博士論文

Effects of Cognitive Behavioral Therapy Led by Peer Counselor on Depressive Symptoms and ART Adherence among People Living with HIV in Yangon, Myanmar: a Cluster-Randomized Controlled Trial

(ミャンマーの HIV 感染者におけるピアカウンセラーによる認知行動療法の抑うつ症状および抗レトロウイルス薬服用遵守に与える影響：クラスターランダム化比較試験)

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Contents

Abstract

Objective: This study aimed to develop a new group-based cognitive behavioral therapy (CBT) led by peer counselors targeting depressive symptoms and antiretroviral therapy(ART) adherence and to investigate its effects on improving depression (primary outcome), ART adherence (primary outcome), and immunological outcome (CD4 count) (secondary outcome) among people living with HIV (PLHIV) in Yangon, Myanmar, using a cluster randomized controlled trial design.

Methods: An intervention program was developed consisting of eight elements including ART adherence. Six ART institutions (clusters) in the Yangon Region were randomly assigned to the intervention and control groups, stratifying urban and per-urban settings. The intervention groups were offered a cognitive behavior therapy program for 8 weeks and the control group was offered usual ART counseling. The outcomes were measured using a structured questionnaire at the baseline, 3-month and 6-month follow-ups: Myanmar version of the Beck Depression Inventory II (mBDI-II), Hopkins Symptom Checklist for Depression (HSCL-D), a four-item scale for ART adherence, CD4 cell counts. Outcomes were analyzed by linear mixed models with maximum likelihood to express the effect of intervention.

Results: The overall depressive level in the intervention group was significantly decreased compared with that in the control group in both depression scales (mBDI-II: b= -8.1, SE= 2.9, p= 0.006, d= -1.0, HSCL-D:b= - 5.5, SE= 2.4, p= 0.023, d= -0.8). ART adherence was not significantly improved. The small effect of intervention can be seen on CD4 count (Cohen's d 0.4).

Conclusion: This cluster randomized controlled trial showed that peer-led cognitive behavioral therapy is feasible, acceptable and displayed efficacy in improving depressive symptoms and CD4 count among PLHIV who currently are taking ART and have depressive symptoms.

1. Introduction

HIV and PLHIV

According to the World Health Organization, approximately 37.9 million (95% CI 32.7 – 44.0 million) people across the world suffer from HIV (1). Infection with the human immunodeficiency virus (HIV) causes the progressive failure of the immune system, which subsequently can lead to increased vulnerability to infections and other immunological disorders and increased risk of different types of cancer (2). With increased access to highly active antiretroviral therapy (HAART), HIV is no longer considered a terminal disease, but rather a chronic disease (3).

HIV and Depression

However, a new diagnosis of HIV carries threats to wellbeing as well as personal psychology. In addition, infected individuals may face the disease progress, social stigma, occupational disability, social isolation, long-term physical discomfort and illness, and physical changes (4-6). All this can lead to uncertainty about the future, social isolation, loss of self-esteem, and failure to adjust (5). This stage of chronic diseases conditions and stress consistently has been associated with mental ill health; depressive symptoms are the most common mental health problem in people living with HIV (PLHIV) worldwide (3, 4, 7, 8). Findings from a meta-analysis (4) of studies that PLHIV are nearly two times more likely to have had a recent episode of major depressive disorder than HIV-negative individuals (4). The prevalence rate of depressive symptoms among PLHIV was ranged from 12.8% to 78%; there was no significant difference in the rate of depressive symptoms among low-, middle- and high-income countries (9). However, another systematic review described that the prevalence rate of depressive symptoms in PLHIV as 31% (95% CI – 28 – 34%); a higher prevalence rate of depressive symptoms was found in developing countries, such as Nigeria,

Uganda, India, and Thailand (10). In addition, the highest prevalence rate of depressive symptoms was found in the South-East Asia region at 40% (95% CI 30% to 49%) (10), and PLHIV are a high-risk group for developing clinical and non-clinical depression. Therefore, prevention and treatment of depressive symptoms is an important factor for PLHIV.

