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ORIGINAL RESEARCH

Predictors of Current CD4+ T-Cell Count Among Women of Reproductive Age on Antiretroviral Therapy in Public Hospitals, Southwest Ethiopia

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Background: HIV/AIDS is one of the major global public health problems. CD4 is a glycoprotein found on the surface of different immune cells. CD4 cell counts determine the need for screening and prophylactic interventions against common opportunistic infections in those with advanced HIV disease. Thus, this study aimed to assess the predictors of current $CD4^+$ T-cell count among women of reproductive age on antiretroviral therapy in public hospitals, southwest Ethiopia.

Methods: A cross-sectional study was conducted from February to April 2018. A total of 422 participants in the three public hospitals were selected using a systematic random sampling method. Linear regression analyses were used to determine the important predictors of current $CD4^+$ T-cell count at p-values of <0.05.

Results: A total of 422 women with a median age of 37.00 years participated in this study. More than one in ten (12.8%) respondents experienced immunological failure. An increased current $CD4^+$ T-cell count was observed among patients with a tertiary level of education [β = 56.45, 95% CI (3.5, 109.4)], baseline WHO clinical stage II [β = 44.06, 95% CI (5.3, 82.9)], initial regimen of AZT+3TC+EFV [β = 167.23, 95% CI (100.4, 234.1)], with increased baseline $CD4^+$ T-cell count [β = 0.35, 95% CI (0.2, 0.5)], and with increased time duration on ART [β = 14.36, 95% CI (6.304, 22.4)]. On the other hand, the current $CD4^+$ T-cell count was lowered among patients with poor baseline adherence, opportunistic infection, and viral load of ≥1000 by 181.06 cells/mm^3, 101.62 cells/mm^3, and 137.53 cells/mm^3 compared to good baseline adherence, no opportunistic infection and undetectable viral load, respectively.

Conclusion: The immunological failure was relatively low. Maintaining adherence, early identification and treatment of opportunistic infections, and minimizing viral load to undetectable levels may further decrease immunological failure.

Keywords: predictors, CD4+ T-cell count, women, reproductive age, antiretroviral therapy, Ethiopia

Background

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is one of the major public health problems. Globally, 75.7 million people have become infected with HIV since the start of epidemic up to the end of 2019, whereas 38.0 million people were living with HIV in 2019; of which 1.7 million people were newly infected. HIV/AIDS accounted for 32.7 million deaths from AIDS-related illnesses since the start of the epidemic.[1]

Since the start of the HIV epidemic globally, HIV-infected women in many regions, especially in South East Asia and sub-Saharan Africa, remained unduly

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high because of vulnerabilities created by unequal cultural, social, and economic status. Globally, in 2019, an estimated 19.2 million women were living with HIV, constituting more than half of all adults aged 15 and over.[2]

Women and girls in the sub-Saharan Africa region accounted for 59% of all new HIV infections in 2019. Moreover, five in six new infections in this region were among adolescents aged 15–19 years. Low socioeconomic status, cultural stigmas, social barriers, insufficient health care facilities, limited health care professionals, and inadequate availability of health related information are the major contributing factors to the high prevalence and disproportionate impact of HIV in developing countries.[3]

In Ethiopia, 1% of adults aged 15–49 years were living with HIV in 2018. About 23,000 people were newly infected with HIV. Furthermore, 11,000 people were died from AIDS-related illnesses in the same year.[4] Women were disproportionally affected by HIV in Ethiopia. For instance, 390,000 of the total 630,000 adults living with HIV were women in 2019. New HIV infections among young women (aged 15–24 years) were two times more than new HIV infections among young men (aged 15–24 years).[5]

Antiretroviral therapy (ART) drugs are recommended by the World Health Organization (WHO) to be given to all people with HIV. These reduce the amount of HIV in the body, stop the progression of HIV disease and decrease the morbidity and mortality related to HIV/AIDS.[1,6] Even though there is no effective cure for HIV, it can be controlled with proper ART drug adherence. HIV treatment does not prevent the transmission of other sexually transmitted diseases.[7]

In 2015, according to the WHO's "universal test and treat" (UTT) strategy, ART should be initiated for all patients diagnosed with HIV irrespective of CD4 cell count.[8] The efficacy of ART is monitored by laboratory and clinical measures, including viral load (VL) and cluster of differentiation 4 (CD4) cell count, while on treatment. The World Health Organization recommends viral load estimation as the gold standard approach to diagnose and confirm treatment failure.[9] However, poor adherence to WHO and national guidelines on VL testing, limited viral load testing machines, overburdened health care workers, and inefficient transport and delivery systems have been reported as major barriers for the implementations of VL testing in resource-limited countries.[10,11] Also CD4 count is currently not recommended for monitoring purposes, it is applied to determine whether HIV patients develop advanced HIV diseases or not.[12]

