate logistic regression. Those of a normal weight (BMI =18-25) were nearly three times as likely to fail to reach a CD_4 cell count of 200 cells/µl by 12 months of treatment (AOR=2.82, 95% CI: 1.27-6.25), as compared to those with a BMI of ≤17 (underweight). Females were more than three times more likely to fail to attain 200 cells/µl by 12 months of treatment compared to males (AOR= 3.42, 95% CI: 1.53-7.59).

DISCUSSION

The study analysis reveals that CD_4 cell count recovery is a feasible tool for monitoring ART outcome in a resource limited setting like Ethiopia. In this study, CD_4 cell count recovers rapidly during the first six months of treatment, as evidenced by the six monthly median and mean changes. There was little subsequent change in median CD_4 cell count indicating that immune recovery was optimally achieved in the earlier phases of treatment. The

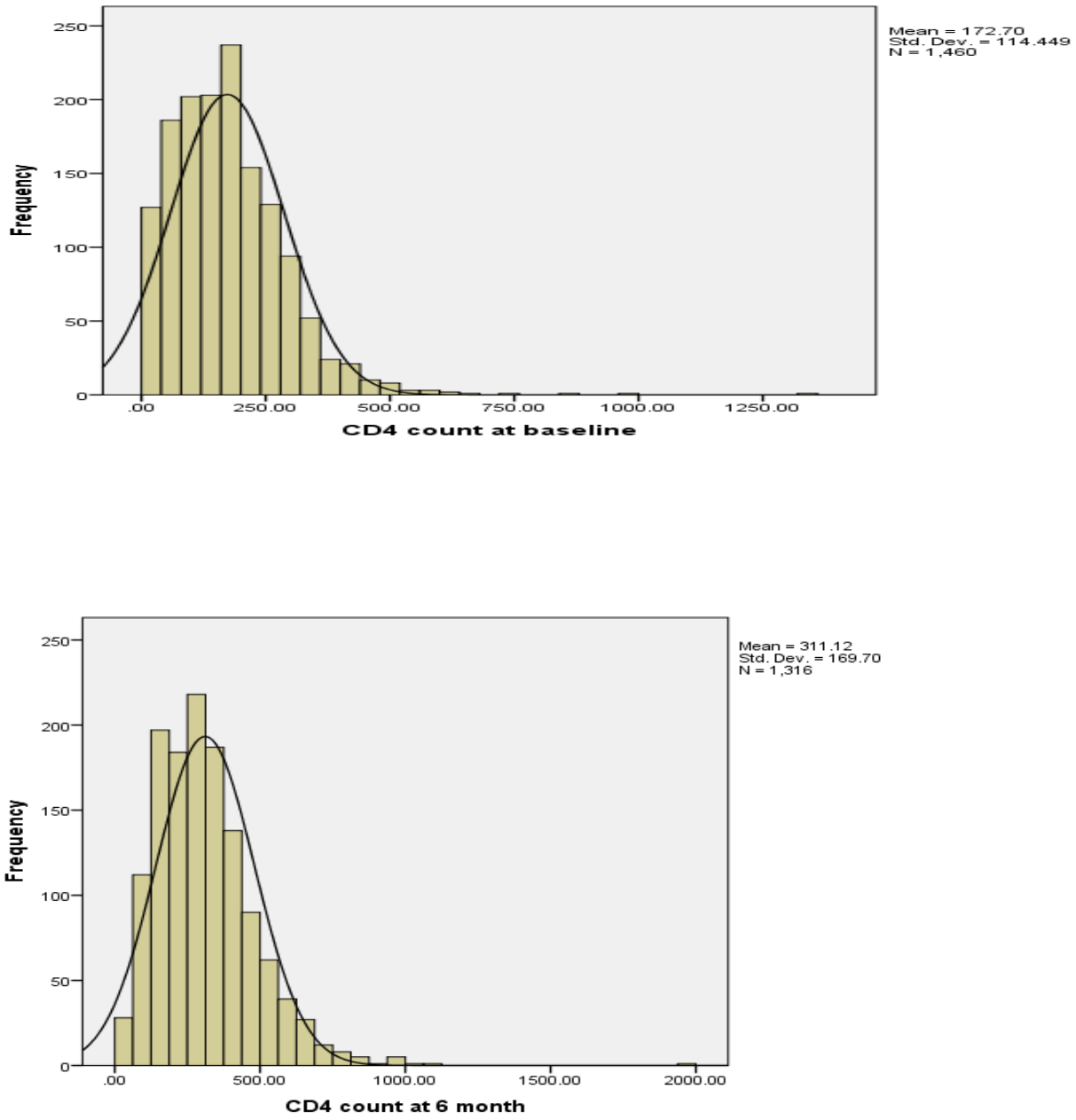

Figure 1. Graph showing absolute frequency distribution of CD_4 cell count (A) at baseline (n=1460) and (B) after 6 months of treatment (n=1316).

study observations corroborate similar studies that revealed that the most rapid and significant recovery of CD_4 cell count occurs during the first six months of treatment (Boulassel et al., 2012; Wright et al., 2011; Asfaw et al., 2015; Bennett et al., 2002).

A prospective study of South African patients revealed recovery is most rapid during the first 16 weeks months of treatment (Lawn et al., 2006). Thus, response in the early weeks and months of treatment is a robust predictor of ART treatment success, and adherence during early treatment is crucial for immunological recovery.

We observed steady and persistent CD_4 cell count recovery in those with baseline CD_4 cell counts of<200 cells/µl and 201 to 350 cells/µl (Figure 2). However,

