

The Immunological and Clinical Progress of Adult HIV Positive Patients Who Were on Antiretroviral Therapy and Follow-Up for More Than Two Years: Retrospective Cohort Study at University of Gondar Comprehensive Hospital

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Abstract

Introduction: Antiretroviral Therapy (ART) shows a great impact on immunological restoration and viral load suppression in individuals living with the Human Immune Deficiency Virus (HIV). Currently, among 38.4 million individuals living with HIV in the globe, around 28.7 million are under ART. Good adherence and follow-up of ART treatment decrease the morbidity and mortality rates of HIV positive individuals and increase the quality of life. Although it is a retrospective cohort study, we aimed to assess how ART regimens influence the restoration of immunological and hematological parameters, and the clinical progression after 2 and half years of ART treatment and follow-up.

Methodology: Retrospectively, we reviewed the medical records of HIV patients. Based on our follow-up requirements, we collected the medical records of 320 HIV patients retrospectively and followed them for 2 and half years. All the socio-demographic data with immunological, hematological, BIM, and clinical data of HIV patients under follow-up were collected every six months for 30 months period. Data were entered into SPSS version 23 and graph pad prism version 5.1 (graph pad software, San Diego, CA). The data were described and statistically analyzed with simple frequency and repeated measures of ANOVA.

Result: Among the 320 HIV patients who followed, 61.9% were females. In this study, The CD4 T cell count showed significant improvement from the baseline to the 12th, 18th, 24th, and 30th month follow-up; from the 6th to 18th, 24th, and 30th month follow-up, and from 12th month to 24th and 30th month, indicating that ART significantly restored the immune response in HIV patients across the follow-up periods. The Body Mass Index (BMI) also showed similar significant improvement patterns with the CD4 T cell count. There was a significant improvement in the World Health Organization (WHO) clinical stage of HIV patients after follow-up as indicated by our result that the majority of HIV patients at baseline were at WHO stage III 168 (58.5%), however, after 2 and half year follow-up, only 16.3% remained at WHO stage III. In addition, at baseline (before initiation of ART), the proportion of HIV patients at WHO clinical stage I was only 12.8%, and that was increased to 44% at the end of the follow-up period. The burden of opportunistic infections also significantly decreased from 413.1% at baseline to 0.9% after follow-up. The hematological parameters such as total WBC count, platelet count, and hemoglobin levels were also significantly improved through the course of the follow-up periods.

Conclusion: Our study showed that good ART treatment and good follow-up of HIV management in patients with HIV can bring indispensable progress in their immunological, hematological, and clinical parameters.

Keywords: HIV, ART, CD4 T cell, WHO, Body Mass Index (BMI)

Abbreviation: ART: Antiretroviral Therapy; ADIS: Acquired Immune Deficiency Syndrome; BMI: Body Mass Index; CD: Cluster of Differentiation; HIV: Human Immune Deficiency Virus (HIV); WBC: White Blood Cell

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Introduction

Immunological restoration and viral load suppression are the fundamental advantages of Antiretroviral Therapy (ART) for people living with Human Immunodeficiency Virus (HIV) [1]. In the world, 38.4 million people are living with the Human Immunodeficiency Virus (HIV). From these, 28.7 million are on ART. In the African region, 25.6 million are with HIV and 78% are on ART treatment [2].

HIV targets the human immune system and weakens the infected individual immune defense mechanism, which in turn caused susceptibility to infections and certain types of cancers [3]. The successful implementation of ART treatment and follow-up in different socioeconomic status groups improves the life HIV positive individuals. It decreases the morbidity and mortality rate of people living with HIV and also reduces new infections [4].

The virus infects immune cells, especially certain cell that has CD4 markers like T-helper cells, monocytes, macrophages, glial cells, chromaffin cells, and Langerhans' cells [5]. The chemokine receptors; CCR5 and CXCR4 play a great role in the viral entry to the cell, the propagation of HIV infection, and the final progression of the ADIS disease [6].