According to the WHO, advanced HIV disease for adults, adolescents, and children ≥five years is defined as a "CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 events at presentation for care".[12] Worldwide, about one-third of all HIV-positive patients in active care are living with advanced HIV disease. These patients are more prone to develop opportunistic infections including severe bacterial infections, tuberculosis, and cryptococcal meningitis, which can result in an increased risk of morbidity and mortality.[12,13]

CD4 is a glycoprotein found on the surface of different immune cells such as T helper cells, monocytes, macrophages, and dendritic cells,[14] and CD4 T-cell count is the most important marker or indicator of immune function in patients living with HIV. CD4 T-cell count remains the best predictor of morbidity and mortality in HIV-positive individuals.[12,15] It is one of the key determinants of the need for screening and prophylactic interventions against common opportunistic infections in those with advanced HIV disease, HIV-related malignancies, and immune reconstitution inflammatory syndrome (IRIS) following ART initiation and needing close clinical monitoring.[10,12] Moreover, CD4 cell counts can help to identify patients in need of critical care and support diagnostic decision-making at baseline and in patients returning to care after a period of treatment interruption.[16] It is also used to correlate the immunological classification of HIV infection with clinical staging of HIV-related diseases.[17,18]

There are different contributing factors which could have an effect on immunological failure and these turn to an increase in morbidity and mortality of women associated with advanced HIV disease.[19,20] For instance, higher baseline CD4$^+$ T-cell count, long duration on ART, younger age, patients from a military health care facility, good adherence, viral load suppression and early initiation of treatment contributed positively to the increment of the CD4 count.[21,22] Whereas, patients on ART regimen of 1e (TDF-3TC-EFV), 2f (AZT-3TC-ATV/r), and 2h (TDF-3TC-ATV/r), and a viral load >1000 copies were negatively associated with recent CD4 count.[21–23] Besides, factors like urban residency[24] and white ethnicity were associated with increased CD4 count.[25] Whereas old age, lower CD4 count at baseline,[26] severe clinical-stage, tuberculosis (TB) coinfection,[27] poor nutritional status, pregnancy, stress, smoking status, and drug use have been investigated as predictors of low CD4 count.[28–30]

Identification of factors affecting $CD4^+$ T-cell counts for HIV patients maybe plays an important role in their care program and their survival.[31] Therefore, the findings of this study could be an input for policymakers towards the predictors of current $CD4^+$ T-cell count in women of reproductive age on ART and to develop strategies towards their immunological recovery. Moreover, knowing the predictors of $CD4^+$ T-cell count helps the programmers develop and implement strategies towards screening, early provision of treatment and prevention of major opportunistic infections, in order to reduce the morbidities and mortalities associated with advanced HIV disease.[12,32] Thus, this study was aimed to assess the predictors of current $CD4^+$ T-cell count among women of reproductive age on antiretroviral therapy in public hospitals, southwest Ethiopia.

Methods and Materials

Study Design and Period

An institutional-based cross-sectional study design supported with record review was carried out at public hospitals in southwest Ethiopia from February 2018 to April 2018.

Study Setting

The study was carried out in three public hospitals of southwest Ethiopia: Mizan-Tepi University Teaching Hospital, Gebretsadik Shawo General Hospital and Tepi General Hospitals. These hospitals are located in Benchi-Maji Zone, Kefa Zone, and Sheka Zone, respectively. Currently, Mizan-Tepi University Teaching Hospital is expected to provide service for more than 829,000 people. While Gebretsadik Shawo General Hospital and Tepi General Hospitals are expected to provide care for more than 500,000 people.[33] The total number of HIV patients in Bench Maji Zone, Kaffa Zone, and Sheka Zone were 8913, 3128, and 4237, respectively, in 2018. At the time of data collection, there were 1776 (Bench Maji Zone), 849 (Kaffa Zone), and 1487 (Sheka zone) HIV clients on ART.

Inclusion and Exclusion Criteria

Women of reproductive age (15–49 years) who were on ART for at least 6 months and who had a baseline CD4+ T-cell count were included. Women who were critically ill, unable to give responses and blood specimens were excluded. Moreover, women who had incomplete secondary data records were excluded from the study.

Sample Size Determination

The sample size was calculated using a single population proportion formula $n= (Z\ \alpha/2)^2\ p\ (1-p)/d^2$, where n = was the sample size, d = degree of precision = 0.05; and Z α/2 = 1.96 by assuming 95% confidence interval. Since there was not any research done in the study area, we took population proportion of 0.5 (50%) to get the maximum sample size. Then, by adding 10% non-response rate, the final sample size was 422.