Table 3. Predictors of CD_4 cell count response during ART. Responses are defined as (A) risk of immunological non-response (an increase of <50 cells/µl) or (B) failure to attain an absolute CD_4 cell count of ≥ 200 cells/µl following 12 months of treatment.

Variable		(A) Non response at one year (an increase of <50 cells/µl) at 12 month of treatment		(B) Failure to attain ≥200 cells/µl at 12 months of treatment (n=1140)	
		COR(95%CI)	AOR (95%CI)	COR(95%CI)	AOR (95%CI)
sex	Male	1	0.88(0.61-1.28)	1.00	1.00
	Female	1.14 (0.84-1.54)	1	3.68 (1.95-6.94)	3.42 (1.53-7.59)
Age category	Less than 25	1	1.68 (0.78-3.63)	1.00	1.00
	25-45	1.77 (0.95-3.30)	1.45 (0.85-2.50)	0.68 (0.20-2.32)	0.89 (0.23-3.53)
	>45	1.77 (1.12-2.80)	1	0.28 (0.07-1.11)	1.21 (0.23-6.40)
CDB category	<100	6.27 (2.98-13.160	5.17 (2.17-12.32)	-	-
	101-250	4.10 (2.03-8.27)	2.91 (1.29-6.53)	-	-
	251-350	3.41 (1.60-7.30)	2.80 (1.16-6.75)	-	-
	Greater than 351	1	1.00		
WHO stage	Stage I	1	1.04 (0.46-2.350	1.00	1.00
	Stage II	1.09 (0.63-1.90)	1.01 (0.52-1.96)	2.08 (0.46-9.39)	3.49 (0.47-25.98)
	Stage III	0.96 (0.58-1.570	0.79 (0.44-1.41)	1.25 (0.35-4.41)	2.96 (0.49-17.80)
	Stage IV	1.34 (0.69-2.60)	1.00	0.65 (0.17-2.55)	1.5 (0.21-10.43)
BMI category	Underweight	1	1.00 (0.30-4.24)	1.00	1.00
	Normal	1.01 (0.68-1.51)	1.10 (0.27-4.48)	2.19 (1.10-4.34)	2.82 (1.27-6.25)
	Overweight	1.05 (0.53-2.01)	1.38 (0.30-6.32)	3.41 (0.43-27.67)	6.88 (0.74-63.97)
	Obese	0.87 (0.23-3.32)	1.00	----	---
Regimen type	TDF+3TC+EFV	1	1.00 (0.60-1.70)	1.00	1.00
	TDF+3TC+NVP	1.10(0.61-1.96)	1.45 (0.67-3.12)	1.32 (0.27-6.49)	0.32 (0.05-2.14)
	AZT+3TC+EFV	0.71(0.45-1.00)	0.79 (0.42-1.47)	0.81 (0.33-2.00)	0.43 (0.13-1.43)
	AZT+3TC+NVP	1.54(0.91-2.60)	1.81 (0.88-3.70)	0.74 (0.31-1.77)	0.22 (0.06-0.77)
	D4T+3TC+EFV	1.37(0.84-2.20)	0.38 (0.69-2.63)	2.05 (0.79-5.34)	1.09 (0.28-4.17)
	D4T+3TC+NVP	0.93(0.92-2.95)	1.00	3.72 (1.25-11.13)	0.98 (0.26-3.770