The transmission of the virus is both through the release of a cell-free virus and cell to cell communication of the virus. Some studies indicated the mechanism of cell to cell transmissions, through the formation of HIV-1 infectious synapses, HIV-1 virological synapses, and synapse-independent cell-cell transmission. These cell to cell modes of transmission influence the generation and maintenance of latent features of the HIV-1 infection as well the generation of the pathogenesis of the virus [7-9]. To reduce this transmission, the World Health Organization recommends that people should start ART treatment as early as possible after they are diagnosed HIV positive. Based on this, all regions in the world including sub-Saharan countries like Ethiopia develop a guideline for early ART initiation [10].

Late ART initiation has a great impact on disease progression, transmission, and poor outcomes after ART initiation. In addition, poor follow-up and adherence to ART also caused the high rate of morbidity and mortality rate of HIV patients and other HIV associated diseases [11]. Poor follow-up and adherence of people with HIV treatment make immune improvement very slow and may cause virological failure, which finally may lead to the development of drug resistance [12].

On the other hand, HIV positive individuals with good adherence and follow-up had good immunological and Virological progression. It also reduces the mortality and morbidity associated with Acquired Immune Deficiency Syndrome (AIDS) [13]. WHO recommends an

early treatment initiation of ART for HIV positive individuals regardless of their age, CD4 count, and viral load? It is evidenced that ART had great benefits for HIV patients in many countries by reducing the morbidity and mortality of the disease [14].

It has been demonstrated that treatment of HIV-1 infected individuals with ART reduces the viral replication up to the non-detectable level of the virus in the plasma [15]. This helps to improve the CD4 T cell level, delays disease progression and promotes survival of the HIV positive individuals [16].

So HAART plays a great role in the reduction of morbidity and mortality in the HIV-1 infected population. Our study also confirmed the improvement of immunological and clinical conditions of HIV-1 infected individuals who are under ART and followed for more than two years.

Materials and Methods

Study design

A retrospective cohort study design was applied to review the medical records of HIV patients from the ART initiation up to more than two years of clinical follow-ups. The medical records of HIV-positive individuals were selected based on our study requirements. We selected 320 HIV patients' medical records that has proper follow-up for two and half years, with all the required clinical, immunological, and hematological data, and the data was collected every six months intervals, starting from the baseline (before the initiation of ART) up to two and half years on ART.

Data collection and analysis

The clinical, immunological, hematological, and drug regimen types were collected using data collection sheet forms from the medical records of HIV patients. All the data are transferred into SPSS version 23 and graph pad prism version 5.1 (graph pad software, San Diego, CA). Data completeness and cleaning were done by cross-checking with the data collection sheets.

Simple frequency analysis was done to show the social-demographic and clinical characteristics of study participants. The repeated measure of ANOVA followed by Turkey's multiple comparison tests was applied to see the significant changes in immunological, hematological, and BMI through the time interval under HAART management. A p-value less than 0.05 are considered significant.

Results

Socio-demographic characteristics

Among 320 medical records reviewed, the majority; (61.9%) were females. The median age with Interquartile Range (IQR) of the

participants was 38 (32-46) years. Around 74.1% of the participants came from urban areas and 40.9% were at the level of secondary education (Table 1).

Variables		Frequency
Sex	Male	122 (38.1%)
	Female	198 (61.9%)
Age	Median year (IQR)	38 (32-46)
Resident	Rural	83 (25.9%)
	Urban	237 (74.1%)
Educational status	No formal education	46 (15.3%)
	Primary education	88 (27.5%)
	Secondary education	131 (40.9%)
	Tertiary education	52 (16.3%)

Table 1. Socio-demographic characteristics of the study participants.

