Original Article

A randomized prospective study to assess health-related quality-of-life outcomes of antiretroviral therapy in human immunodeficiency virus-positive adults

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Abstract

Introduction: Health-related quality of life (HRQOL) in human immunodeficiency virus (HIV)-positive individuals is substantially challenged due to disease, opportunistic infections, lifelong commitment, and tolerability to antiretroviral therapy (ART) and various social, physical, and psychological domains. **Aim:** This study was conducted to assess the magnitude of the impact on HRQOL in HIV-positive people from early access to ART. **Settings and Design:** This was a randomized, prospective, open-label study, conducted at the ART center attached to the Government Medical College, Amritsar. **Subjects and Methods:** This study comprised 240 HIV-infected adults in the age group >18 years who presented to the ART center. Approval from the Institutional Ethics Committee was obtained. Informed consent was taken from all the enrolled participants after explaining the study therapy and its benefits and side effects. Patients who presented early in their course of disease and had baseline CD4 count ≥350/mm^3 were recruited in early arm and those with <350/mm^3 or the development of symptomatic HIV-related disease in the late arm. Following stratification, both groups were 1:1 randomized by permuted block randomization. The primary objective was to assess HRQOL using the World Health Organization Quality of Life-HIV brief instrument (WHOQOL-HIV). **Statistical Analysis Used:** The summary domain and total HRQOL scores were calculated using method developed by the WHOQOL-HIV group. Unpaired *t*-test was applied for statistical analysis, with level of significance expressed as $P < 0.05$. **Results:** Out of the total 240 HIV-positive patients, 120 who met eligibility criteria were recruited for the final analysis. There was a significant difference between HRQOL score of Physical domains and Psychological domains, between early and late arms at baseline and at the end of 9 months. **Conclusions:** Quality of life is an important holistic measure for assessing the health of people living with HIV/AIDS.

Key words: Acquired immune deficiency syndrome, antiretroviral therapy, CD4 counts, health-related quality of life, human immunodeficiency virus

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INTRODUCTION

Human immunodeficiency virus (HIV) infection is a global pandemic. It can progress to cause acquired immune deficiency syndrome (AIDS), which is a lethal disease characterized by the destruction of the immune system, specifically CD4 cells.[1]

Current treatment strategies are to combat the toxic effect of HIV on host cells, mainly CD4 T-lymphocytes. The goal of therapy is to suppress viral replication as much as possible for as long as possible.[2] The current standard of care is to use at least three drugs simultaneously for the entire duration of treatment.[3]

Antiretroviral therapy (ART) has significantly prolonged survival in people living with HIV infection or AIDS (PLWHA). ART is no longer a palliative treatment for HIV, but a paradigm for a chronic manageable condition.[4]

Early initiation of ART is needed to reduce morbidity and mortality from HIV infection and to reduce HIV transmission.[5] It is now strongly evident from various randomized controlled trials that initiating ART at higher CD4 count entails individual benefit in addition to population benefit by preventing HIV transmission to non-HIV-infected partners.[6,7] Thus, universal recommendations advocate early initiation of ART regardless of CD4 count in HIV-infected individuals. Health-related quality of life (HRQOL) in HIV-positive individuals is substantially challenged due to disease; opportunistic infections; lifelong commitment and tolerability to ART; and various Social, Physical, and Psychological domains.[8]

Our study aims to evaluate the HRQOL of HIV/AIDS patients using the World Health Organization Quality of Life-HIV brief instrument (WHOQOL-HIV BREF).

SUBJECTS AND METHODS

The present study was a prospective, randomized, open-label trial; the duration of the study was 9 months. The HIV-positive participants were randomized to start immediate ART (early arm) or to delayed treatment if CD4 count was 350 cells/mm^3 or the development of symptomatic HIV-related disease (delayed arm). The primary outcome was to assess various domains of HRQOL. Patients were stratified into two groups based on baseline CD4 count. The stratification of the patients into early versus late was based on baseline CD4 count when they first reported at the antiretroviral therapy center (ART center). The patients who reported at the ART center early in their course of disease having CD4 count between 350 and 500 cells/mm^3 were recruited in the early arm. The patients who reported at the ART center late in their course of disease having baseline CD4 count <350 cells/mm^3 were recruited in the late arm. Thus, one group had CD4 count ranging from 350 to 500 cells/mm^3 and the other group with CD4 count <350 cells/mm^3. Following stratification, both groups were 1:1 randomized by permuted block randomization. Patients were divided into three blocks. Each block represented patients belonging to categories A, B, and C according to the Centers for Disease Control and Prevention (CDC) classification system. Within each block, patients belonging to Group 1 were on early initiated antiretroviral therapy and Group 2 patients were on late initiated antiretroviral therapy.