Sampling Procedure

We applied a systematic random sampling method to select the study participants. First, 180, 120, and 150 women of reproductive age who were on ART per month werre taken from MTUTH, Bonga general Hospital, and Tepi General Hospital, respectively. Then, in the three months follow-up, a total of 1350 women of reproductive age who were on ART (540 from MTUTH, 360 from Bonga General Hospital, and 450 from Tepi General Hospital) were inspected for VL and $CD4^+$ T-cell count. Then, the sample sizes were proportionally allocated to each hospital (169 from MTUTH, 112 from Bonga General Hospital, and 141 from Tepi General Hospital). The sampling interval (kth) was calculated as the total number of women of reproductive age on ART follow-up during the data collection period divided by the sample size (1350/422 = 3.19 = 3). Then every third participant was interviewed after the first eligible participant was selected by lottery method (Figure 1).

Operational Definition

Baseline data: refers to the laboratory and clinical data before initiation of ART.

Current $CD4^+$ T-cell count: refers to the $CD4^+$ T-cell count during the period of data collection.

Adherence: refers to starting ART treatment, keep all medical appointments, and taking drugs every day and exactly as prescribed. For this study, adherence was calculated as;

$$Adherance = \frac{\text{No of doses of ART taken}}{\text{No of prescribed doses of ART}} \text{ x } 100\%,$$ Finally, the result was categorized as; good adherence if >95%, fair adherence if 85–95%, and poor adherence if <85% of doses were taken.[34–36]

Immunological failure: was defined as persistent CD4 below 100 cells/mm^3, or a drop of CD4 cell count below baseline pre-treatment level, or a drop of CD4 cell count of 50% from the peak treatment value all in the absence of

an ongoing co-infection and after a minimum of 6 months of ART.[37]

Study Variables

Dependent Variables

Current $CD4^+$ T-cell count.

Independent Variables

Socio-demographic characteristics like; age, sex, residence, marital status, education, occupation, and other clinical characteristics like HIV/AIDS co-infection, baseline $CD4^+$T-cell count, regimen type, WHO clinical staging, viral load, adherence, and duration of ART.

Data Collection Tools and Procedure

Data were collected by six trained health professionals' using structured questionnaires which were developed and adapted from reviewing different relevant literatures.[38,39] Three health professionals' supervised the data collection process. The pretest was done among 5% of the sample size in health centers that were out of the study settings and then the coherence and skipping pattern of the questionnaire were corrected.

Specimen Collection and Laboratory Procedure

Upon completion of the questionnaire, about 5–8 mL of venous blood was collected from each patient on the same venipuncture for $CD4^+$ T-cell count and viral load tests. After the whole blood was drawn, it was placed into two separate vacutainer tubes containing ethylene diamine tetra-acetic acid (EDTA) with anticoagulant (EDTA). About 3 mL of whole blood was used for $CD4^+$ T-cell count. Centrifugation of the remaining 5 mL of whole blood was done for 20 minutes at 3000 rpm and plasma was separated for the viral load test. Immediately the samples were stored at room temperature for $CD4^+$ T-cell count and at −80 °C for viral load testing and then processed within 24 hours and 5 hours, respectively.

Using the FACS Calibur flow cytometery (BD, CA, America), quantification of $CD4^+$ T-cell count was done. $CD4^+$ T-cell count was done by adding 50 µL whole blood to a reagent tube containing 20 µL of monoclonal antibodies followed by vortexing and incubation for 30 minutes under dark conditions. Plasma viral load was measured using Quantitative Real-Time PCR HIV-1 assay by the COBAS® AmpliPrep instrument (Roch, Homburg, Germany).

Data Quality Assurance

The quality of data was assured by using a pre-tested and properly designed questionnaire. Furthermore, the data collectors were trained on data and sample collection procedures.

The quality of the laboratory results was guaranteed by applying all quality control measures during sample collection and actual processing by following strict laboratory procedures. Standard operational procedures recommended by the manufacturers regarding centrifugation of whole blood, pipetting, transportation of samples, and aliquoting were strictly followed using standard protocol and laboratory bio-safety precautions.

Data Processing and Analysis

The data was entered using EPI INFO version 7 and exported to statistical packages for social science (SPSS) version 21.0 for data cleaning and analysis. Descriptive statistics such as mean, frequencies and percentages were used to summarize data. Bivariate and multiple regression analysis were done. Variables with p-values <0.05 were included in the multiple regression. The independent association between explanatory variables and current CD4 count was determined at p values < 0.05.

Results

Socio-Demographic Characteristics of the Respondents

A total of 422 women of reproductive age on ART were enrolled in the study yielding a response rate of 100%. The median (IQR) age of the participants was 37.00 (33.0–43.0) years. More than half (290, 68.7%) of the participants were urban residents, and 216 (51.2%) were protestant religion followers. Of the total participants, nearly half (196, 46.4%) of them were currently married. Concerning the respondents' educational status, most (159, 37.7%) of them were illiterate (Table 1).