Clinical characteristics of HIV patients were improved after two and half years of HAART treatment

At the baseline (before ART drug initiations), 58.1% of HIV patients were at WHO stage III, 17.5% were at stage II, 11.6% were at stage IV and 12.8% were at stage I. However, after being linked to the ART clinic and taking ART drugs for two and half years, 44.1% of

HIV patients were at stage I, 39.1% were at stage II, 16.3% were at stage III and only 0.6% were at stage IV, indicating that the clinical condition (considering WHO staging as a parameter) has been improved dramatically after initiation of ART and follow-up. From the baseline of pre-ART status, 42 (13.1%) of the study were positive for opportunistic infections but throughout the follow-up in the ART clinic for two and half years the prevalence reduced to 3 (0.9%) (Table 2).

Characteristic	Time	WHO I	WHO II	WHO III	WHO IV
1. WHO stages	Baseline	41 (12.8%)	56 (17.5%)	186 (58.1%)	37 (11.6%)
	6 months	27 (8.4%)	79 (24.7%)	186 (56.9%)	32 (10.0%)
	12 months	29 (9.1%)	101 (31.6%)	164 (51.2%)	26 (8.1%)
	18 months	76 (23.8%)	128 (40.0%)	111 (34.7%)	5 (1.6%)
	24 months	96 (30.0%)	141 (44.1%)	77 (24.1%)	6 (1.9%)
	30 months	141 (44.1%)	125 (39.1%)	52 (16.3%)	2 (0.6%)
2. Opportunistic infection (OPI)		Negative		Positive	
	Baseline	278 (93.4%)		42 (13.1%)	
	6 months	299 (93.4%)		21 (6.6%)	
	12 months	320 (100%)		0 (0.0%)	
	18 months	313 (97.8%)		7 (2.2%)	
	30 months	317 (99.1%)		3 (0.9%)	
Type of ART drugs		AZT+3TC+NVP	AZT+3TC+EFV	AZT+3TC+ATV/r	AZT+3TC+NVP/r
	Baseline	-	-	-	-
	6 months	214 (66.9%)	89 (27.8%)	15 (4.7%)	1 (0.3%)
	12 months	215 (67.2%)	94 (29.4%)	10 (3.1%)	1 (0.3%)

18 months	217 (67.8%)	88 (27.5%)	13 (4.1%)	2 (0.6)
24 months	216 (67.5%)	91 (3.4%)	11 (3.4%)	2 (0.6)
30 months	212 (66.3%)	95 (29.7%)	11 (3.4)	2 (0.6)

Note: (AZT=Zidovudine, TC=Lamivudine, NVP=Nevirapine, EFV=Efavirenz, Ir=ritonavir)

Table 2. Clinical characteristics of the study participants.

Hematological profiles and BMI level of HIV patients was significantly improved after follow-up with ART treatment

The total White Blood Cell (WBC) count, Neutrophil count, Platelet count, and Hgb level as well as the BMI status of HIV patients were assessed, to see whether the HARRT treatment improved the hematological profiles and nutritional status of HIV patients within 2 and half years of follow-up. The mean total WBC count was significantly increased after 24 months of HAART treatment compared with the baseline (6.4×10^3 cell/ml vs. 5.82×10^3 cell/ml; $P < 0.05$) and 6 months follow-up (6.4×10^3 cell/ml vs. 5.86×10^3 ; $P < 0.05$). However, the mean neutrophil count was not significantly different in the baseline and across each follow-up period. The platelet count and the Hgb level significantly increased across the follow-up periods compared with their corresponding baseline levels. The platelet count shows a strongly significant difference from baseline to 24 months ($P < 0.0001$), and Hgb concentration shows the strongest significant change from the baseline to the 30th month ($P < 0.001$). Both the platelet count and Hgb level didn't show any significant difference starting from the six months of ART taking to the next 12th, 18th, 24th, and 30th months of ART follow-up (Figure 1), which might indicate that the platelet count and Hgb level restored to the normal level within the first 6 months once after HIV patients are under ART.