Impact of Co-morbid Depression

Chronic depressive symptoms has been associated with the clinical and immunological progression of AIDS (11). Higher depressive symptom score corresponded to virologic failure (viral load >150 copies/ml), and suppressed immune system (CD4 count <200 cells/mm^3) (12). In addition, one cohort study stated that more cumulative depressive symptoms can lead to a faster progression to the AIDS stage (13-15).

In addition, a high level of adherence to HARRT is necessary to maximize the treatment outcome. ART adherence above 95% is necessary to maintain positive virology and clinical outcome (8, 16). However, depressive symptoms are associated with ART non-adherence (17-20), and leads to an AIDS condition as well as higher mortality (15). The association between depressive symptoms and ART adherence has been seen consistently across countries with different income levels (low, middle, or high) (8, 9). Depressive symptoms are one of the barriers for PLHIV to achieve high ART adherence. Therefore, the treatment of depressive symptoms is also one of the important factors for successful HIV treatment.

CBT for Depression

Cognitive behavioral therapy (CBT) is based on the cognitive model of mental illness, initially developed by Dr. Aaron T. Beck (21). CBT is a structured, short-term, present-oriented psychotherapy for depression, directed toward solving current problems and

modifying dysfunction (inaccurate and/or unhelpful) thinking and behavior (21). It is a time-sensitive, structured, present-oriented form of psychotherapy that helps individuals identify goals that are most important to them and then overcome the obstacles (22). CBT alters an individual's maladaptive thinking and behaviors by reducing the maladjustment of moods, and it improves an psychological problem (23). In addition, CBT has been shown to be an effective treatment for depressive symptoms in many chronic disease conditions (24-26).

CBT for Depression among PLHIV

CBT has been known as highly effective among PLHIV with depressive symptoms. A systematic review of studies examining the effect of psychosocial interventions on depression among PLHIV shows that CBT has been particularly effective for depressive symptoms(27). However, most studies have been implemented in high-income countries (28, 29), with very little representation from low- and middle-income countries (30). Evidences from one systematic review of low- and middle-income countries stated that CBT was effective for common mental disorders in PLHIV; however, a high risk of bias was presented in these studies (31). Therefore, CBT studies among PLHIV with the sign of depressive symptoms are needed in low resources settings but still are limited.

In addition, evidences from the previous research indicated that group-based CBT leads to gaining knowledge and skills that enhance the social connection and support and allow better coping with adverse situation and stigma (32). These changes lead to a reduction in depressive symptoms and better ART adherence (32). Previous meta-analysis of psychotherapy among PLHIV stated that group psychotherapy was efficacious; especially group-based cognitive behavior targeting depressive symptoms appear to be efficacious with moderate effect size (0.37) (33).One meta-analysis found no difference between group-based CBT and individual CBT on depressive symptoms (34). The rates of attendance and drop-out

were significantly higher in group-based CBT than in individual CBT (34, 35).

Involvement of Peer Counselors

Tindall (1995) broadly defined peer helping as “a variety of interpersonal helping behaviors assumed by nonprofessionals who undertake a helping role with others” (p.7) (36). Peers have several qualities that differ from those of other professional and non-professional health care providers (37). First, peers share key personal, characteristics and experiences with their clients or patients. Second, their characteristics and experiences influence the clients in the particular ways, so thus their status as peers is thought to give added value to the health services they provided. Finally, peers can complete short-term, competency-based training like other non-professional health workers (37, 38).

