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Trends of Immuno-virological Response Among HIV-Infected Patients Receiving Highly Active Anti-retroviral Therapy at Hawassa, Southern Ethiopia

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Abstract: Background: Immunological and virological response evaluation is one of a critical tool for assessing treatment outcome, regimen change and patient's management. However, data concerning any change in immunological and virological response in HIV infected patients using anti-retroviral treatment (ART) is scarce in Ethiopia. Method: This retrospective cohort study was conducted from April 2010–September 2013 at ART clinic of Hawassa University referral hospital. A total of 86 HIV-infected patients receiving Tenofovir, Stavudine and Zidovudine based regimen with either of Efavirenz or Nevirapine during ART initiation. Lamivudine is common for all. Adequate immune-virological response for most patients under treatment is defined as an increase in CD4 cells of 50–150/µl per year and viral load (VL) drops to undetectable level (<150 copies/ml) after ≥ 6 months of ART. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) Version 20. Results: mean CD4+ cells count shows significant increment at 6, 12, 18 and 24 months after ART treatment among patients having VL <5 (log10) compared to those VL ≥5 (p=0.04; 0.002; < 0.0001; 0.001) respectively. Female have insignificantly better Mean CD4+ cells throughout 24 months. Also patients over 50 years of age do show an immune response after ART initiation. But, in relative to younger patients, their CD4 cells recovery is insignificantly sluggish. CD4+ cells and body weight of concordant positive responders show significant rising trend at 6, 12, 18, 24 months when compared to discordant responders + concordant non-responders (0.003 vs. 0.05; <0.0001 vs. 0.04; 0.001 vs.0.008; 0.001 vs.0.03) respectively. Moreover logistic regression models were applied and significant factors associated with discordant immuno-virological response were patient's body weight (AOR=0.14; 95% CI: 0.03-0.7; p=0.02) and residence (AOR=20.3; 95% CI: 2.2-188; p=0.008). Conclusion: Immuno-virological response evaluation is a critical tool for assessing treatment outcome, regimen change and patient's management and the response trend decision should include both CD4+ cells and viral load results concurrently.

Keywords: Immuno-virological Response, ART, HIV, Hawassa, Ethiopia

1. Introduction

Even though, the absence of curative therapy for Human Immunodeficiency Virus (HIV) /acquired immunodeficiency syndrome (AIDS), the introduction of antiretroviral therapy (ART) has seen a decline in the morbidity and mortality associated with HIV infection in the worldwide [1, 2]. This is a consequence of the ability of ART to suppress HIV viraemia to undetectable levels and allow immune restoration, resulting in an increase in circulating CD4 cells [3]. Current antiretroviral therapy (ART) is highly effective in dropping the viral load of the HIV to undetectable levels and providing a consistent increase in the number of CD4+ T lymphocytes [4, 5]. Patient responses and clinical diagnostic measures to ART show differences based on individual, population

characteristics and the type of setting where treatment is delivered [6]. The immunological response in a successful ART is judged by an increase in CD4 cells of 150–200/µl in the first year and then more progressively [7]. An adequate immunological response for most patients under treatment is defined as an increase in CD4 cells of 50–150/µl per year, generally with quicker response during the first 3 months [8]. Whereas appropriate adherence to ART, is expected to be the viral load (VL) drops to undetectable level (<150 copies/ml) after ≥ 6 months of ART [9]. In practice, not all ART patients attain the desired concordant response of viral suppression with CD4 cell count increase; but around 20 - 40% of patients do not show a significant increase in CD4 cell count despite viral suppression [10]. Discordant immune response may arise either as a result of failed immune reconstitution or the excessive destruction of CD4 cells and it consequences of developing AIDS and even it may leads to death [10, 11].

Immunological and virological response evaluation is one of a critical tool for assessment of treatment outcome, regimen change and patient's management. Therefore, this retrospective cohort study aimed to assess the trends of immunological and virological response among HIV-infected patients receiving ART at Hawassa University Referral Hospital, Southern Ethiopia

2. Methods

2.1. Study Setting and Study Population

Hawassa University teaching Hospital is a referral hospital and it was established in November, 2005. It serves for more than 10 million people and provides health services for populations of south nations and nationalities regions (SNNPR) and others. In addition this hospital is one of the health facilities which provide ART service for HIV infected patients in the region.