The study comprised 240 HIV-infected adults in the age group >18 years who presented to the ART center attached to the Government Medical College, Amritsar. The sample size was determined considering a regional prevalence of HIV (0.19%) and a degree of precision of 0.05.[9]

Informed consent was taken from all the patients enrolled after explaining the study drugs and their benefits and side effects, and approval from the Institutional Ethics Committee, Government Medical College, Amritsar, was obtained.

The inclusion criteria were as follows:

- Treatment-naïve HIV-infected patients (male, female and transgender) in the age group >18 years.

The exclusion criteria were as follows:

- Diagnosis of any clinical AIDS event before randomization (including esophageal candidiasis and chronic herpes simplex infection)
- Presence of HIV progression such as oral thrush, unexplained weight loss, or unexplained fever
- Cardiovascular event (myocardial infarction, angioplasty, coronary artery bypass grafting, and stroke) within 6 months before randomization
- Non-AIDS-defining cancer, excluding basal and squamous cell skin cancer, within 6 months before randomization
- Dialysis within 6 months before randomization
- Current imprisonment or compulsory detention (involuntary incarceration) for the treatment of a psychiatric or physical illness
- Current pregnancy or breastfeeding (a negative serum or urine pregnancy test is required within 14 days before randomization for women of childbearing potential).

A complete history was obtained from every patient included in the study. During history taking, particular attention was paid to high-risk behaviors for HIV and symptoms that might indicate illness such as fever, weight loss, shortness of breath, or diarrhea. A history

of tuberculosis, fungal or yeast infections, liver infection (hepatitis), cold sores (oral herpes), or any other sexually transmitted disease was obtained.

The patients were subjected to complete physical examination such as temperature, weight, pallor, lymph node status, and abdominal examination to rule out enlarged liver or spleen.

Patients were diagnosed HIV positive based on serological test using enzyme-linked immunosorbent assay, by detecting HIV-specific antibody. All HIV-positive patients received ART regimen, as per the National AIDS Control Organization guidelines, based on clinical presentations and laboratory investigations.[10]

Immunological status of the patients was assessed by CD4 count. Patients were classified based on baseline CD4 count according to the CDC classification system[11] [Appendix 1].

The WHOQOL-HIV BREF was employed for the assessment of HRQOL of HIV/AIDS patients belonging to each of the two groups.[12] This was a multidimensional profile, which include twenty-nine facets, each having one item under six domains. Five of these facets were specific to HIV/AIDS. The six domains are described as follows:

- Domain 1: Physical
  1. Pain and discomfort
  2. Energy and fatigue
  3. Sleep and rest

50. Symptoms of PLWHA*

- Domain 2: Psychological
  4. Positive feelings
  5. Thinking, learning, memory, and concentration
  6. Self-esteem
  7. Bodily image and appearance
  8. Negative feelings
- Domain 3: Level of Independence
  9. Mobility
  10. Activities of daily living
  11. Dependence on medication or treatments
  12. Work capacity
- Domain 4: Social Relationships
  13. Personal Relationships
  14. Social support
  15. Sexual activity

51. Social inclusion

- Domain 5: Environment
  16. Physical safety and security
  17. Home environment
  18. Financial resources
  19. Health and social care: accessibility and quality
  20. Opportunities for acquiring new information and skills
  21. Participation in and opportunities for recreation/leisure activities
  22. Physical environment (pollution/noise/traffic/climate)
  23. Transport
- Domain 6: Spirituality/Religion/Personal Beliefs
  24. Spirituality/Religion/Personal Beliefs (SRPB)

52. Forgiveness and Blame

53. Concerns about the Future

54. Death and Dying

*Facets that are highlighted in bold are specific to the PLWHA, and as such have been added to the original WHOQOL instrument.