Therefore, peers play an essential role in HIV prevention and treatment are as including educating PLHIV, offering social supports, providing information for the social supports, and working together with PLHIV to identify the barriers, and ways to overcome them, to access the treatment (39, 40).One systematic review showed that the effects of peer intervention for viral suppression and ART adherence were inconsistent(41), as were findings on the effect of peer-led psychotherapy. One peer-led social support intervention conducted in the United States stated that no effect was found on depression and ART adherence among PLHIV (42). However, another study demonstrated that problem-solving therapy provided by lay health workers was effective in improving depressive symptoms among primary health care clinic attendees with possible HIV (43). A study conducted in the United States found that CBT provided by health workers who were experienced with the HIV prevention program was effective for reducing depressive symptoms (44). Group-based motivational interview intervention of health behavior improved the depressive symptoms reported by a mother living with HIV in South Africa (45). Therefore, the effect of peer-led CBT on

depression and ART adherence is not clear, and it needs more research, particularly in a country with low health care resources.

Myanmar Situation

The HIV epidemic in Myanmar is in a decreasing trend; however, an estimated HIV incidence per 1000 adults was at a haltof0.23 in 2017 (46, 47). Antiretroviral therapy (ART) coverage has been scaled up in Myanmar since 2010, and in 2015, about 106,490 PLHIV had access to free ART in Myanmar (48). Starting in 2015, ART was provided to PLHIV who hadaCD4 count ≤ 500; currently, 54.5% of eligible PLHIV are on ART (48). The Ministry of Health and Sport and its partner organizations increased the number of ART facilities across the country to improve access to ART. One study conducted in Myanmar stated that 84% of PLHIV had ≥ 95% adherence rate (49).

Myanmar has a large treatment gap for mental disorders; the ratio of human resources working in the mental health facilities or private practice per 100,000 general population was 0.477 (50). The prevalence of depression among PLHIV who attend the public ART centers in Yangon was 30.12% and was associated with the percentage missing ART during the last month (51). Because of the limited human resources, no psychological services are available for PLHIV at the primary health care level. A potential possible approach to improve the situation would be task shifting: trained peer counselors in primary health care who can contribute to the treatment of depressive symptoms. One study found that lay health workers provided psychological interventions in developing countries that were effective for depressive symptoms (52). Psychological intervention delivered by peer counselors must be simple and brief; therefore, peer counselors can effectively provide treatment and supervise depressive symptoms.

A systematic review of mental health interventions in Myanmar suggested that

psychotherapeutic interventions could be effective in Myanmar; however, the study conducted was not methodologically strong, and randomized controlled trials are lacking in Myanmar (53). A community-based psychosocial intervention conducted in Myanmar reported that depressive symptoms were improved; however, there was no comparison group, and the population comprised marginalized people, including PLHIV (54).

To the best of our knowledge, there is no study of CBT for depressive symptoms or ART adherence led by peer counselors has been conducted among PLHIV anywhere in the world. Therefore, in this study, I aimed 1) to develop a new group-based cognitive behavioral therapy (CBT) led by peer counselors targeting depressive symptoms and ART adherence and 2) to investigate the effectiveness of the program in improving sub-threshold depression among PLHIV in Yangon, Myanmar. I also examined the effect of the intervention program on ART adherence and on improving the ART adherence and immunological outcome (CD4 count) as the secondary outcomes. To the best of my knowledge, this study was the first cRCT to investigate the effects of group-based CBT led by peer counselors on depressive symptoms, including ART adherence in PLHIV.

I hypothesized that the level of depressive symptoms and ART adherence (as the primary outcomes), and CD4 count (as the secondary outcomes) among PLHIV would be improved in the intervention group compared with the control group. The findings from this study should be useful for mental health prevention and treatment of PLHIV and the development of long term intervention program for PLHIV in developing countries. In addition, it should contribute to the policy formation of the HIV control program in Myanmar.

2. Methods

Setting

This trial was conducted in Yangon; this previous capital of Myanmar is a densely populated area (716 people per Km^2) with a very diverse social and economic situation. Around 65% of PLHIV were estimated to be in five regions and states of Myanmar, including the Yangon region (55). This trial was conducted in collaboration with a non-government organization (NGO), Myanmar Positive Group (MPG), and the University of Tokyo. MPG is a National Network of PLHIV who contributes fight against the HIV epidemic in Myanmar. In the Yangon Region, 33 ART institutions provide the services; among these, MPG provides the counseling services at eight ART institutions. Other ART institutions are run by the National AIDS Programme (NAP) and other NGOs. Among these ART institutions, six located in both urban (Latha, Kyi Myint Dine) and peri-urban (Insein, North Okklapa, Mingalardon, Waibagi) areas were included in this study (Supplementary Figure 1) (56).