Clinical Characteristics of Women of Reproductive Age on ART

Women with HIV were on ART for the median (IQR) of 8 (6–10) years. At the baseline, more than half (217, 51.4%) of the respondents were on WHO clinical stage III, 257 (60.9%) of them had $CD4^+$ T-cell count of <200 cells/mm^3, and 354 (83.9%) of them had good ARV drug adherence. During data collection time, the majority (405, 96%) of the participants were on WHO clinical stage II, and 174 (41.2%) of them

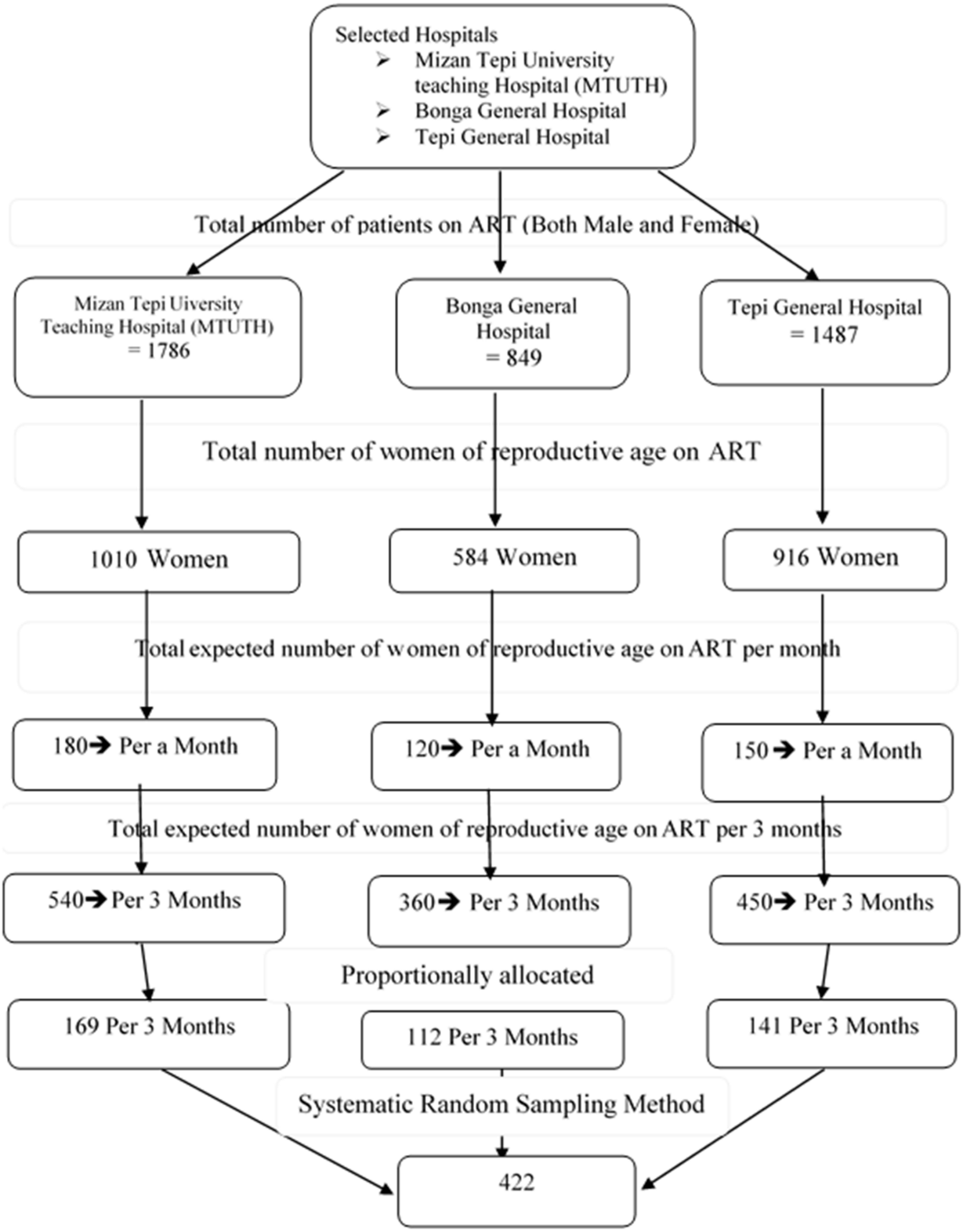

Figure 1 Schematic representation of the sampling procedure of HIV positive women of reproductive age on ART at the Public Hospitals from February 1st to April, 2018.

had a $CD4^+$ T-cell count of ≥500 cells/mm^3. Nearly half (180, 42.7%) of the participants switched ART regimens from first-line regimens to either other first-line regimens (169, 93.9%) or second-line regimens (11, 6.1%). The reasons for switching were mostly due to toxicity (98, 23.2%) followed by pregnancy (33, 7.8%) (Table 2).

