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ORIGINAL ARTICLE

MAGNITUDE AND PREDICTORS OF ADEQUATE IMMUNOLOGIC RESPONSE IN SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE ART CLINIC, ADDIS ABABA, ETHIOPIA: A RETROSPECTIVE COHORT

Tewodros Getinet, MSc[1*], Yoseph Worku, MD, MPh[1], Fanna Adugna, MPh[1], Sisay Tanie, MSc[1]

ABSTRACT

Background*: One of the measures that can be used to assess effectiveness of antiretroviral therapy (ART) is a change in CD4 cells counts. The aim of this study is to determine the magnitude and factors associated with immunologic response (AIR) in Saint Paul's Hospital Millennium Medical College (SPHMMC).*
Methods: *A retrospective cohort study was conducted by recruiting individuals who were enrolled in SPHMMC ART clinic from September, 2011 to September, 2016. The data were extracted using abstraction tool adopted from the patient's chart, managed and analyzed using SPSS, Version 20.0. Descriptive summaries were used to understand describe study participants a characteristic of study participants and logistic regression was used to model the odds of having AIR. SPSS, Version 20.0. was used for data management and analysis.*
Result*: Among the total of 662 individuals that participated in this study 445(67.2%) had AIR. Disclosing HIV status (Adjusted Odds Ratio (AOR) =1.79 [95% Confidence Interval (CI): 1.16, 2.76]); increase in base line hemoglobin (AOR =1.14 [95% CI: 1.05, 1.24]); being stage II (AOR =2.66 [95% CI: 1.29, 5.45]); and having working functional status (AOR =1.84 [95% CI: 1.03, 3.29]) were associated with increased odds of having AIR. And attending primary education (AOR =.55 [95% CI: .31, .96]) and increase in baseline CD4 (AOR =.90 [95% CI: .84, .96]) were significantly associated with reduced odds of having AIR.*
Conclusion*: Disclosing HIV status increased the odds of having AIR by 79% and being in lower educational level reduce the odds of having AIR by 45%. The government and other concerned bodies should work in encouraging people living with HIV (PLHIV) to disclose their status and educating the community should be given attention.*
Key words: *Adequate Immunologic Response, ART, Ethiopia, HIV, SPHMMC.*

INTRODUCTION

Once a person gets infected with Human Immunodeficiency Virus (HIV), the virus multiplies primarily in the white blood cells. Through time, the virus damage or kill specific immune cells, and leaves the body vulnerable for other infections by weakening the immune system. The disease can be characterized by loss of significant amount of immune cells, mild and persistent swollen glands. Even though, an individual may look and feel healthy, the only way to be certain about one's status is to test for his/her HIV status (1, 2).

Globally, since the start of the epidemic, about 78 million people have been infected with HIV and 35 million people died from AIDS and related illnesses (1, 2). It is the leading cause of disease burden and major public health problem in sub-Sahara African countries (3-6). About 11.6 million estimated African children were orphaned (1, 7). Ethiopia, as one of these countries has been affected by the epidemic with a prevalence of 1.16 % (8).

Antiretroviral Therapy (ART), the only available treatment for HIV/AIDS, has dramatically reduced HIV related morbidity and mortality among HIV positive individuals (9, 10). Its introduction has altered the course of the HIV/AIDS epidemic (11-13). It also provides strong health benefits at both individual and population levels (14-16). After its introduction, new HIV infections (cases) declined by 33% between 2005 and 2013, globally (1, 17). Ethiopia has introduced ART program in 2003 and made it free of charge by 2005. And then the facilities providing ART services has expanded to health centers levels, enabling the enrolment of hundreds of thousands of AIDS patients free of charge (18, 19).

World Health Organization (WHO) has recommended initiation of ART in everyone living with HIV, regardless of CD4 count in 2015 (20). In Ethiopia by the year 2016, the number of PLHIV was 718,500, while patients who started ART were around 420,000. In the year 2017, 722,248 people were estimated to be living with HIV, and all of them were in need of ART (8, 21).