The patients answered each question based on individual items. The response was rated on a 5-points Likert scale. For positive feeling facets, 1 indicates low or negative, whereas 5 indicates high or positive perception. For some negatively phrased items (e.g., Pain and Discomfort, Negative Feelings, Dependence on Medication, Death, and Dying), the scoring was reversed so that higher score reflects better HRQOL. Items were organized by a response scale (capacity, frequency, intensity, or satisfaction). The summary domain and total HRQOL scores were calculated using the scoring method developed by the WHOQOL-HIV group. The mean score of items within each domain was used to calculate the domain score. The mean scores were then multiplied by 4 in order to make domain scores comparable with the scores used in the WHOQOL so that scores range between 4 and 20.

Assessment program

Follow-ups were done at 90, 180, and 270 days. At each visit, CD4 count and CDC clinical staging were evaluated. HRQOL scores were evaluated at baseline and at 270 days.

Statistical analysis

Analysis was based on data obtained from patients who completed 9 months of study phase. Data generated from the study were tabulated with respect to all parameters at specific intervals. The results were expressed as mean ± standard deviation (SD) of each variable. Unpaired *t*-test was applied for statistical analysis of various parameters between the two groups. Statistical significance was expressed as $P < 0.05$ for each parameter. Statistical analysis was done by using Microsoft Excel.

RESULTS

A total of 240 patients were screened and 134 were

recruited, out of which 13 deceased and one lost to follow-up. Final evaluation was done on information acquired from 120 patients who finished 9 months of routine ART regimen, tenofovir + lamivudine + efavirenz. After randomization, 58 were in the early arm (CD4 counts >350/mm^3) and 62 in the late arm (CD4 counts <350/mm^3) [Table 1].

The mean (±SD) age observed in the early arm was 34.59 (±9.60) years and in the late arm, 37.44 ± 12.06 years (*t*-test value = −1.437; P = 0.156). Thirty-two (55.2%) patients were male and 26 (44.8%) were female in the early arm, whereas 42 (67.7%) were male and twenty (32.3%) were female in the late arm (χ^2 = 2.003; P = 0.157) [Table 1].

CDC stage at baseline (0 day) was A1 for four (6.9%) patients in the early arm, whereas none of them was in the late arm. In the early arm, 50 (86.2%) were in A2 stage; three (5.2%) in B2; one (1.7%) in C2; and none in A3, B1, B3, C1, and C3 stages. In the late arm, 24 (38.7%) in A2; 15 in A3; three (4.8%) in B2; two (3.2%) in B3; five (8.1%) in C2; 13 (21.0%) in C3; and none in A1, B1, and C1 stages at baseline (χ^2 = 45.719; P < 0.001). At 90 days, CDC stage was A1 for four (6.9%) patients in the early arm; 51 (87.9%) were in A2 stage; two (3.4%) in C1; one (1.7%) in C2; and none in A3, B1, B2, B3, and C3 stages. In the late arm, CDC stage was two (3.2%) in A1; 30 (48.4%) in A2; 16 (25.8%) in A3; two (3.2%) in B3; 12 (19.4%) in C3; and none in B1, B2, C1, and C2 stages (χ^2 = 39.021, P = 0.000). At 180 days, 29 (50%) were in CDC stage A1; 26 (44.8%) in A2; one (1.7%) in C1; two (3.4%) in C2; and none in A3, B1, B2, B3, and C3 CDC stages in the early arm. In the late arm, five (8.1%) were in CDC stage A1; 37 (59.7%) in A2; five (8.1%) in A3; two (3.2%) in B2; three (4.8%) in B3; one (1.6%) in C1; three (4.8) in C2; six (9.7%) in C3; and none in B1 CDC stage (χ^2 = 34.967; P = 0.000). At 270 days, 29 (50%) were in CDC A1 stage; 25 (43.1%) in A2; one (1.7%) in B2; two (3.4%) in C1; one (1.7%) in C2; and none in A3, B1, B3, and C3 stages in the early arm. In the late arm, ten (16.1%) were in CDC A1 stage; 38 (61.3%) in A2; nine (14.5%) in A3; one (1.6%) in C2; four (6.5%) in C3; and none in B1, B2, B3, and C1 stages (χ^2 = 27.837; P = 0.000) [Table 2 and Figure 1].