Results of Simple and Multiple Linear Regression Analysis

The simple linear regression analysis revealed that residence, educational status, baseline WHO clinical stage, type of initial regimen, baseline adherence, opportunistic infection, baseline $CD4^+$ T-cell count, viral load, and time duration on ART were significantly associated with current $CD4^+$ T-cell count ($p<0.05$). Those variables were included in the multiple regression models.

In order to adjust for possible confounding factors, multiple linear regression analysis was applied after confirming that all assumptions were met. The relationship between the independent variables (IVs) and the current $CD4^+$ T-cell count was linear. There was no multicollinearity of variables where variance inflation factor (VIF) scores fall between 1.092 and 1.943 indicated that it was below 10. The values of the residuals were independent or uncorrelated where the Durbin-Watson statistic was 1.978 indicating that the value was close to 2 not below 1 and above 3. The variance of the residuals was constant or homoscedasticity was met where the variances of the current $CD4^+$ T-cell counts were the same for all levels of the independent variables and the plot of standardized residuals versus standardized predicted values indicated that there were no signs of funneling. The normal P-P Plot indicated that the values of the residuals were normally distributed and there were no influential cases biasing the model where the Cook's distance values were all under 1 suggesting that no individual cases were likely to be significant outliers.

Predictors of Current CD4+ T-Cell Count

After adjusting for possible confounding factors using a multiple linear regression model considering all the above mentioned assumptions; educational status, baseline WHO clinical stage, type of initial regimen, baseline adherence, opportunistic infection, baseline $CD4^+$ T-cell count, viral load, and time duration on ART remained significantly associated with current $CD4^+$ T-cell count. However, resident was not significantly associated with current $CD4^+$ T-cell count. This study finding indicated that about 44.7% of the variation in current $CD4^+$ T-cell count was explained by our model (R Square = 0.447, P-value < 0.0001).

For each additional year a respondent stays on ART, the current $CD4^+$ T-cell count increased by 14.36 cells/mm^3 of blood ($p < 0.001$). Similarly, for each increment of cells/mm^3 of blood in the baseline $CD4^+$ T-cell count, the current $CD4^+$ T-cell count increased by 0.354 cells/mm^3 of blood ($p < 0.0001$). The current $CD4^+$ T-cell count of respondents whose educational status were certificate and above were higher than illiterate by 56.45 cells/mm^3 of blood ($p < 0.037$). The current $CD4^+$ T-cell count of women on ART who were on baseline WHO clinical stage II were higher than those who were on baseline WHO clinical stage III by 44.06 cells/mm^3 of blood ($p = 0.026$). Women of reproductive age on ART who took an initial regimen of AZT+3TC+EFV had higher current $CD4^+$ T-cell count than those who took AZT+3TC+NVP by 167.23 cells/mm^3 of blood ($p < 0.0001$). The current $CD4^+$ T-cell count of women of reproductive age on ART with poor adherence was less than those with good adherence by 181.06 cells/mm^3 of blood ($p < 0.0001$). Similarly, the current $CD4^+$ T-cell count of respondents who had opportunistic infections were less than their counterparts by 101.62 cells/mm^3 of blood ($p < 0.0001$). Finally, respondents with a viral load of ≥1000 copies/mm^3 had lower current $CD4^+$ T-cell count than those respondents with an undetectable viral load by 137.53 copies/mm^3 ($p < 0.01$) (Table 3).

Discussion

Initiation of ART for women of reproductive age with HIV/AIDS is very crucial for the decrement of viral load in the blood, increment of $CD4^+$T-cell count, and prevention of opportunistic infection.[40,41] Understanding the factors determining the current $CD4^+$ T-cell count which in turn influences viral load in the blood is very critical for HIV-positive women to decide for the coming pregnancy and also it helps to develop integrated reproductive health care services.[42,43] Thus this study aimed to assess the predictors of current CD4+ T-cell count among women of reproductive age on antiretroviral therapy attending public health hospitals in southwest Ethiopia.

In the current study, the immunological failure was found to be low as compared to the studies conducted in South Africa, 19.0%,[44] Tanzania, 17.1%,[45] southern

Table 1 Socio-Demographic Characteristics of Women of Reproductive Age on ART (n = 422) in Public Hospitals, south-west Ethiopia, 2018

Variables	Frequency	%
Place of residence		
Urban	290	68.7
Rural	132	31.3
Age of respondents		
Median(IQR) in years	37.00 (33.0–43.0)	
Marital status		
Single	64	15.2
Married	196	46.4
Divorced	108	25.6
Widowed	54	12.8
Religion		
Protestant	216	51.2
Orthodox	105	24.9
Muslim	101	23.9
Ethnicity		
Bench	128	30.3
Oromo	89	21.1
Amhara	67	15.9
Kaffa	40	9.5
Sheka	36	8.5
Meini't	35	8.3
Tigre	16	3.8
Dizzi	11	2.6
Respondent's educational status		
Illiterate	159	37.7
Primary	111	26.3
Secondary	94	22.3
Certificate and above	58	13.7
Respondent's occupational status		
Farmer	31	7.3
Merchant	44	10.4
Student	12	2.8
Government employee	31	7.3
Daily worker	64	15.2
Housewife	146	34.6

Ethiopia, 20.3%,[46] and northern Ethiopia, 22%.[47] This might be due to the differences of the study population and study periods. For instance, the study subjects for the study conducted in southern Ethiopia were children.