[1]Public Health Department, St Paul's Hospitals Millennium Medical College, Addis Ababa, Ethiopia.
*Corresponding author Email address: tedomanchu@gmail.com/tewodros.getinet@sphmmc.edu.et

After initiation of ART, its effectiveness can be measured with a change in CD4 counts. The change in CD4 count is the difference between base line CD4 and follow up CD4 counts. The base line CD4 count is the initial CD4 count measured when a patient isput on ART. There will be follow up CD4 counts measured after being enrolled on ART to assess immune system reconstitution. Therefore, there will definitely be a change in CD4 counts, that can be either negative, zero or positive. The drug controls the HIV infection by reducing viral replication in the body which in most cases measured by an increase in CD4 cells count (11, 22). With an effective ART, CD4 cell count may increase up to more than 50 CD4 cells /mm^3 within weeks after viral suppression (1, 23). It is recommended that after 3 months of treatment with ART, a patient should gain 50–150 CD4 cells/mm^3 per year, and an increment below this range could imply poor response to the treatment (24, 25).

To the investigators knowledge, there is no literature that documented the magnitude and predictors of AIR in the study setting. Therefore, the aim of this study is to estimate the magnitude and identify predictors of AIR among PLHIV who are enrolled in SPHMMC ART clinic.

METHODOLOGY

Study Area and Period

The study was conducted in SPHMMC which is the second largest hospital in Ethiopia. It is located in the North West parts of Addis Ababa (capital city), Gulele Sub City. The hospital was established in 1968 with the aim of providing clinical service for low income families. Currently, the hospital hosts a 10 years young medical college which makes it a teaching hospital. The hospital provides clinical service for people living in and outside Addis Ababa, and 40% of its clinical clients are from Oromia region. The data collection for the current study took 5 months (Dec., 2017 to April, 2018).

Study participants

All PLHIV whose age was at least 15 years, were enrolled in SPHMMC ART clinic and started ART from September, 2011 to September, 2016.

Study Design

We used a retrospective cohort study design to investigate factors associated with AIR among PLHIV patients who initiated ART.

Sample Size

All adult PLHIV (i.e. aged 15 years and above) who started ART in SPHMMC ART clinic in the period September, 2011 to September, 2016.

Data Collection

Nurses working in the ART clinic collected the data using a data abstraction sheet adopted from the chart in the clinic. The patient chart used as the source document had information on socio demographic variables, clinical information, and follow up measures.

Study Variables

Outcome Variable: Immunologic Response of study participants (Response categories: Adequate versus Inadequate)

Independent Variables: Gender, Age, Marital Status, Level of Education, Past History of Tuberculosis(TB), base line Body Mass Index(BMI), base line Hemoglobin, base line WHO Clinical Stage, Sharing HIV Status, Base line Functional Status, Current Substance Use, Base line CD4, baseline Evidence of TB.

Standard / Operational Definitions

Adequate Immunologic Response: If a PLHIV gain an increment of greater than or equal to 50 CD4 cells/mm^3 between base line and the six month CD 4 cell count after initiation of ART (24, 25).

Inadequate Immunologic Response: If a PLHIV gain an increment of less than 50 CD4 cells/mm^3 between base line and the six month CD 4 cell count after initiation of ART (24, 25).

Data Quality Management

We trained data collectors and the data extraction was pre-tested. The investigators supervised the data collection, checked the data for completeness and accuracy before leaving the actual data collection site. To minimize entry error we used double entry.

Data Analysis

The data collected were managed and analyzed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Descriptive statistics like; frequencies, percentages, mean with standard deviation (SD), median with inter quartile range (IQR) and graphs were used to summarize characteristics of study participants. We used logistic regression assess variables which are significantly associated with the odds of having AIR. First, a simple binary logistic regression was fitted for each of the independent variables to select potential predictors for the multiple binary logistic regression.

And predictors with a p-value ≤ 0.2 were considered for the multiple binary logistic regression. Findings with p-value of < 0.05 were reported as being statistically significant.

Ethical Consideration

The proposal was approved by the Institutional Review Board (IRB) of SPHMMC. A support letter was written to the ART clinic, and permission was obtained from the clinic head. Privacy and confidentiality was maintained by not exposing individual identifiers, not transferring the data to the third party and by using the data only for the research purpose.

RESULT

Description of ART Patients by different Characteristics

There were 1,113 PLHIV who initiate ART in SPHMMC ART clinic during September, 2011 to September, 2016. Of these 662 (59.5%) satisfied the study inclusion/exclusion criteria and had complete information.

Mean (SD) age was 36.16 (9.46) years and the range was 15 to 70. Among the study participants, 411(62.1%) were females, 292(44.1%) were married, of 497(75.1%) attended up to secondary education, 583(88.1%) said they had no past history of TB, 548(82.8%) disclosed their HIV status either for family or friend and 563(85%) did not use substance currently **(Table 1)**.