In the early arm, the mean CD4 counts at 0, 90, 180, and 270 days were 426.71, 432.10, 525.22, and 552.21, respectively. In the late arm, mean CD4 counts at 0, 90, 180, and 270 days were 192.94, 223.45, 311.97, and 348.08, respectively. The mean difference in CD4 counts at 0, 90, 180, and 270 days was 233.771, 208.652, 213.256, and 204.126, respectively (t_0 = 14.487, P_0 = 0.000; t_{90} = 9.566, P_{90} = 0.000; t_{180} = 7.367, P_{180} = 0.000; t_{270} = 6.488, and P_{270} = 0.000) [Table 3].

At baseline (0 day), the mean of HRQOL score was 13.17, 11.89, 11.69, 11.78, 11.77, and 13.55 for domains 1, 2, 3, 4, 5, and 6, respectively, in the early arm. In the late arm, the mean HRQOL scores were 11.76, 10.75, 11.19, 11.23, 11.28, and 12.74 for domains 1–6, respectively, at day 0. The mean difference for HRQOL score at day 0 was 1.41, 1.41, 0.50, 0.55, 0.49, and 0.81 for domains 1–6, respectively. At 270 days, the mean HRQOL scores were 14.33, 12.81, 13.24, 12.22, 11.93, and 13.84 for domains 1–6, respectively, in the early arm. In the late arm, the mean HRQOL scores were 13.47, 12.25, 12.66, 11.87, 11.57, and 13.63 for domains 1–6, respectively, at 270 days. The mean difference for HRQOL score at 270 was 0.86, 0.57, 0.58, 0.35, 0.37, and 0.22 for domains 1–6, respectively, at 270 days [Table 4 and Figure 2].

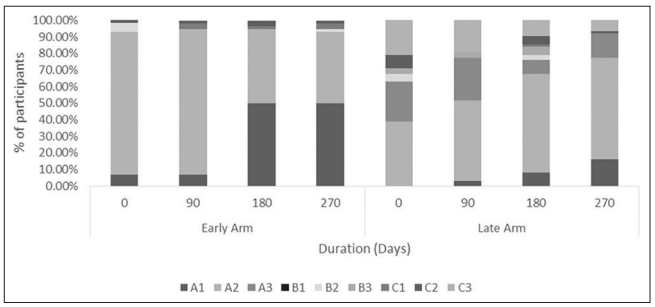

Figure 1: Centers for Disease Control and Prevention staging

Table 1: Demographic data

Demographic data	Total sample (*n*=120)		Test value	*P*
	Early arm (*n*=58; 48.33%), *n* (%)	Late arm (*n*=62; 51.67%), *n* (%)		
Age (years), mean±SD	34.59±9.60	37.44±12.06	*t*=−1.437	0.156
Gender (counts; percentage within arm)				
Male	32 (55.2)	42 (67.7)	χ^2=2.003	0.157
Female	26 (44.8)	20 (32.3)		
Marital status (counts; percentage within arm)				
Married	33 (56.9)	39 (62.9)	χ^2=1.261	0.738
Single	14 (24.1)	11 (17.7)		
Widowed	9 (15.5)	11 (17.7)		
Divorced	2 (3.4)	1 (1.6)		

SD=Standard deviation

Table 2: Centers for Disease Control and Prevention stage

CDC stage	0 day (%)		90 days (%)		180 days (%)		270 days (%)	
	Early arm	Late arm	Early arm	Late arm	Early arm	Late arm	Early arm	Late arm
A1	6.90	0.00	6.90	3.20	50.00	8.10	50.00	16.10
A2	86.20	38.70	87.90	48.40	44.80	59.70	43.10	61.30
A3	0.00	24.20	0.00	25.80	0.00	8.10	0.00	14.50
B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
B2	5.20	4.80	0.00	0.00	0.00	3.20	1.70	0.00
B3	0.00	3.20	0.00	3.20	0.00	4.80	0.00	0.00
C1	0.00	0.00	3.40	0.00	1.70	1.60	3.40	0.00
C2	1.70	8.10	1.70	0.00	3.40	4.80	1.70	1.60
C3	0.00	21.00	0.00	19.40	0.00	9.70	0.00	6.50
χ^2	45.719		39.021		34.967		27.837	
P	<0.001***		<0.001***		<0.001***		<0.001***	

***P<0.001 (highly significant). CDC=Centers for Disease Control and Prevention

Table 3: CD4 counts (cells/mm³)