Criteria to include records of eligible cases were age ≥18 years, receiving ART for a minimum of 24 months and have a good ART adherence (adherence rate ≥ 95%). In addition records of the eligible cases must have five consecutive CD4+ cells count and three consecutive viral load results starting from baseline of ART commencement. Female patients with history of pregnancy were excluded.

2.2. Study Design

This retrospective cohort study was conducted from April 2010 to September 2013 among HIV infected patients using ART at Hawassa University referral hospital, Hawassa, Southern Ethiopia.

2.3. Data Collection and Assessment

2.3.1. Data Collection

Demographic, clinical, laboratory results and other related data were extracted from each eligible patient card by using a standard format.

2.3.2. Outcome Assessment

Immune response was defined as a minimum absolute increase in the CD4 cell count minimum 50 cells/µl within 6-12 months after ART initiation [8]. Viral suppression was defined as a VL become <150 copies/ml or undetectable after ≥6 months of ART initiation [9].

Therefore, depending on clinical practices the immuno-virological responders were categorized in to three groups through CD+ cells count and VL level within 6-12 months after ART commencement:-

1. Concordant responders (VL<150copies/ml and CD4+ cells increase ≥ 50/µl)
2. Concordant non-responders (VL >150copies/ml/CD4+ cells increase < 50 cells/µl)
3. Discordant responders which is sub divided as immunological non-responders (VL >150copies/ml and CD4+ cells increase ≥ 50/µl) or (VL <150copies/ml and CD4+ cells increase <50 cells/µl), in comparison with baseline values [12, 13, 14].

Finally every six month change in CD4+ cells count was calculated for each individual patient as: (concentration [X month after ART initiation] – concentration [A month]). Moreover percentage change was calculated for each individual patient as: ((concentration [X month after ART switch] – concentration [A month]) / concentration [switch baseline]) X100, adopted from van Leth F et al., 2004 [15].

2.4. Statistical Analysis

Data entry and Database management was completed using EPI-INFO 2002. Statistical analyses were done using Statistical Package for Social Sciences (SPSS) Version 20. Categorical variables were summarized as frequencies and percentages while mean values and standard errors were tabulated for normally distributed variables. Median values and interquartile range (IQR) were tabulated for skewed variables. Chi-square test and fisher exact test were used for categorical variables while comparison of quantitative variables at the ART initiation to every six month was analyzed with student *t*-test or Mann-Whitney *U*-test for those variables did not follow normal distribution. The alpha level was set at 5% for significance.

2.5. Ethical Considerations

The study was approved by the institutional review board (IRB) of Hawassa University College of Medicine and Health Science.

3. Results

3.1. Socio-demographic and Behavioral Characteristics of the Study Participants

A total of 86 participants were met the inclusion criteria. The mean age of the study subjects was 33±10.5 years (females 31.4±10.2 and males 35.6 ±10.7); with the minimum and maximum ages were 18 and 60 years. According to WHO definition, first-line HAART regimens

were combinations of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 non nucleoside reverse transcriptase inhibitors (NNRTIs). NRTIs backbone drugs are Stavudine (d4T), Zidovudine (AZT), Tenofovir (TDF) and lamivudine (3TC); whereas NNRTIs are Efavirenz (EFV) and Nevirapine (NVP). All regimens included lamivudine (3TC). The number of patients on d4T/3TC/EFV, ZDV/3TC/EFV, and TDF/3TC/EFV regimens were 1(1.1%), 7 (8.1%) and 66(76.7%) respectively; whereas patients on ZDV/3TC/NVP, and TDF/3TC/NVP were 4(4.7%) and 8 (9.3%) respectively. Furthermore baseline median CD4+cells count was 160 with the IQR of 107-203 cells/µl; and Socio-demographic and other characteristics are described in table-1.