Study Design

This cluster randomized controlled trial was conducted from May 2018 to February 2019, in Yangon. The ART institutions were as a unit of randomization. After a baseline study, ART institutions were assigned randomly into an intervention or a control group in a 1:1 ratio. The randomization was conducted with ART institutions that were stratified by the size of the institution (the number of staff members, 3 -15and > 15) (57). This study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN-CTR, ID = UMIN000031442). The manuscript was reported according to the guidelines in the Consolidated Standards of Reporting Trials (CONSORT) for cRCTs (58).

Participants

PLHIV who registered at MPG in Yangon (both urban and peri-urban areas) were recruited for this study. The participants were taking ART at public hospitals and clinics within the urban and peri-urban areas of Yangon (56). The average cluster size was set at 40 PLHIV. For the baseline individual participants, adults older than 18 years were recruited if: they had sufficient knowledge of Myanmar language, were taking ART more than one month, did not have any difficulty with hearing and speaking, and were not taking antidepressant.

The participants who had a Beck Depression Inventory II (BDI-II) score greater than 10 at the baseline screening, and no suicidal thoughts and experiences were invited to either the intervention or control group with the purpose of not missing sub-threshold depressive participants (59). Psychological treatments, like CBT, have a significant effect on sub-threshold depression (60).

The study protocol was approved by the research ethics committee of Graduate School of Medicine at the University of Tokyo (No. 11908) and the Ethics Review Committee of Department of Medical Research at Ministry of Health and Sports, Myanmar (Ethics/DMR/2018/061). In addition, the study protocol was approved by the National AIDS Programme (NAP), Ministry of Health and Sports, Myanmar. Informed consent was obtained from all participating PLHIV.

CBT Interventions

PLHIV in the intervention group were offered a structured, manualized 8-session program for depression and ART adherence adapted from the previously established manual (61-64). The previously established manual had been developed for a telephone psychotherapy intervention (61, 63, 64); therefore, the manual was modified to fit with a group-based intervention. The supplementary Table 1 shows the content of the intervention program. The manual was prepared with detailed examples and plans, worksheets and

homework. The manual was tested among four PLHIV as a group before the start of the main intervention in Yangon. After the pilot testing, the manual was rewritten extensively to make it satisfactory for Myanmar adult PLHIV living with sub-threshold depressive symptoms. The examples included in the manual were fully developed to meet the local context and nature of HIV and ART.

A pre-tested 95-page participants' manual was used by both participants and peer counselors; it contained all the materials to be covered in each session with the space to write down their own feelings together with examples. Both peer counselors and participants needed to work on the homework and weekly activity plan to know the difficulties and the problems. For the quality control of the intervention, the manual in Burmese was set for the whole intervention, and this manual was reviewed and modified by two health professionals who are experts in the psychiatric field.

Each session was designed to be completed within 60 to 90 minutes; however, the actual length depended on the participants' and counselors' assessment and needs. Sessions were meant to take place at weekly intervals and were performed as planned. Each session started with relaxing meditation and check-in and a brief review of the previous session and the homework (Supplementary Table 1). The initial session started with team building, the background of the CBT model, a theoretical explanation about depression, motivational interviewing, and the importance of ART adherence (65). Session 2 to 4 focused mainly on behavior activation with increasing pleasant activities through personal experiment (66). Session 5 through 7 focused on problem identification and challenging negative thoughts with a series of examples, focused mainly on cognitive reconstruction (67). In the last session, the counselors and participants reviewed together the cognitive and behavioral skills they had learned during the 8-week program and created their own written self-care plan for self-monitoring, identification and preparing for the high-risk situation.