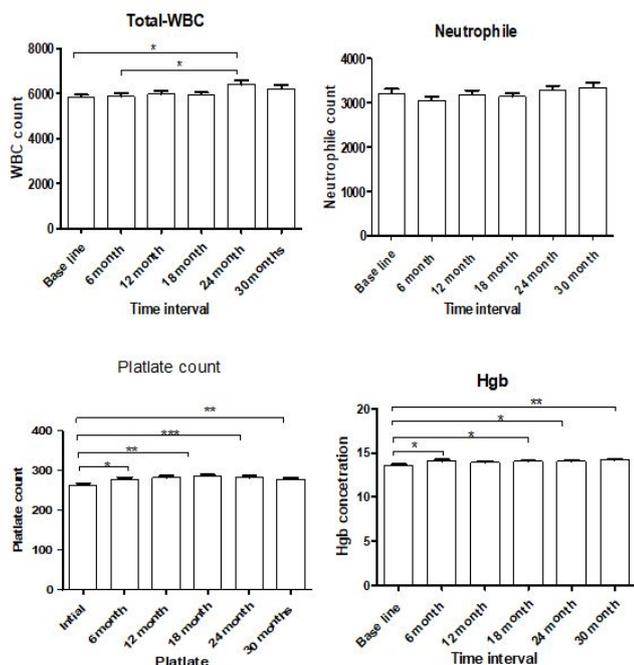


Figure 1. Total WBC, neutrophil and platelet count, and hemoglobin level within every six-month intervals for two and half years. (* $p < 0.05$), (** $P < 0.01$), (** $P < 0.001$)).

The CD4 T cell count was significantly improved after HARRT treatment and Follow-up

The CD4 T cell count was significantly improved in the follow-up periods of the 12th, 18th, 24th, and 30th months with ART treatment compared with the baseline. The level of CD4 T cell count was also significantly increased at the 18th, 24th, and 30th months of follow-up and HAART treatment compared with the 6-month CD4 T cell count). In the same pattern, the level of CD4 count at the 24th and 30th month follow-up periods was increased compared to the level of CD4 count from the 12th month period. Nevertheless, the CD4 T cell level from the baseline to the six months of measurement, and from the six-month to twelve-month measurement didn't show any significant change, which indicated that for the CD4 T cell count to be improved in HIV patients, there might need a longer period of HAART treatment and follow-up (Figure 2).

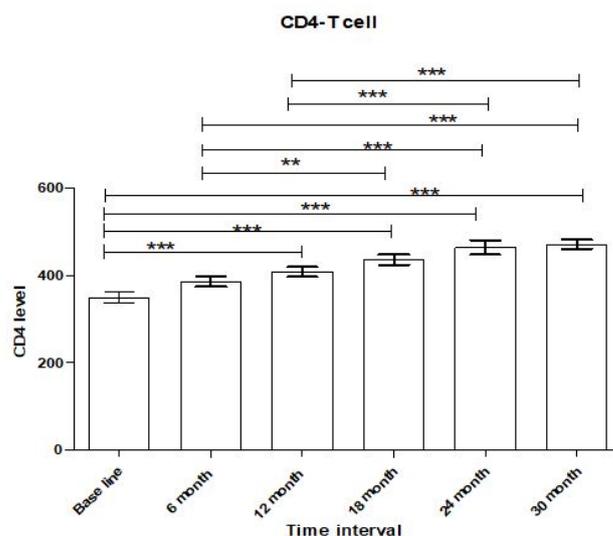


Figure 2. CD4 T cells count of the study participants within every six-month interval for two and half years. (* $p < 0.05$), (** $P < 0.01$), (** $P < 0.001$)).

The body mass index of HIV patients significantly increased after HARRT treatment and follow-up

One of the main parameters to monitor the nutritional status of HIV patients and usually utilized as a good indicator is the Body Mass Index (BMI) of the individual. In our study, the BMI level from the baseline to the next 6th, 12th, 18th, 24th, and 30th months of ART treatment showed a strong significant change in every six-month interval follow-up ($P < 0.0001$). The same pattern of BMI level increment was observed from the 6th month measurement to the next 12th, 18th, 24th, and 30th months of measurement with a strong significant level ($P < 0.0001$). On the other hand, the BMI level from the 12 months of measurement to the next 18 and 24 months of follow-up didn't show any significant change, however, the BMI level

showed significant improvement only at the 30 months of follow-up compared to 12 months follow-up period (Figure 3).