Table 1. *Characteristics of the study population at Hawassa University referral hospital, Hawassa, southern Ethiopia.*

Characteristics	No (%)	Characteristics	No (%)
Sex = female	54(62.8)	Opportunistic infections (OIS)	
Male	32(37.2)	No	34(39.5)
Age in years		Tuberculosis	21(24.4)
≤ 20	12(14.0)	Herpes zoster	10(11.6)
21-30	35(40.7)	Oral Candidasis	5(5.8)
31-40	22(25.6)	Herpes simplex	2(2.3)
41-50	10(11.6)	Pneumonia and others	14(16.3)
>50	7(8.1)	Risk factors HIV infections	
Educational status		No	70(81.4)
Illiterate	15(17.4)	Casual partners	10(11.6)
Primary	34(39.5)	Soft/hard drugs	2(2.3)
Secondary	29(33.7)	Alcohol + khat chewing	2(2.3)
Tertiary	8(9.3)	Tobacco + alcohol	2(2.3)
Marital status		Condom use	
Single	16(18.6)	Never use	66(76.7)
Married	50(58.1)	Rarely	19(22.1)
Separated	3(3.5)	Always	1(1.2)
Widow/widower	12(14.0)	Baseline CD4+ count in cells/µl	156(71.1)
Divorced	5(5.8)	< 100 cells/µL	19(22.1)
WHO clinical stage		100-200 cells/µL	45(52.3)
I	9(10.5)	>200 cells/µL	22(25.6)
II	30(34.9)	Baseline Viral load, log_{10} mean (SD)	5.3(0.75)
III	40(46.5)	< 5	29(33.7)
IV	7(8.1)	≥5	57(66.3)
Residence			
Rural	21(24.4)		
Urban	65(75.6)		

WHO, world health organization; SD, standard deviation; HIV, human immunodeficiency virus

3.2. CD4+cells Count in Relation to Baseline Viral Load Level

The mean CD4+ cells of month-6, 12, 18 and 24 were significantly higher in VL<5log group when compared with VL ≥5log group; p value: 0.04, 0.002, <0.0001 and 0.001 respectively. Also change in month -12 and 24 were significantly higher in patients with VL<5log group (table-2). More over there were no significant deference in females vs. males regarding mean VL (log_{10}) during baseline ART of treatment (5.2 vs. 5.5; p=0.07) respectively and patients with age ≥ 50 had insignificantly higher viral load compared to age <50 (5.4 vs.5.3; p=0.83) respectively.

Table 2. *Comparison of CD4+ cells in relation with baseline viral load level at Hawassa University referral hospital, Hawassa, southern Ethiopia.*

	Based on baseline viral load level (log_{10})		
Variable	**VL*< 5**	**VL*≥5**	**P value**
CD4+count in cells/µl (mean, SE)			
CD4+cells (0 month)	172(10.3)	149(10.2)	0.16
CD4+cells (6 month)	309(27)	249(14.4)	*0.04*
CD4+cells (12 month)	357(26.3)	260(17.1)	*0.002*
CD4+cells (18 month)	417(25)	299(18.9)	*<0.0001*
CD4+cells (24 month)	452(28)	319(22.6)	*0.001*
Change in CD4+cells at 6 month	136(25.7)	100(13.8)	0.17
Change in CD4+cells at 12 month	185(24.1)	111(16.3)	0.01
Change in CD4+cells at 18 month	59.9(14.3)	38.2(12.3)	0.28
Change in CD4+cells at 24 month	279.8(28.6)	170(22.9)	0.005
Percent change in CD4+count at 6 month	98.1(22)	1.3(25.4)	*0.44*
Percent change in CD4+count at 12 month	26.7(10)	43.3(5.7)	*0.13*
Percent change in CD4+count at 18 month	23.8(6.1)	9.4(4.7)	*0.53*
Percent change in CD4+count at 24 month	33.3(10.2)	7.7(3.7)	*0.77*

SE, standard errors; VL, viral load

3.3. Trends of 24 Months CD4+ Cells Count

CD4+ cells count was higher among females when compared with males but not significant. The CD4+ count was insignificantly higher among patients with age of ≤ 50 years old except CD4+ count of baseline.

Also patients with oral candidasis and Herpes zoster infection have insignificantly higher mean CD4+ cells at ≥ 6 months of ART treatment when compared non-infected cases. Conversely TB-non infected patients and patients using NVP based regimens have higher CD4+cells count (table-3).