The counselors who provided the CBT in this study were peer counselors. Peer counselors were recruited from PLHIV who currently were taking ART and who had received HIV and ART adherence counseling training and provided counseling services to PLHIV at MPG. MPG provides counseling services in 12 regions of Myanmar, and in total, 41 peer counselors are working with MPG. In the study area, the Yangon region, 10 peer counselors were providing the services. Before the training of CBT, we announced the study program and recruited peer counselors. In total, six peer counselors participated in the CBT training program, and four candidates were selected to be peer counselors. None of them had experienced or received training for psycho-education, such as CBT.

These peer counselors were asked to attend a program-specific CBT training program. The program was 6 full days run by an experienced clinical psychologist (MSc Clinical Psychology), and facilitated by physician who had experience as an ART doctor. During the training, role plays and readjusting of examples were done together by the research team, peer counselors, and a clinical psychologist. All peer counselors had different counseling experiences and education background (Supplementary Table 2). Therefore, we set a criterion of more than one-year of ART counseling experiences for the peer counselors, and selected four peer counselors from the six, based on their counseling experiences.

We provided group-based CBT to two groups of 10PLHIV each. Two of the four peer counselors provided CBT, and the remaining two served as moderators/facilitators. In addition, one supervisor observed and monitored the CBT group therapy to assure the quality of CBT and provided regular discussion for difficulties. All these intervention programs were took place at one of the MPG office.

PLHIV in the control group received the usual ART adherence counseling program of MPG (treatment as usual, TAU). The ART adherence counseling included topics on the side effects of ART, difficulties that occur during ART, ways to overcome the obstacles of taking

ART for a long time, and the importance of family support. ART counseling session 2 includes support for the physical and mental changes after taking ART, ways for secure sexual activities, and condom promotion. ART adherence session 3 consists of checking the ART diary, pill count, consulting for any non-adherence, explaining drug resistance and its complications, and discussing the positive way to live. ART counseling was provided to every PLHIV who started ART treatment in Myanmar. The same peer counselors who provided the CBT program provided ART adherence counseling to PLHIV in both the intervention and control groups.

All participants were given the "MPG Care and Support Program Treatment Calendar" to write down any medication missed, side effects they suffered, and other details. Besides the common program, questionnaire-based feedback regarding the assessment of depressive symptoms and ART adherence was provided three times (baseline, 3- and 6-month follow-ups).

Outcomes

Primary outcomes

Depressive symptoms and ART adherence of participants were measured using the questionnaire at the baseline, the 3- and 6-month follow-ups. All effects of the intervention program were evaluated based on the individual-level variables.

Depressive Symptoms

Depressive symptoms were defined in this study by using Beck's Depressive Inventory II (BDI-II). The BDI-II scale(68), is a21 items questionnaire from the Beck Institute of Cognitive Therapy and Research which has been validated in psychiatric outpatients with a coefficient alpha was 0.91(69). For each item, the participants were asked how often they experienced the symptoms related to depression during the previous two

weeks. Individual items were scored on a scale of 0-3. Total scores for depressive symptoms ranged from 0 to 63, where higher scores indicate greater depressive symptoms. BDI-II was used as the screening tool to enter the intervention program. The Myanmar version of BDI-II (mBDI-II) was tested and validated among substance users who live in Hseni Township, Northern Shan State of Myanmar, and the coefficient alpha was 0.93 (70).

Hopkins Symptom Checklist Depression Measure (HSCL-D; 15 items) (71) was used in this study to measure depressive symptoms (72). For each item, the participants were asked how often they experienced the symptoms related to mental health during the previous two weeks. Individual items were scored from 0, “none of the time” to 3,“almost all of the time." The total score for symptoms ranged from 0 to 45, with the higher scores indicating more mental health problems. HSCL-D in Burmese language was tested and validated among the Burmese immigrants who lived in the Thailand-Myanmar border, and test-retest/inter-rater reliability (r) was acceptable (r= 0.84) (73).