recovery in patients with baseline CD_4 cell=351-500 cells/µl and CD_4 cell count >500 cells/µl fluctuated (rapid rise and fall). This fluctuation may be the result of this study small sample size for patients with baseline CD_4 cell count ≥351 cells/µl. Similar variation was observed in all subpopulations of similarly small sample size.

A high proportion of patients exhibited immunologic non-response (an increase of ≤50 cells/µl) at 12 months of treatment (19.3%), a proportion similar to that observed in a study conducted in Northern Ethiopia (22.7%) (Asfaw et al., 2015). Multivariate logistic regression revealed CD_4 cell count recovery was associated with baseline CD_4 cell count. Patients with low baseline CD_4 cell count exhibit greater non-response rates than those with higher baseline CD_4 cell count. A similar finding was observed in the EuroSIDA cohort study, where lower CD_4 count recovery was associated with lower rate of recovery (Florence et al., 2003). Some findings are in contrast to this study observations, in which lower response was associated with higher baseline CD_4 cell count (Lawn et al., 2006; Florence et al., 2003).

For those with a baseline CD_4 cell count of less than 200 cells/µl, failure to reach200cells/µl by 12months of treatment was associated with female gender, normal BMI (18 to 25) and D4T+3TC+NVP regimen. BMI was additionally significantly associated using a final multi-variate model. Patient with normal BMI (18 to 25) were three times more likely to fail to attain 200 cells/µl by 12 months of treatment than underweight patients. We observed a positive association between lower BMI and CD_4 cell. However, this association is inconsistently observed as evidenced from a study of a large sample size (n=8381) consisting of three cohorts. The study