Duration	Arm	*n*	Mean±SD	Mean difference	*t*	*P*
0 day	Early	58	426.71±72.382	233.771	14.487	<0.001***
	Late	62	192.94±102.688			
90 days	Early	58	432.1±71.362	208.652	9.566	<0.001***
	Late	62	223.45±155.087			
180 days	Early	58	525.22±157.267	213.256	7.367	<0.001***
	Late	62	311.97±159.714			
270 days	Early	58	552.21±175.064	204.126	6.488	<0.001***
	Late	62	348.08±169.15			

***P<0.001 (highly significant). SD: Standard deviation

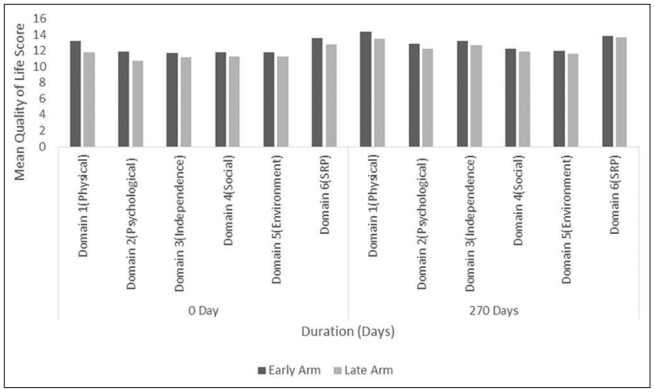

Figure 2: Health-related quality of life

DISCUSSION

This was a prospective, randomized, open-label study; the duration of the study was 9 months. The HIV-positive participants were randomized to start immediate ART (early arm) or to delayed treatment if CD4 count was 350 cells/mm³ or the development of symptomatic HIV-related disease (delayed arm). The primary objectives of the study were to compare the effects of early and delayed initiation of antiretroviral therapy on HRQOL of HIV-positive adults.

CDC staging of the recruited patients was done based on CD4 cell counts, symptomatic conditions, and HIV indicator conditions. At day 0, most of the HIV-positive patients were asymptomatic A2 stage but more in early (86.2%) than late (38.7%) treatment group. More patients were having symptomatic (B2 = 4.8% and B3 = 3.2%) and AIDS indicator conditions (C2 = 8.1% and C3 = 21.0%) in late than early treatment group. There was a statistically significant difference (P = 0.000) between CDC staging in both groups at day 0. At 90 days, most of the patients were in A2 stage but more in early (87.90%) than late (48.40%) treatment group. In the late group, two (3.20%) patients improved to A1 stage with 90 days of treatment. However, AIDS indicator conditions were more in late (C3 = 19.40%) than early group (C1 = 3.20% and C2 = 1.70%) at 90 days. There was a statistically significant difference (P = 0.000) between CDC stages in both groups at 90 days. In the early group, most of the patients were asymptomatic (A1 = 50.00% and A2 = 44.80%), and only three had AIDS indicator conditions (C1 = 1.70% and C2 = 3.40%) at 180 days. In the late arm, most of the patients were in asymptomatic A2 stage (59.70%) but ten had AIDS indicator conditions (C1 = 1.60%, C2 = 4.80%, and C3 = 9.70%) at 180 days. There was a statistically significant difference (P = 0.000) between CDC stages in both groups at 180 days. At 270 days, most of the patients were asymptomatic in both early (A1 = 50.00% and A2 = 43.10%) and late (A1 = 16.10%, A2 = 61.30%, and A3 = 14.50%) treatment groups. AIDS indicator conditions were present in three (C1 = 3.40% and C2 = 1.70%) patients in the early arm, which was less than that in the late arm (C2 = 1.60% and C3 = 6.50%). Moreover, there were no patients in advanced CDC stage C3 in the early arm, whereas four (6.50%) were present in the late group. There was a statistically significant difference (P = 0.000) between CDC stages in both groups even at 270 days [Table 2].

CD4 counts were assessed to compare the immunological status of the patients in both groups at baseline followed by ART at 90, 180, and 270 days.