Table 3. *Trends of CD4+ cells count in some independent variables at Hawassa University referral hospital, Hawassa, southern Ethiopia.*

	CD4+ cells (Mean, SE)					CD4+ count, % change (Mean, SE)			
Variable	**Month 0 (Baseline)**	**Month6**	**Month 12**	**Month 18**	**Month 24th**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Sex= Female	164(8.5)	275(17)	306(19)	357(19)	382(23.5)	1.0(21.4)	16(6.4)	32.8(9.7)	5.9(3.5)
Male	144(82)	259(21)	271(25.7)	308(28)	334(31.4)	1.4(33.7)	12.7(8)	25.5(9.8)	12(5.1)
P value	0.20	0.55	0.26	0.14	0.22	0.34	0.76	0.62	0.30
Age ≤50year	155(8)	274(14.8)	298(16.8)	342(18)	371(21)	1.2(20.4)	15(5.6)	31(7.9)	9.5(3.1)
>50 year	169(24)	235(24.6)	255(24.6)	312(42)	313(42.5)	67.3(26)	13.5(10)	23(8.4)	-1.1(7)
P value	0.55	0.36	0.37	0.55	0.33	0.32	0.93	0.71	0.24
TB = No	162(8.4)	281(16)	298(17.4)	344(19)	373(22)	1.0(17.9)	13.2(5)	24(5.9)	8.7(3.5)
Yes	140(17)	232(21)	277(31)	322(31)	336(35)	1.6(51)	19.7(14)	48(22.3)	6.8(4.8)
P value	0.23	0.11	0.56	0.55	0.41	0.23	0.59	0.14	0.78
HZ = No	157(8.4)	266(14.4)	290(16.3)	331(17)	359(20)	1.2(20.5)	16(5.7)	68(7.8)	9.2(3.1)
Yes	153(18)	297(36)	314(41)	393(44)	402(56.3)	1.1(26.3)	4.8(6.4)	43.9(14)	1.0(8.9)
P value	0.88	0.45	0.62	0.22	0.47	0.83	0.48	0.84	0.36
Candida= No	157(7.8)	267(12.4)	289(14.6)	336(16)	363(18.6)	1.1(18)	12.9(5.1)	29.7(7.3)	8.8(3)
Yes	149(44)	308(124)	353(117)	370(112)	372(133)	1.2(90)	45.2(27)	37.7(30)	-0.8(14)
P value	0.80	0.48	0.33	0.63	0.91	0.99	0.14	0.79	0.44
NNRTI=EFV	150(8.1)	260(14.4)	282(16)	334(18)	366(21)	1.2(21)	14.4(4.9)	32.9(7.9)	10(3.2)
NVP	193(21)	327(34.8)	357(43.4)	368(34)	352(43.9)	84.6(21)	17(20.9)	13(10.9)	-5(5.4)
P value	0.05	0.08	0.09	0.47	0.80	0.47	0.86	0.34	0.05

TB, tuberculosis; HZ, Herpes zoster; NNRTI, non-nucleoside reverse transcriptase inhibitors; EFV, Efavirenz ; NVP, Nevirapine; SE, standard errors

3.4. Trends of Immuno-Virological Responses of Patients

Concordant positive responders were 60.5% at 6 months of treatment and this value was increased to 62.8% at 12 month and concordant negative responders were decreased from 9.3% to 8.1%. Also discordant responders' proportion reduced from 6 to 12 months (30.2 % to 29.0%) respectively and among this proportion, patients with CD4-VL+ decreased from 20.9% to 13.9%). In contrast patients with CD4+VL- were increased from 9.3% to 13.9% (figure-1).

Furthermore trends of mean CD4+ cells and body weight of the participants in between concordant positive responders vs. discordant responders + concordant negative responders: in both parameters concordant responders have significantly higher CD4+ cells and body weight except the baseline of HAART commencement (figure-2).