Table1: Baseline Characteristics of ART Patients in SPHMMC, Addis Ababa, Ethiopia, 2011-2016 (n=662)

Variables	Categories	n (%)
Gender	Male	251(37.9)
	Female	411(62.1)
Marital Status	Never Married	155(23.4)
	Married	292(44.1)
	Separated	29(4.4)
	Divorced	102(15.4)
	Widowed	84(12.7)
Level of Education	No formal Education	80(12.1)
	Primary	247(37.3)
	Secondary	250(37.8)
	Above Secondary	85(12.8)
Past History of TB	Yes	79(11.9)
	No	583(88.1)
HIV Status Disclosure	Yes	548(82.8)
	No	114(17.2)
Substance Use	Yes	99(15.0)
	No	563(85.0)
BMI	< 18.5	132(19.9)
	18.5-24.9	432(65.3)
	25-29.9	80(12.1)
	≥ 30	18(2.7)
WHO Clinical Stage	I	204(30.8)
	II	112(16.9)
	III	266(40.2)
	IV	80(12.1)
Functional Status	Working	589(89.0)
	Ambulatory	57(8.6)
	Bed Ridden	16(2.4)

At baseline 432 (65.3%) study participants had normal (18.5-24.9) body mass index (BMI), 266(40.2%) were at WHO clinical stage III, and 589(89%) had working functional status (**Table 1**). The median base line CD4 (IQR) was 172.50(90.75, 267.00) and median baseline Hemoglobin (IQR) was 13.20(12.00, 14.30).

Magnitude of Adequate Immunologic Response among the different Characteristics of ART Patients

The magnitude of AIR was 67.2% (445/662), among PLHIV, 153(23.11%) had AIR in the range 50–150 CD4 cells/mm^3 after six months of ART initiation (**Figure 1**).

In all the characteristics of PLHIV the magnitude of AIR is higher except in case of base line functional status, and base line CD4 status; where 6(37.5%) of bedridden and 35(49.3%) of PLHIV with CD 4 cell count of at least 350 cells/mm^3 has AIR. There was no significant gender difference (male: 166(66.1%); Females: 279(67.9%)) (**Table 2).**

patients put on ART were 379(69.2%) among PLHIV who disclosed their HIV status either to family or friend, 59(73.8%) among PLHIV without formal education, 205(70.2%) among married PLHIV, 394 (67.6%) among PLHIV with no past history of TB, and 382(67.9%) among substance non-users (**Table 2)**.

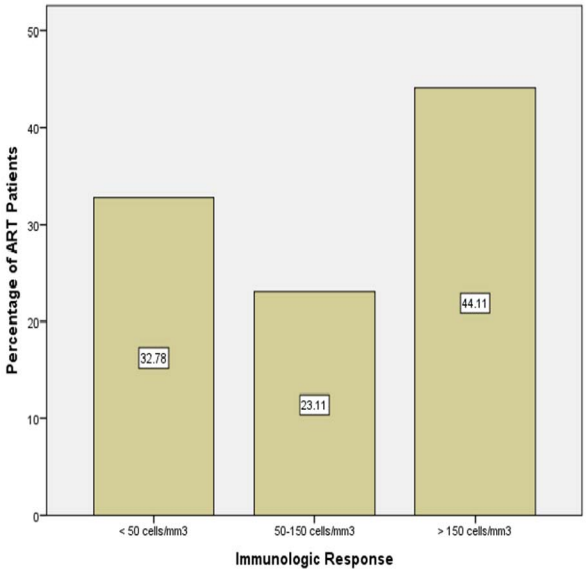

Figure 1: Immunologic Response of ART Patients in SPHHMC ART Clinic, Addis Ababa, Ethiopia, 2011-2016 (n=662)

Table2: Cross tabulation of Immunologic Response with Baseline Characteristics of ART Patients in SPHMMC, Addis Ababa, Ethiopia, 2011-2016 (n=662)