ART Adherence

Adherence is defined as the extent to which a person takes a medication according to the medical prescription, inclusive of timing, dosage and consistency, and in terms of right doses, right time, and following the dietary recommendations(49, 74). ART adherence was measured by a self-reported questionnaire using a multi-method tool (four methods)proposed in a previous study (75). The questionnaire included (1) a4-day visual analogue scale (VAS) (percent of pills reported missed over the last 4 days), (2) pill identification test (PIT) (know the pill name, pill numbers per dose, time and additional information), (3) pill count, and (4) a4-day structured self-report scale on missing dose. This tool was developed and tested among PLHIV living in the resource-constrained setting (75). In addition, the multi-method tool had no significant difference from the objective measures to measure ART adherence (76). The answers to all questions were entered into the table of adherence (Supplementary

Table 2) and the overall adherence was calculated according to the table. The table has three columns that were ticked according to the participants' answers. If the answers spread over two columns, the adherence level of the right column was used; and if the answers spread over three columns, the middle level of adherence was used.

Secondary Outcome

Immunological Outcome

As the secondary outcome, one of the immunological outcomes, CD4 count, was recorded from the participant's record and used as the continuous variables. The CD4 count is performed after the confirmation of HIV positive status, and it expressed in cells/mm^3. The CD4 cell count is tested every 6 months until PLHIV are stable on ART (on ART for at least 1 year, no current illness or pregnancy, a good understanding of lifelong adherence and evidence of treatment success) (77).

Demographic Variables

Age sex, ethnicity, education, and marital statuses were the demographic variables. In addition, participants were asked about lifetime and recent smoking, alcohol, and substance use status.

Process evaluation

Program satisfaction

To measure the satisfaction of the program, the intervention group participants were asked to rate their satisfaction with the program on a 6-point Likert scale. This satisfaction questionnaire was given only once at the end of the whole CBT program.

Sample Size Calculation

The required sample size was calculated according to the guidelines on the Consolidated Standards of Reporting Trials (CONSORT) for cluster RCTs (78), taking into account the intra-class correlations (ICC) nested by ART institutions. The sample size in the cluster randomized controlled trial should be multiplied by the design effect (1+[m-1] ρ), where m is the average cluster size, and ρ is ICC. In the previous study of Sub-Saharan Africa, ICC for mental health status measured by SF8 among PLHIV attending at HIV clinic was 0.054 (95% CI, 0.03 - 0.12) (79). For another primary outcome, ART adherence, ICC was 0.042 (95% CI, 0.02 - 0.10) (79). Therefore, the estimated ICC for the primary outcome for this study was set to 0.05. The cluster size was set to six. An effect size of an intervention program for individual depressive symptoms was estimated based on the previous meta-analysis (80), and the effect size (d) of cognitive behavioral intervention for depressive symptoms among PLHIV was 0.22. The effect size (d) of depression and antiretroviral therapy adherence association among PLHIV was 0.18 (20). The required sample size ranged from142 to 208 PLHIV from six ART institutions; they were recruited in the case of alpha error probability of 0.05; power of the test 0.80. G*Power V.3.1.9.2 was used to determine the sample size in this study.

Randomization

The six ART institutions were randomized to intervention or control groups. The randomization was stratified into two strata based on the size of the institution (3 -15 staff, > 15 staff) (57)because the intervention effect might be different based on staff numbers and services provided by the institution. This is because those hospitals have more staff members and better diagnosis and treatment facilities than ART clinics. Permuted-blocked randomization (blocked size= 2) was adopted for equal randomization. Randomization was performed by a researcher not involved in this study, using a computer program that

generated random numbers. The randomization result was registered by a research assistant in the presence of the research team. None of the participants who participated in the study were notified of the results of randomization; therefore, the assessments of the depressive symptoms and ART adherence (self-reported) were blinded. In the meantime, peer counselors were notified of the randomization results.