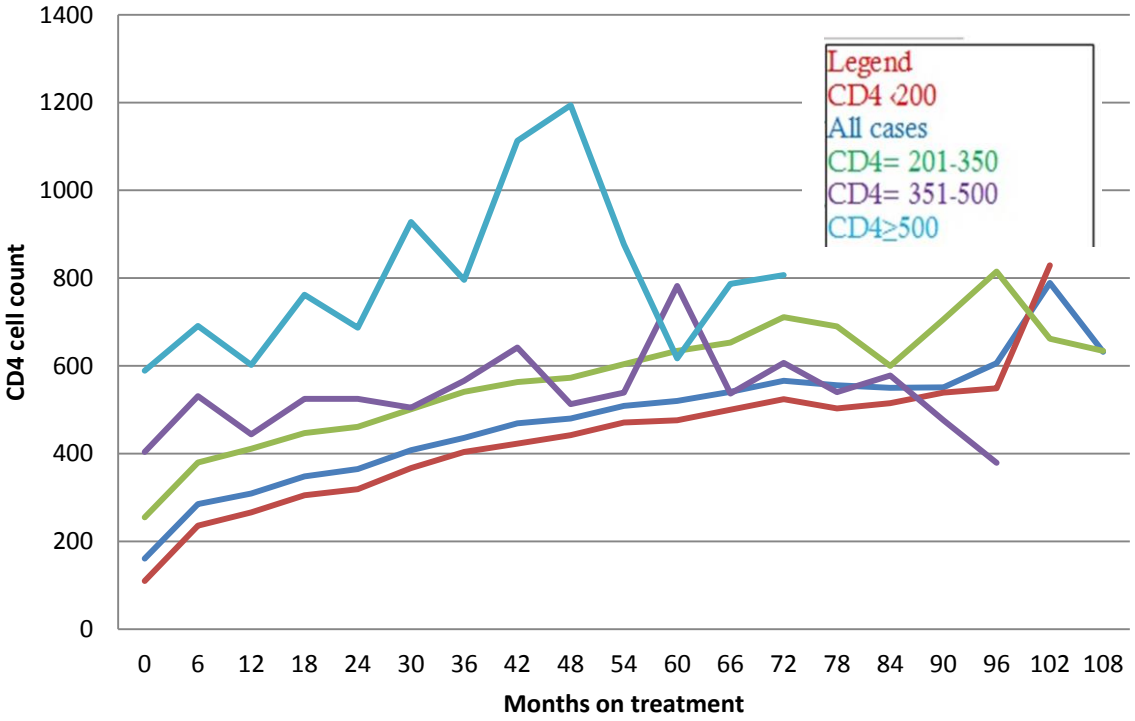

Figure 2. Graph showing six monthly median CD4 cell count changes for overall CD4 cell count, CD4 count less than 200 cells/ µl, CD4 cell count 201-350 cells/ µl, CD4 351-500 cells/ µl and CD4 count greater 500 cells/ µl.

concluded a BMI of approximately 30kg/m^2 at ART initiation was associated with greater CD_4 cell count recovery at 12 months compared with higher or lower BMI values (Koethe et al., 2015). These findings have no clear explanation yet. The study observed confidence interval for obese and overweight patients is likely due to the sample size.

In the study cohort we included all samples. Excluded populations were medical records of age less than 15 and which did not have baseline CD_4 cell count. Pediatrics have different treatment characteristics and differently treated from general population. Absence of baseline CD_4 cell count is unlikely to introduce sig-nificant bias. As a result, the internal validity of this paper is not significantly questionable. The findings of this study can be generalized to adult HIV-infected treatment-naïve patients in public health settings in Ethiopia, or even in other resource-constrained settings in Sub- Saharan Africa because of similar health service facility.

However, interpretation of these findings requires considering the limitations thereof. The limitations arise from the inherent characteristics of retrospective studies. We are unable to analyze important variables like mortality rate and adherence. The absence of these data might have affected the study estimation. Further prospective study designs are required to make confident conclusions.

In conclusion, we observed that recovery of CD_4 cell count is most rapid during the first six months of treatment. However, significant proportions of patients exhibit immunologic non-response. Patients with the lowest CD_4 counts in this setting have diminished capacity for immune recovery. These findings support the efficacy of ART in patients with a CD_4 cell count >500 cells/µl. Future prospective studies are required to corroborate the study observations regarding the long-term prospects for immune recovery among patients treated in ART programmes.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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REFERENCES

Asfaw A, Ali D, Eticha T, Alemayehu A, Alemayehu M, Kindeya F (2015). CD4 cell count trends after commencement of antiretroviral therapy among HIV-infected patients in Tigray, Northern Ethiopia: A retrospective cross-sectional study. PloS one 10(3):e0122583. Bennett KK, DeGruttola VG, Marschner IC, Havlir DV, Richman DD: Baseline predictors of CD4 T-lymphocyte recovery with combination antiretroviral therapy. J. Acquir. Immune Defic. Syndr. 31(1):20-26.