Variables	Categories	Immunologic Response	
		Adequate n (%)	Inadequate n (%)
Gender	Male	166(66.1)	85(33.9)
	Female	279(67.9)	132(32.1)
Marital Status	Never Married	98(63.2)	57(36.8)
	Married	205(70.2)	87(29.8)
	Separated	19(65.5)	10(34.5)
	Divorced	66(64.7)	36(35.3)
	Widowed	57(67.9)	27(32.1)
Level of Education	No formal Education	59(73.8)	21(26.2)
	Primary	151(61.1)	96(38.9)
	Secondary	173(69.2)	77(30.8)
	Above Secondary	62(72.9)	23(27.1)
Past History of TB	Yes	51(64.6)	28(35.4)
	No	394(67.6)	189(32.4)
HIV Status Disclosure	Yes	379(69.2)	169(30.8)
	No	66(57.9)	48(42.1)
Substance Use	Yes	63(63.6)	36(36.4)
	No	382(67.9)	181(32.1)
BMI	< 18.5	83(62.9)	49(37.1)
	18.5-24.9	293(67.8)	139(32.2)
	25-29.9	57(71.2)	23(28.8)
	≥ 30	12(66.7)	6(33.3)
WHO Clinical Stage	I	143(70.1)	61(29.9)
	II	88(78.6)	24(21.4)
	III	168(63.2)	98(36.8)
	IV	46(57.5)	34(42.5)
Functional Status	Working	409(69.4)	180(30.6)
	Ambulatory	30(52.6)	27(47.4)
	Bed Ridden	6(37.5)	10(62.5)

Predictors of adequate immunologic response

Summary findings from logistic regression are presented in **Table 3**. Education Level, HIV status disclosure, Baseline WHO Clinical Stage, Baseline Functional Status, Baseline CD4 and Baseline Hemoglobin have a p-value ≤ 0.2, which makes them candidate for the multiple binary logistic regression.

Table 3: Baseline Predictors of adequate immunologic response among ART patients in SPHMMC ART clinic, Addis Ababa, Ethiopia, 2011-2016 (n=662)

Variables	Categories	COR(95%CI)	p-value	AOR(95%CI)	p-value
Age		.99 (.97, 1.01)	.278		
Gender	Male	.92 (.66, 1.29)	.642		
	Female	1			
Marital Status			.619		
	Never Married	.81(.46, 1.43)	.474		
	Married	1.12(.66, 1.88)	.680		
	Separated	.90(.37, 2.19)	.817		
	Divorced	.87(.47, 1.60)	.651		
	Widowed	1			
Level of Education			.061*		.032**
	No formal Education	1.04(.52, 2.08)	.907	1.16(.56, 2.37)	.695
	Primary	.58(.34, 1.00)	.052	.55(.31, .96)	.036**
	Secondary	.83(.48, 1.44)	.515	.75(.42, 1.32)	.318
	Above Secondary	1		1	
Past History of TB	Yes	.87(.53, 1.43)	.591		
	No	1			
HIV Status Disclosure	Yes	1.63(1.08, 2.47)	.020*	1.79(1.16, 2.76)	.008**
	No	1		1	
Substance Use	Yes	.83(.53, 1.29)	.410		
	No	1			
BMI			.618		
	< 18.5	.85(.29, 2.40)	.755		
	18.5-24.9	1.05(.39, 2.87)	.918		
	25-29.9	1.24(.42, 3.69)	.701		
	≥ 30	1			
WHO Clinical Stage			.006*		.021**
	I	1.73(1.02, 2.96)	.044	1.70(.89, 3.25)	.107
	II	2.71(1.44, 5.10)	.002	2.66(1.29, 5.45)	.008**
	III	1.27(.76, 2.11)	.362	1.25(.70, 2.22)	.450
	IV	1		1	
Functional Status	Working	2.34(1.43, 3.82)	.001*	1.84(1.03, 3.29)	.040**
	Ambulatory/Bed Ridden	1		1	
CD4??		.95(0.90, 1.01)	.091*	.90(.84, .96)	.001**
Hemoglobin		1.14(1.06, 1.23)	.001*	1.14(1.05, 1.24)	.002**

?? Baseline CD4 is divided by 50 * p-value ≤ 0.2 ** p-value < 0.05

All variables included in multiple logistic regression model were significantly associated with the AIR (p-value < 0.05). Being in stage I or III was not significantly different compared to being in stage IV in terms the odds of having AIR, whereas, there was a significant difference between II Vs IV (**Table 3**).