In the current study, numbers of factors which are responsible for the reconstitution of the immune system of women of reproductive age with HIV were identified as independent predictors of the current $CD4^+$ T-cell count. An increased current $CD4^+$ T-cell count in response to ART was observed among women with educational status of certificate and above compared to illiterate women. Similarly, participants with a high educational level had good immunological recovery, and are less prone to comorbidities associated to HIV infection in the studies conducted in KwaZulu-Natal, South Africa,[48] and in India.[49] This might be due to the fact that education may help HIV positive women be aware of the importance of early identification of their status of HIV/AIDS. Educated women may also have good adherence with ART drugs which will bring the reconstitution of the immune system and increment of current $CD4^+$ T-cell count.

The current $CD4^+$ T-cell counts of women on ART who were on baseline WHO clinical stage II were higher than those who were on baseline WHO clinical stage III. WHO reports revealed that early detection of HIV/AIDS and initiation of ART promotes an increased $CD4^+$ T-cell count and a decreased viral load.[18,50] Our finding is also supported by study findings in Uganda[51] and Northern Ethiopia.[52] Patients with advanced HIV status have poorer immunological recovery than those with early HIV status because opportunistic infections (OIs) are more common in patients with advanced HIV status. These OIs might contribute to the decrement of current $CD4^+$ T-cell counts.[53] Moreover, women with advanced HIV status commonly experience a decreased CD4 cell count, and this in turn means the women experience advanced HIV disease, which is at a high risk of death even after starting ART.[12]

The current study also revealed that women with an initial regimen of first-line ART drugs specifically AZT +3TC+EFV were significantly associated with increased $CD4^+$ T-cell count. Consistent with the current study finding, a high immunological response among patients on TDF/3TC/EFV was also observed from a study conducted in Nepal.[54] However, studies conducted in Europe[55] and Ethiopia[52] indicated that the initial ART regimen class was not statistically significant with the immunologic response and CD4 count did not differ by ART regimen classes. This discrepancy might be due to sample size differences or due to biological characteristics. For instance, our study only focused on women of reproductive age, whereas the study conducted in Nepal include both sexes.[54]

The current $CD4^+$ T-cell count of women of reproductive age on ART with poor adherence was less as compared with those with good adherence. Different studies conducted in China,[56] Abidjan, Côte d'Ivoire,[57] and

Table 2 Clinical Characteristics of Women of Reproductive Age on ART in Public Hospitals, southwest Ethiopia, 2018

Variables	Frequency	%
Duration of HAART(years)		
≤ 6	117	27.7
>6	305	72.3
Median (IQR) of ART duration (In Years)	8 (6–10)	
Baseline WHO clinical stage		
I	65	15.4
II	152	36.0
III	165	39.1
IV	40	9.5
Baseline $CD4^+$ T-cell count (cells/mm^3)		
<200	257	60.9
200–349	128	30.3
350–499	26	6.2
≥500	11	2.6
Baseline ARV drug adherence		
Good	354	83.9
Fair	35	8.3
Poor	33	7.8
WHO stage during data collection		
I	13	3.1
II	405	96
III	4	0.9
$CD4^+$ T-cell count during data collection (cells/mm^3)		
<200	32	7.6
200–349	96	22.7
350–499	120	28.5
≥500	174	41.2
Viral load count (copies/mm3)		
Undetected	233	55.2
0–19	79	18.7
20–999	40	9.5
≥1000	70	16.6
Initial regimen		
d4T+3TC+NVP	89	21.1
d4T+3TC+EFV	36	8.5
AZT+3TC+NVP	128	30.3
AZT+3TC+EFV	35	8.3
TDF+3TC+EFV	67	15.9
TDF+3TC+NVP	40	9.5
Pediatric (d4T +3TC+NVP)	16	3.8
Pediatric 4C (AZT+3TC +NVP)	11	2.6
Opportunistic Infection		
No	259	61.4
Yes	163	38.6
Switching		
No	242	57.3
Yes	180	42.7
Switching drug Type		
To 1st line drug	169	93.9
To 2nd line drug	11	6.1
Second regimen		
AZT+3TC+NVP	62	14.7
AZT+3TC+EFV	32	7.6
TDF+3TC+NVP	26	6.2
TDF+3TC+EFV	47	11.1
ABC+ddl+LPV/R	13	3.1
Reasons for Switching Drug		
Toxicity	98	23.2
Pregnancy	33	7.8
TB	24	5.7
Immunological failure	13	3.1
Default	7	1.7
Age	5	1.2
Immunological Failure		
No	368	87.2
Yes	54	12.8
Components of Immunological Failure		
CD4 Falling More Than 50%	32	59.3
CD4 Falling Below Baseline	19	35.2
CD4 Persistently Below 100 cells/mm^3	3	5.5

Abbreviations: ARV, antiretroviral; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; d4T, stavudine; 3TC, lamivudine; NVP, nevirapine; AZT, zidovudine; ABC, abacavir; ddl, didanosine; LPV/R, lopinavir/ritonavir.