Berhe T, Melkamu Y, Amare A (2012). The pattern and predictors of mortality of HIV/AIDS patients with neurologic manifestation in Ethiopia: a retrospective study. AIDS Res. Ther. 9:11.

Boulassel MR, Chomont N, Pai NP, Gilmore N, Sekaly RP, Routy JP (2012). CD4 T cell nadir independently predicts the magnitude of the HIV reservoir after prolonged suppressive antiretroviral therapy. J. Clin. Virol. 53(1):29-32.

Calmy A, Balestre E, Bonnet F, Boulle A, Sprinz E, Wood R, Delaporte E, Messou E, McIntyre J, El Filali KM, Schechter M, Kumarasamy N, Bangsberg D, McPhail P, Van Der Borght S, Zala C, Egger M, Thiébaut R, Dabis F: Mean CD4 cell count changes in patients failing a first-line antiretroviral therapy in resource-limited settings. BMC Infect. Dis. 12:147.

Evan W, Robert S, Benita Y, Richard H, Michael V, Julio S (2003). Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy. AIDS 17:711-720.

Federal Democratic Republic of Ethiopia (FDRE) (2014). National guidelines for comprehensive HIV prevention, care and treatment. Addis Ababa, Ethiopia: FMOH; 2014. Available at: https://aidsfree.usaid.gov/sites/default/files/ethiopia_natl_gl_2014.pdf

Federal Ministry of Education (FMOE) (2008). Report on Progress towards Implementation of the UN Declaration of commitment on HIV/AIDS, Ethiopia. In: Edited by HAPCO. Addis Ababa. Available at: http://data.unaids.org/pub/report/2008/ethiopia_2008_country_progress_report_en.pdf

Florence E, Lundgren J, Dreezen C, Fisher M, Kirk O, Blaxhult Aea: Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV Med. 4(3):255-62.

García F, de Lazzari E, Plana M, Castro P, Mestre G, Nomdedeu M, Fumero E, Martínez E, Mallolas J, Blanco JL, Miró JM, Pumarola T, Gallart T, Gatell JM (2004). Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. J. Acquir. Immune Defic. Syndr. 36(2):702-713.

Jerene D, Endale A, Hailu Y, Lindtjorn B (2006a). Predictors of early death in a cohort of Ethiopian patients treated with HAART. BMC infect. Dis. 6:136.

Jerene D, Naess A, Lindtjorn B (2006b). Antiretroviral therapy at a district hospital in Ethiopia prevents death and tuberculosis in a cohort of HIV patients. AIDS Res. Ther. 3:10.

Johansson KA, Jerene D, Norheim OF (2008). National HIV treatment guidelines in Tanzania and Ethiopia: are they legitimate rationing tools? J. Med. Ethics 34(6):478-483.

Kanters S, Nachega J, Funk A, Mukasa B, Montaner JS, Ford N, Bucher HC, Mills EJ (2014). CD4(+) T-cell recovery after initiation of antiretroviral therapy in a resource-limited setting: a prospective cohort analysis. Antivir. Ther. 19(1):31-39.

Kaufmann GR, Bloch M, Finlayson R, Zaunders J, Smith D, Cooper DA (2002). The extent of HIV-1-related immunodeficiency and age predict the long-term CD4 T lymphocyte response to potent antiretroviral therapy. AIDS 16(3):359-367.

Kilaru K, Kumar A, Sippy N, Carter A, Roach T (2006). Immunological and virological responses to highly active antiretroviral therapy in a non-clinical trial setting in a developing Caribbean country. HIV Med. 7:99-104.

Koethe JR, Jenkins CA, Lau B, Shepherd BE, Silverberg MJ, Brown TT, Blashill AJ, Anema A, Willig A, Stinnette S, Napravnik S, Gill J, Crane HM, Sterling TR (2015). Body mass index and early CD4 T-cell recovery among adults initiating antiretroviral therapy in North America, 1998-2010. HIV Med. 16(9):572-577.