DISCUSSION

The study revealed that slightly above two-third of PLHIV had AIR. Educational status; disclosing HIV status; baseline CD4; base line functional status; baseline haemoglobin; and base line WHO clinical stage were significant predictors of AIR. Gender, Age and marital status were not significant predictors of AIR.
In this study, slightly above two-third of PLHIV had AIR, which was somehow high compared to some studies (6), where about 60% of PLHIV had immunologic response in the six month period. The finding indicates that there is a better improvement in the program effectiveness; this justification can be ascertained by looking the previous findings where it focused on any increase in CD 4 in the past six month, while the current study focused on adequate increase in the same period.

Gender was not a significant predictor of immunologic response which was in line with the findings of some studies (6, 26); it may be due to the fact that the studies were from the same country with the current study in contrast with other studies (1); conducted in other countries. Age was also not significant which was in contrast with previous findings (1, 6, 26); it may be due to the fact that the current study focused on adequate changes, while the other studies focused on any changes. Marital status has no effect on immunologic response which is in line with a previous finding (1); it may be due to the fact that the studies were done in capital cites and in contrast with the other finding (26); which is conducted out of the capital city. Therefore, program people in the study setting should serve PLHIV irrespective of their gender, age and marital status, while learning from other literatures as well.

In this study, educational status was found to be significant predictor of immunologic response which was in line with the findings of another study (26). The chance of AIR for those completed only primary education was .55 times less likely compared to those who completed above secondary education. That is PLHIV who completed only primary level education had 45% lower odds of AIR compared to PLHIV who completed above secondary level education. This may be due to the fact that PLHIV who were at lower educational level, may not have enough awareness to the treatment and its adherence which has impact on treatment response. Disclosing HIV status was a significant predictor of immunologic response. The chance of AIR for those who disclose their HIV status either to family or friend was 1.79 times higher compared to those who did not disclose. That is disclosing HIV status increases the chance of AIR by 79%.

Disclosing status takes off the stress from the PLHIV and it avoid fear of attending ART clinics at the same time it may boost support from relatives, which have great Psychological effect and encourage PLHIV to adhere and continue with the treatment.

This study revealed that baseline CD4 was a significant predictor of immunologic response which was in line with (6, 26), for every one unit (50 CD4 cells /mm^3) increase in the baseline CD4, the odds of AIR is 0.90 times less. That is, for every one unit increase in the baseline CD4, the odds of AIR decrease by 10%. It does not mean that having good base line CD4 does not help for immunologic response, but this study focused on adequate responses, that needed higher change in CD4 within six months of period and such kind of higher treatment response was expected in those PLHIV with lower base line CD4. Baseline hemoglobin was found to be significant predictor of immunologic response, this finding was in line with that of the previous study (26). For a unit increase in baseline hemoglobin, the chance of AIR is 1.14 times higher. That is a unit increase in baseline hemoglobin will increase the chance of AIR by 14%. The base line haemoglobin level plays a crucial role in getting fast and adequate treatment response.

The base line WHO clinical stage had significant effect on immunologic response, which was in line with (26). The chance of AIR for stage II is 2.66 times higher than stage IV. That is, being in stage II has a high chance of AIR. Base line functional status had also a significant effect on immunologic response which was in line with the findings of previous studies (6, 11, 26) and in contrast with that of another study (1). The chance of AIR for baseline working status is 1.84 times higher as compared to baseline ambulatory/bed ridden status. That is, being in working functional status at baseline increases the chance of AIR by 84%. PLHIV who are at early stage of the disease are more likely to be in working functional status, and those in working functional status are more mentally as well as physically active. Being mentally as well as physically active facilitates treatment response.

This study had some limitations; the use of SPSS limited us from estimating the relative risk (incidence ratio) as it is the good measure of risk for cohort study. Some of the information relied on self response of participants which may liable to response bias (substance use; disclosure of HIV status).

Data obtained in this study were from a single hospital this may affect the generalizability of the results the community and other lower level hospitals/ clinics that may have different set up with the study setting (Tertiary level Hospital).

Conclusion and Recommendation

In this study, about two third of PLHIV had AIR. Education Level, HIV status disclosure, Baseline WHO Clinical Stage, Baseline functional status, Baseline CD4 and Baseline Hemoglobin were significant predictors of immunologic response. Disclosing HIV status, increase in baseline hemoglobin, being stage II and working functional positively influence AIR. While, attending primary education and increase in baseline CD4 negatively influence AIR. The government and other concerned bodies should work in encouraging PLHIV to disclose their status, educating the community about the use of ART and introduce guidelines for early initiation of ART and monitor its adherence.

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Competing interests

The authors declare that this manuscript was approved by all authors in its current form and that no competing interest exists.

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