Table 4: Health-related quality of life score

Domains	Arm	Mean±SD	Mean difference	*t*	*P*
0 day					
Domain 1 (Physical)	Early	13.17±2.272	1.41	3.151	0.002**
	Late	11.76±2.641			
Domain 2 (Psychological)	Early	11.89±1.826	1.14	2.923	0.004**
	Late	10.75±2.427			
Domain 3 (Level of Independence)	Early	11.69±1.392	0.50	1.756	0.082
	Late	11.19±1.697			
Domain 4 (Social Relationship)	Early	11.78±2.044	0.55	1.344	0.181
	Late	11.23±2.432			
Domain 5 (Environment)	Early	11.77±1.992	0.49	1.315	0.191
	Late	11.28±2.048			
Domain 6 (Spirituality/ Religion/Personal Beliefs)	Early	13.55±2.202	0.81	1.686	0.095
	Late	12.74±3.019			
270 days					
Domain 1 (Physical)	Early	14.33±2.047	0.86	2.076	0.040*
	Late	13.47±2.481			
Domain 2 (Psychological)	Early	12.81±1.402	0.57	1.641	0.104
	Late	12.25±2.311			
Domain 3 (Level of Independence)	Early	13.24±2.011	0.58	1.474	0.143
	Late	12.66±2.297			
Domain 4 (Social Relationship)	Early	12.22±1.845	0.35	0.937	0.351
	Late	11.87±2.272			
Domain 5 (Environment)	Early	11.93±1.839	0.37	1.043	0.299
	Late	11.57±2.009			
Domain 6 (Spirituality/ Religion/Personal Beliefs)	Early	13.84±2.434	0.22	0.458	0.648
	Late	13.63±2.724			

*P<0.05 (significant), **P<0.01 (very significant). SD=Standard deviation

The mean difference for CD4 counts in both groups was maximum at baseline (233.771) and minimum at 270 days (204.126). There was a statistically significant difference in CD4 counts at baseline (P = 0.000) as well as following ART at 90 (P = 0.000), 180 (P = 0.000), and 270 days (P = 0.000). A large observational modeling study suggested CD4 counts at ART initiation as the most important factor in predicting posttreatment recovery[13] [Table 3].

QOL is an important holistic measure for assessing the health of PLWHA. HRQOL scores were calculated using the scoring method developed by the WHOQOLHIV group. The maximum score in both groups was for domain 6 (Spirituality/Religion/Personal Beliefs), at baseline as well as at the end of the study. At baseline, the mean difference of HRQOL scores between early and late groups was statistically significant for domain 1 (P = 0.002) and domain 2 (P = 0.004) but was insignificant for domain 3 (P = 0.082), domain 4 (P = 0.181), domain 5 (P = 0.191), and domain 6 (P = 0.095). At 270 days, the mean difference of HRQOL score was statistically significant for domain 1 (P = 0.040) but was insignificant for domain 2 (P = 0.104), domain 3 (P = 0.143), domain 4 (P = 0.351), domain 5 (P = 0.299), and domain 6 (P = 0.648) [Table 4 and Figure 2]. A study was conducted to determine if immediate compared to deferred initiation of ART in healthy PLWHA had a more favorable impact on HRQOL, or self-assessed physical, mental, and overall health status. The HRQOL was assessed by participant self-administered questionnaires, containing a single-item Visual Analog Scale and the Short-Form 12-Item Health Survey version 2. There were modest but significant QOL improvements during follow-ups in those immediately initiating ART compared to deferred ones.[14] Another study was conducted to evaluate the QOL of PLWHA receiving ART using the WHOQOL-HIV BREF scale. The maximum score was for domain 6 (Spirituality/Religion/Personal Beliefs) as in our study.[15] A cross-sectional study conducted to assess HRQOL and its related factors in HIVAIDS patients taking ART, found moderate outcomes across the six domains of WHOQOL-HIV BREF scale as observed in our study.[16]

CONCLUSIONS

Early initiation of ART has a positive impact on the immunological status of HIV-positive individuals by improving CD4 counts with the course of treatment. HIV- and AIDS-related events were much commonly observed in early treatment arm than late one. There were significant differences between the two groups in terms of CDC stages at baseline as well as post ART initiation throughout the study period. There was a significant difference in HRQOL scores between the two groups in Physical and Psychological domains. In summary, QOL is an important holistic measure for assessing the health of PLWHA. While there is significant improvement in the Physical and Psychological domains of HRQOL through treatment approach, there is a need to address other domains through focused counseling approach.

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Conflicts of interest

There are no conflicts of interest.

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