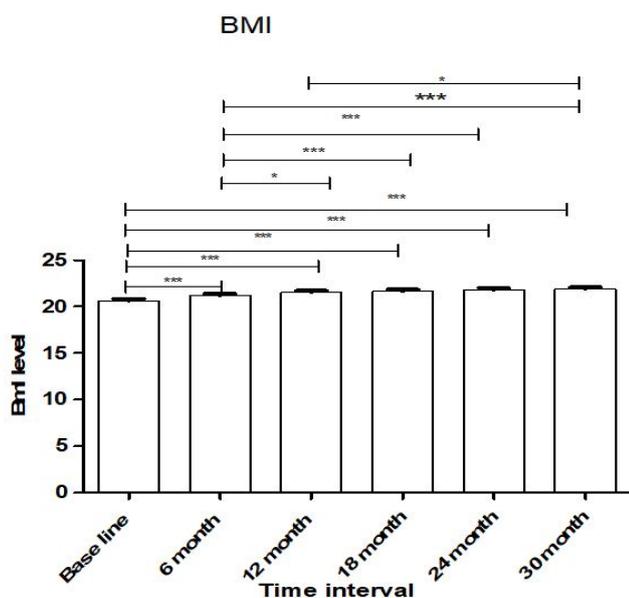


Figure 3. BMI level progression within two years on ART within every six-month intervals for two and half years. (* $p < 0.05$), **($P < 0.01$), ***($P < 0.0001$)).

Discussion

The development of good culture for fighting HIV/AIDS disease needs many aspects, like health education of the community, creating awareness about the mode of transmission and treatment, and proper treatment and adherence of HIV positive individuals. The treatment and management of HIV showed a great impact on reducing the morbidity and mortality of HIV positive individuals. The quality of life of HIV patients showed great progress after the development of ART [17].

Our retrospective cohort study also showed that ART is one of the big life changers for these people who have HIV in their blood. The immunological parameter (CD4 T cell), and hematological profiles (WBC count, platelet count, Hgb, and BMI levels) showed a significant improvement after ART initiations.

The immunological parameter, the CD4 T cell counts showed a significantly increased progression from the baseline to the next 12th, 18th, 24th, and 30th months of ART initiation and follow-up. From the 6th month follow-up to the next 18th, 24th, and 30th month of follow-up, and from the 12th month of follow-up to the next 24th and 30th months of follow-up. All the significant changes in the CD4 T cell count were achieved through HAART treatment for more than 6 months and above follow-up. It has been demonstrated that antiviral therapy could suppress the HIV RNA in the plasma of the patients [18,19]. The decrease in the HIV viral load increases Interleukin-2 (IL-2) producing T-cells, which could enhance the T cell proliferation and increase the absolute count of both memory and naive CD4 T cell [20]. All these immunological progressions are mostly achieved through good adherence to HIV treatment. The management of people with HIV, managing and treating opportunistic infections like oral candidiasis, chronic intestinal helminths infections, intestinal trophozoite infections, chronic diarrhea diseases, and other opportunistic infections. Treating HIV itself by HAART based on the national guideline.

Treating peoples with prophylaxis for diseases that will develop through immune compromisation like TB are the main factor for the progression of the immunological profiles of HIV patients.

Moreover, through adherence, council, and follow-up, HIV patients during their visit to the HIV clinic, serious attention to their nutritional status, and supplementing nutrition help to maintain the micronutrient levels like others in the patients. That makes maintains micronutrients in their system and helps to increase the production and the function of immune cells as well all hematological profiles in the presence of HIV in addition to viral suppression. Due to this, our study exhibits that the BMI level from the baseline to the next consecutive visits showed significant change in every six-month interval.