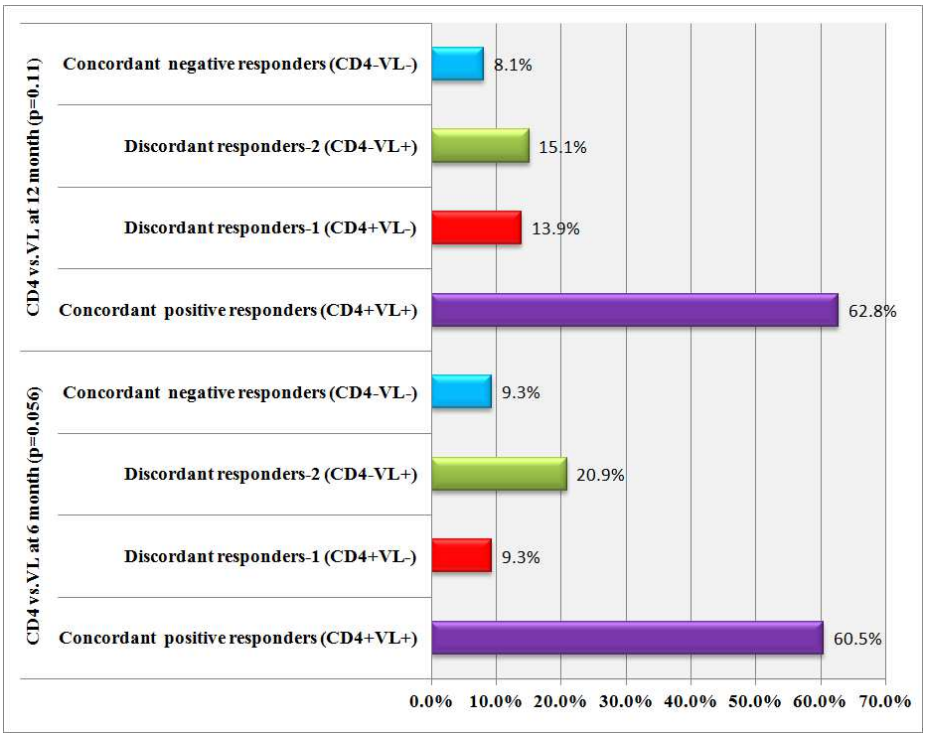
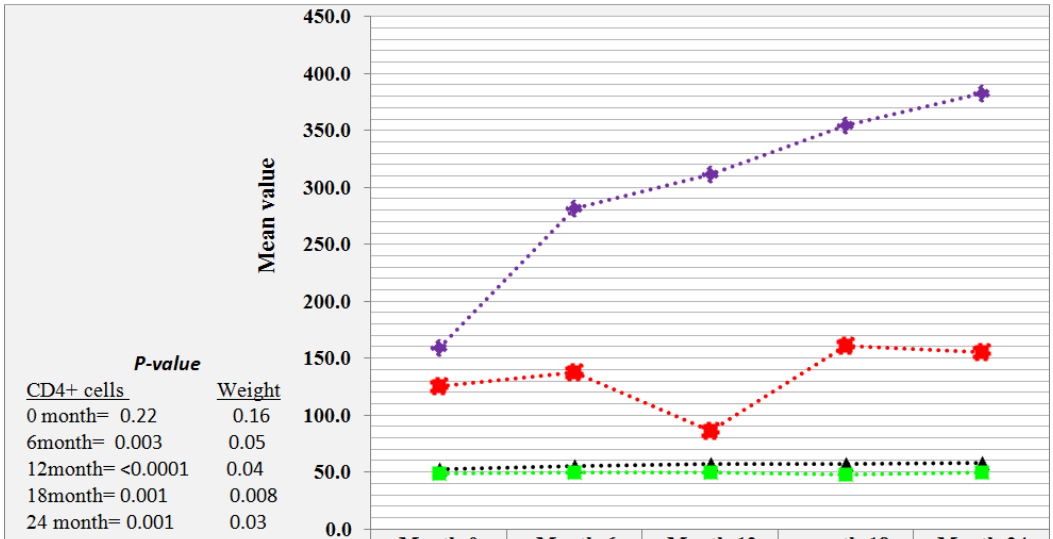


Figure 1. *Characteristics of immunological and virological response from 6-12 months after ART at Hawassa University referral hospital, Hawassa, southern Ethiopia.*



CR, concordant positive responders; DR+CNR, discordant responders + concordant negative responders

Figure 2. *Comparison of CD4+ cells count and body weight in relation with immunological and virological response at Hawassa University referral hospital, Hawassa, southern Ethiopia.*

3.5. Factors Associated with Immuno-Virological Discordant Responders

Univariate analysis was applied to assess the association of independent factors at 12 months of ART treatment: being living in rural (crude odds ratio =3.6; 95% CI: 1.0-13.8), and being body weight < 50 kg (crude odds ratio =0.39; 95% CI: 0.14-1.0) were found to be boarder (p= 0.05) with immune-virological discordant responders. However, on the multivariate analysis the association was adjusted for being living in rural (adjusted odds ratio = 20.3; 95% CI: 2.2- 188), being body weight < 50 kg (adjusted odds ratio = 0.14; 95% CI: 0.03-0.7) were significantly associated risk factors of immuno-virological discordant responders (table-4).