Lange CG, Valdez H, Medvik K, Asaad R, Lederman MM (2002). CD4+ T-lymphocyte nadir and the effect of highly active antiretroviral therapy on phenotypic and functional immune restoration in HIV-1 infection. Clin. Immunol. 102(2):154-161.

Lawn SD, Myer L, bekker LG, Wood R (2006). CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. BMC Infect. Dis. 6:59.

Lederman HM, Williams PL, Wu JW, Evans TG, Cohn SE, McCutchan JA, Koletar SL, Hafner R, Connick E, Valentine FT, McElrath MJ, Roberts NJ Jr, Currier JS (2003). Incomplete immune reconstitution after initiation of highly active antiretroviral therapy in human immunodeficiency virus-infected patients with severe CD4+ cell depletion. J. Infect. Dis. 188(12):1794-1803.

Lok JJ, Bosch RJ, Benson CA, Collier AC, Robbins GK, Shafer RW, Hughes MD (2010). Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. AIDS 24(12):1867-1876.

Luz PM, Grinsztejn B, Velasque L, Pacheco AG, Veloso VG, Moore RD, Struchiner CJ (2014). Long-term CD4+ cell count in response to combination antiretroviral therapy. PLoS One 9(4):e93039.

McKinnon LR, Kimani M, Wachihi C, Nagelkerke NJ, Muriuki FK, Kariri A, Lester RT, Gelmon L, Ball TB, Plummer FA, Kaul R, Kimani J (2010). Effect of baseline HIV disease parameters on CD4+ T cell recovery after antiretroviral therapy initiation in Kenyan women. PLoS One 5(7):e11434.

Ministry of Health (MoH) (2005). Health Sector Strategic Plan (HSDP-III) 2005/6-2009/10. Planning and Programming Department. . In. (Ed.) Ababa. Available at: http://can-mnch.ca/wp-content/uploads/2013/09/Ethiopia-Health-Sector-Development-PlanHSDP-III.pdf

Mutimura E, Addison D, Anastos K, Hoover D, Dusingize JC, Karenzi B, Izimukwiye I, Mutesa L, Nsanzimana S, Nash D (2015). Trends in and determinants of CD4+ cell count at antiretroviral therapy initiation after changes in national ART guidelines in Rwanda. AIDS 29(1):67-76.

Naftalin CM, Wong NS, Chan DP, Wong KH, Reidpath DD, Lee SS (2015). Three different patterns of CD4 recovery in a cohort of Chinese HIV patients following antiretroviral therapy - a five-year observational study. Int. J. STD AIDS 26(11):803-809.

Okulicz JF, Grandits GA, Weintrob AC, Landrum ML, Ganesan A, Crum-Cianflone NF, Agan BK, Marconi VC (2010). CD4 T cell count reconstitution in HIV controllers after highly active antiretroviral therapy. Clin. Infect. Dis. 50(8):1187-1191.

Stephen D, Anthony D, Xavier A, Landon M, Robin W (2008). Early mortality among adults accessing antiretroviral treatment programs in sub-Saharan Africa. AIDS 22:1897-1908.

Waters L, Fisher M, Anderson J, Wood C, Delpech V, Hill T, Walsh J, Orkin C, Bansi L, Gompels M, Phillips A, Johnson M, Gilson R, Easterbrook P, Leen C, Porter K, Gazzard B, Sabin C (2011). Responses to highly active antiretroviral therapy and clinical events in patients with a low CD4 cell count: late presenters vs. late starters. HIV Med. 12(5):289-298.

Wright ST, Carr A, Woolley I, Giles M, Hoy J, Cooper DA, Law MG: CD4 cell responses to combination antiretroviral therapy in patients starting therapy at high CD4 cell counts. J. Acquir. Immune Defic. Syndr. 58(1):72-79.

Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, Harries A (2006). Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. AIDS 20:2355-2360.