On the other hand, the level of CD4 T cells didn't show significant improvement from the baseline up to the 6th month follow-up. At the earliest time of treatment, the ART drugs may not reach all the tissue systems and the immune cells with HIV sanctuaries in these tissues. As a result, the rate of HIV replication may persist, and the viral load might remain high within the first 6 months of ART therapy as observed in this study. From the 6th month follow-up to the next 12th month follow-up, from the 12th month follow-up to the 18th month follow-up, and from the 18th month follow-up to the next 24th month follow-up CD4 T cells don't show any significant changes. This indicates more than six months of HAART taking showed significant progression of CD4 counts as well viral suppression. So high long time of good adherence is indispensable for better progress of the patients.

The WBC count, platelet count, and Hgb n level of the study participants showed a significant progressive improvement as we followed HIV patients from the baseline to the next follow-up periods. This finding has been demonstrated by different research. Most patients living with HIV showed anemia, leukopenia, and thrombocytopenia before HAART taking and follow-up. These clinical laboratory findings are utilized by clinicians for the better management of patients and for the treatment choice of ART drugs. One of the main pathogenesis of HIV is cytopenia since the virus can affect the different stages of the hematopoietic microenvironment and hematopoietic cells, which leads to decreased production of different populations of cells. In addition, the extracellular viral accessory protein Negative factor (Nef) and glycoprotein (gp) 120 can induce Peroxisome Proliferator-Activated Receptor-gamma (PPAR-γ) transcriptional factor in uninfected Hematopoietic Stem Cells (HSCs). This factor suppresses the Signal Transducer and Activator of Transcription-5A (STAT5A), and STAT5B, which have a big impact on the production of matured blood cells. All these causes make HIV positive individuals develop cytopenia and anemia, which are the main clinical feature of the disease pathogenesis.

In addition, early initiation of ART is one of the great factors for good progression of the immunological and hematological profiles of HIV patients, and to prevent other complications like malignancy, neurological disorder, and opportunistic infections. The immunological and hematological improvement through the course of ART treatment has been linked to the viral load reduction progressively from time to time in HIV patients who were under follow-up with ART treatment.

The BMI level showed significant improvement after ART treatment and follow-up. This is in line with previous studies which showed after ART initiation, the BMI level was significantly improved in HIV patients. Due to the improvement of the BMI of HIV patients, there WHO stage through the course of ART treatment showed an improvement. In this study, at the baseline from the total study participants, only 12.5% were at WHO stage one, however, after two and half years of ART follow-up 44.1% of the participants become at the WHO clinical stage one. Furthermore, at the baseline, 58.1% of the HIV patients were at WHO-III and 11.6% were at WHO-IV, and these proportions decreased to 16.3% for WHO-III, and 0.6% for WHO-IV, respectively. During HIV infection, there is catabolism, high inflammation, and the production of inflammatory cytokines. After initiation of HIV treatment, there is a decrease in inflammation and inflammatory cytokines, and significant weight gain is obtained. The opportunistic infection in our study participant is decreased throughout the follow-up periods from the baseline, which has a great role in the progression of BMI.

Conclusion

Our study showed that good ART treatment and good follow-up of HIV management in patients with HIV can bring indispensable progress in their immunological, hematological, and clinical parameters. This will have a great chance to reduce the mortality and morbidity of patients with HIV and increase the quality of life of the patients.

Limitations of the Study

The level of viral load is not included in the study because HIV viral load was not started in the study area during the initiation of ART, and the follow-up period.

Ethical Approval

Ethical clearance was obtained from the university of Gondar, school of biomedical and laboratory science research and ethical review committee. A permission letter was also obtained from university of Gondar comprehensive specialized hospital medical director. All the data collected during the study period was reviewed by HIV clinician for confidentiality.

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Availability of Data and Material

Not available

Author's Contribution

ML, and GB, conceived the idea, and analyzed the data. ML, ZG supervised the data collection. ML GB, AK, and YA participate the write up. ML, GB, YG, TT participate in participate supervision and manuscript preparation.

Competing Interest

All authors don't have any conflict of interests

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