Table 4. *Factors associated with immuno-virological discordant responders at Hawassa University referral hospital, Hawassa, southern Ethiopia.*

Explanatory Variable	Unadjusted OR (95% CI)	*P value*	Adjusted OR(95% CI)	*P value*
Residence				
Urban	1.00		1.00	
Rural	3.6(1.0-13.8)	0.05	20.3 (2.2- 188)	0.008
Body weight (Kg)				
≥50	1.00		1.00	
<50	0.39 (0.14-1.0)	0.05	0.14 (0.03-0.7)	0.02

*NB: sex; age; Tuberculosis infection; ART drugs; opportunistic infections; educational status; marital status; WHO clinical stages were included during logistic regression analysis and only significant were displayed on the table

4. Discussion

The study shows that mean CD4+ T-cell count increments after ART initiation are higher in age <50 years in all stage except ART initiation and also the difference is insignificant when comparing these two age groups. In similar with this finding, a study from Brazil reported that changes in CD4+ counts after HAART initiation were not significantly different in patients ≥ 50 years compared to younger patients [16]. However in contrast to present study a cohort study from 9 African countries, also reports the median increase in CD4+ count was significantly higher at 6 and 12 months after receiving ART in patients younger than 50 years; P < 0.001 for both phases [17]. The slower CD4+ cell reconstitution in older patients may be related to an impaired thymic function [18] and CD4 reconstitution has been shown to be age dependent[19, 20]. In addition this study showed that 54.6% of ART patients were under the category of clinical stage equal to or above III according to WHO criteria; however this rate was lower than the study reported from Bahir Dar, northern part of Ethiopia, which was 69.7% [21]. The rates of clinical stage start to decline after using ART treatment and taking prophylaxis at baseline [22].

We found that females have higher mean CD4+ cells from baseline to 24 months when compared to males. Data on gender differences in trends of CD4 count after commencement of HAART are inconsistent. In line with the other studies report [23, 24] we found no significant differences in CD4+ reconstitution regarding gender. But other reports indicated that females have better immunological reconstitution compared to males [25, 26, 27, 28]. More over our study indicates lower viral load in female when compared to males at the baseline of ART commencement. This in line with several studies [13, 24, 29, 30].

Despite of 62.8% of concordant positives responders (CD4+VL+), 29% of patients did not achieve an adequate immune response (discordant) and also 8.1% concordant negative responders after 12 month of ART initiation in our study. In addition body weight <50 Kg and living in rural are significantly associated factors for discordant response in our study. However other studies revealed that sex, BMI and ART are identified risk factors for discordant response [31, 32].

5. Conclusion

In summary, CD4+ cells count shows significant increment after 6 month of ART treatment among patients having VL <5 (log_{10}) compared to those VL ≥5. Female have insignificantly better Mean CD4+ cells from baseline to 24 months of treatment. Also patients over 50 years of age do show an immune response after ART initiation. But, in relative to younger patients, their CD4 cells recovery is insignificantly sluggish. CD4+ cells and body weight of concordant positive responders show significant rising trend after six month of treatment when compared to discordant responders + concordant non-responders. In addition significant factors associated with discordant immuno-virological response were patient's body weight and residence.

Therefore immuno-virological response evaluation is a critical tool for assessing treatment outcome, regimen change and patient's management and the response trend decision should be done by using both CD4+ cells and viral load concurrently.

Limitations

Even though the sample size was relatively small, it was likely to be representative of patients in routine clinical care in the study area. The strength of the results may have been limited by the proportion of missing data. The outcomes were measured between 6 to 24 months after ART initiation; it is therefore probably that factors associated with discordant immune response may have varied with longer periods of treatment.

Authors' Contributions

A. Tadewos generated and designed the study, performed analysis and interpretation of data including with manuscript drafting and D. Assegu assisted in data entry and critical review. T. Beyene, S. Gutema and M. Regassa assisted in data collection.

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