University of Gondar Referral Hospital, northwest Ethiopia[21,58] revealed that adherence increased CD4 cells. Poor adherence to antiretroviral therapy (ART) may result in less effective viral suppression, poor immunological recovery, drug resistance, treatment side-effects, treatment failure, and subsequently reduced treatment options.[59]

In this study, the current $CD4^+$ T-cell count of respondents who had opportunistic infections was less than their counterparts. This finding is consistent with the studies conducted in the United States,[60] Switzerland,[61] and Saudi Arabia.[62] Depletion of $CD4^+$ cells may leads to cellular and subsequently humoral deficiencies. These deficiencies may in turn bring HIV-related OIs which are usually contributing factors for the $CD4^+$ T-cell count falling below 200/mm^3.[60,63] Depleted $CD4^+$ T-cell count

Table 3 Independent Factors Associated with Current CD4$^+$ T-Cell Count Among Women of Reproductive Age on ART in Public Hospitals, southwest Ethiopia, 2018

Variables	No (%)	Bivariate (Simple Linear Regression Analysis)			Multiple Linear Regression Analysis			
		Unstandardized B Coefficient	95% CI for B	P-value	Unstandardized B Coefficient	Standardized B Coefficient	95% CI for B	P-value
Residence								
Urban	290(68.7)	R	R					
Rural	132(31.3)	−117.9	−161.9, −73.9	0.000	−17.27	−0.036	−55.1, 20.6	0.370
Educational Status								
Illiterate	159(37.7)	R	R					
Primary	111(26.3)	9.3	−42.6, 61.3	12.64	0.025	−30.3, 55.6	0.563	
Secondary	94(22.3)	92.6	37.9, 147.2	0.001	51.96	0.098	7.8, 96.1	0.021*
Certificate and above	58(13.7)	150.4	85.9, 214.8	0.000	56.45	0.088	3.5, 109.4	0.037*
Baseline WHO clinical stage								
I	65(15.4)	45.9	−16.8, 108.6	11.24	0.018	−40.9, 63.5	0.672	
II	152(36.0)	77.8	29.7, 125.9	0.002	44.06	0.096	5.3, 82.9	0.026*
III	165(39.1)	R	R					
IV	40(9.5)	−16.9	−92.3, 58.6	8.38	0.011	−52.6, 69.4	0.787	
Type of initial regimen								
d4T+3TC+NVP	89(21.1)	36.1	−21.2, 93.4	40.26	0.075	−11.2, 91.7	0.125	
d4T+3TC+EFV	36(8.5)	136.6	58.3, 214.9	0.001	155.285	0.197	85.9, 224.6	0.000*
AZT+3TC+NVP	128(30.3)	R	R					
AZT+3TC+EFV	35(8.3)	210.5	131.3, 289.7	0.000	167.23	0.210	100.4, 234.1	0.000*
TDF+3TC+EFV	67(15.9)	−12.0	−74.6, 50.6	−4.33	−0.007	−58.8, 50.2	0.876	
TDF+3TC+NVP	40(9.5)	−31.4	−106.6, 43.8	25.85	0.034	−35.6, 87.3	0.408	
Pediatric (d4T +3TC+NVP)	16(3.8)	25.2	−84.9, 135.3	4.09	0.004	−87.2, 95.4	0.930	
Pediatric 4C (AZT+3TC +NVP)	11(2.6)	−4.6	−134.9, 125.9	−73.68	−0.053	−185.8, 38.5	0.197	
Baseline adherence								
Good	354(83.9)	R	R					
Fair	35(8.3)	−133.2	−206.3, −59.9	0.000	−122.41	−0.154	−186.2, −58.3	0.000*
Poor	33(7.8)	−222.9	−298.0, −147.7	0.000	−181.06	−0.221	−247.6, −114.5	0.000*
Opportunistic Infection								
No	259(61.4)	R	R					
Yes	163(38.6)	−170.9	−210.9, −130.8	0.000	−101.62	−0.225	−138.7, −64.5	0.000*
Baseline CD4$^+$T-cell count		0.3	0.1, 0.4	0.000	0.35	0.257	0.2, 0.5	0.000*

(*Continued*)

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Table 3 (Continued).

Variables		No (%)	Bivariate (Simple Linear Regression Analysis)			Multiple Linear Regression Analysis			
			Unstandardized B Coefficient	95% CI for B	P-value	Unstandardized B Coefficient	Standardized B Coefficient	95% CI for B	P-value
Viral load									
	Undetectable	233(55.2)	R	R					
	1–19	79(18.7)	4.7	−48.9, 58.3	−2.06	−0.004	−46.4, 42.3	0.927	
	20–999	40(9.5)	−36.1	−106.6, 34.3	2.23	0.003	−55.2, 59.6	0.939	
	≥1000	70(16.6)	−189.5	−245.7, −133.4	0.000	−137.53	−0.233	−185.9, −89.1	0.000*
Time duration on ART			15.3	7.9, 22.7	0.000	14.36	0.182	6.304, 22.4	0.001*

Notes: *Significant at (p <0.05).

Abbreviations: R, reference category; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; d4T, stavudine; 3TC, lamivudine; NVP, nevirapine; AZT, zidovudine; ABC, abacavir; ddI, didanosine; LPV/R, lopinavir/ritonavir; WHO, World Health Organization; ART, antiretroviral therapy.

is also a key factor to determine both the urgency of ART initiation and provision of prophylaxis for opportunistic infections.[64]

In this study, viral load was also found to be a significant predictor for the current $CD4^+$ T-cell count where women on ART with a viral load of ≥1000 copies/mm^3 had lower current $CD4^+$ T-cell count than those women with undetectable viral load. This finding agrees with other studies conducted in London[25] and Nepal.[54] These studies showed that maintaining virological suppression resulted in the restoration of current $CD4^+$ T-cell counts.[25,54] Moreover, ongoing HIV replication during treatment can lead to immunological failure, the emergence of drug resistance, limiting future treatment options, and possibly leading to a poorer prognosis.[65]

Duration on ART was also a significant predictor for current $CD4^+$ T-cell count, where for each additional year stay on ART, the current $CD4^+$ T-cell count increased. This study is consistent with a study conducted in Yaounde, Cameroon.[66] This could be explained by which the importance of maintaining virologic control and immunological recovery is based on the current status of HIV pathogenesis, in which continuous and uninterrupted ART regimen is needed to suppress viral replication, reconstitute the immune system and prevent disease progression.[67,68]

In the current study, baseline $CD4^+$ T-cell count was found to be significant, where for each increment of cells/mm^3 of blood in the baseline $CD4^+$ T-cell count, the current $CD4^+$ T-cell count increased. This finding is consistent with studies conducted in Felege Hiwot referral hospital,[22] University of Gondar referral hospital,[21,69] and Tigray Health Research Institute.[23]

The results of the current study have some limitations. First, since a retrospective cross-sectional study design was implemented, it cannot establish a cause and effect relationship between the predictor variables and dependent variable (current $CD4^+$ T-cell count). Second, the viral load test was not routinely performed in all public health hospitals because of the unavailability of the test. Despite these limitations, the result of this study may provide important information which will certainly be useful as an input for the HIV/ART programs.

Conclusion

In this study, the immunological failure was relatively low. Educational status, baseline WHO clinical stage, type of initial regimen, baseline adherence, opportunistic

infection, baseline $CD4^+$ T-cell count, viral load, and time duration on ART were significantly associated with current $CD4^+$ T-cell count. Therefore, maintaining adherence, early identification and treatment of opportunistic infections, and minimizing viral load to undetectable levels may further decrease immunological failure.

Abbreviations

ABC, abacavir; AIDS, acquired immune deficiency syndromes; ART, antiretroviral therapy; ARV, antiretroviral virus; AZT/3TC, zidovudine/lamivudine; CD4, cluster of differentiation 4; DDI, didanosine; EFV, efavirenz; HIV, human immune deficiency virus; LPV/R, lopinavir/ritonavir; NVP, nevirapine; OI, opportunistic infection; SOP, standard operational procedures; TDF, tenofovir disoproxil fumarate; VL, viral load.

Data Sharing Statement

All relevant data are included within the manuscript, but any additional data required are available from the corresponding author upon request. Email: Alex.sayihalem2018@gmail.com.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and after ethical clearance was obtained from the research directorate office of Mizan Tepi University (Ref No: MTU/CHS/12/342/12/08). Written consent was obtained from each study participant after explaining the purpose and objectives of the study. For those participants who were illiterate, a fingerprint was used as a signature after trained interviewers have carefully explained the purpose, benefits, and potential risks before consent were obtained. The interview with study participants was conducted with strict privacy and confidentiality. The test was also performed following the manufacturer's instructions and interpreted accordingly. Then, all necessary information and the results of each study participant were communicated with their physicians for further investigations and management.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

We declare that we have no conflict of interests.

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