Implemented Elements of the Intervention Program

PLHIV from three ART institutions were provided by 8 sessions of manualized CBT program (Supplementary Table 1). PLHIV from the intervention group were divided into two groups based on the availability of the time, and two peer counselors took the leading role and two other peer counselors were moderators/facilitators. Group-based CBT was implemented for eight consecutive weeks, and in the last week, they created their own written personal proposal plan together with peer counselors.

Statistical Analysis

Descriptive statistics included means and standard deviation (SD) for continuous variables and frequencies for categorical variables. Comparisons between the two groups (CBT and Control) were performed using Student's t-test for continuous variables, and cross-tabulation with χ^2 tests for categorical or ordinal variables. Statistical Package for the Social Sciences (SPSS) version 22 was used to perform these analyses.

Linear mixed models (LMM) with maximum likelihood (ML) were used to assess change over time for the two depression measures, ART adherence, and CD4 count. We used the intent to treat analysis such that all data from the randomized subjects were included in the analysis of models. There was no formal data imputation strategy; the use of SPSS version 22 allowed the use of all available data from each subject. The predictors were the

intervention condition (df=1), time (df=2), and the intervention by the time interaction (df=2). Significance was based on $p < 0.05$ and two-tailed.

Changes to the Protocol

Two changes were made to the registered protocol. The first change was inclusion criteria of the program. After the baseline data collection, to cover the sub-threshold depressive population, we changed the inclusion criteria of having an mBDI-II score greater than or equal to 13 into 10. Another change was to make the depressive symptoms be the primary outcome. At the stage of pre-tested and revision of CBT program, the program covers mainly the depression and ART adherence, therefore, we made changes in the protocol.

3. Results

Participant Flowchart

Figure 1 shows the participants' flowchart in this study. The researcher initially approached eight ART institutions; however, six ART institutions participated in this study (75.0%) and completed the baseline. The reasons for not including the other two ART institutions were the collaborator; MPG had newly started the counseling services at these institutions and had fewer PLHIV taking ART there.

The invitation to the study was done through the peer counselors, and the participants who agreed to participate were provided with the baseline questionnaires. From the six ART institutions, 200 PLHIV were sampled, and they completed the baseline survey. An average cluster size among the six ART institutions was 33.3 (SD= 11.8), with PLHIV ranging from 11 to 40. As a result of stratified and permuted-blocked randomization, three ART institutions were allocated to the intervention; the other three ART institutions were designated as the control group. From each group, that met the inclusion criteria, 28 PLHIV were into the intervention group, and 39 PLHIV were designated to the control group. The remaining 133 PLHIV were excluded from the study because they did not meet the inclusion criteria (128 who had mBDI-II score <10; 5 who had suicidal thoughts) (Figure 1).

At the 6-month follow-up evaluation, three ART institutions and 20 PLHIV (71.4%) in the intervention group, and three ART institutions and 31 PLHIV (79.5%) in the control group completed the survey. During the follow-up, eight PLHIV from the intervention group and 17 PLHIV from the control group found to be dropped out because of several reasons. The most frequent reason was to change their contact numbers (n= 13) and followed by a move to another city (n= 4).

Recruitment

Recruitment of participants and the baseline survey at the six ART institutions was conducted from April 2018 to June 2018. The intervention and control groups were followed up for approximately 6-months; the3-month follow-ups were conducted from September 2018 to November 2018, and the last follow-ups were conducted from January 2019 to March 2019.

Baseline Characteristics

Table 1 describes the characteristics of the PLHIV (Ni= 67) and ART institutions (Nj= 6) participating in this study at the baseline. The mean age of the intervention group was 38.8 (SD= 9.9), and the control group was 32.8 (SD= 9.3). In the intervention group, female PLHIV were 67.9% and in the control group, 53.8%. In both groups, roughly 55% of PLHIV had middle and high school level education. In the intervention group, 89.3% of the participants were married; however, only 51.3% in the control group were married. The mean of ART duration (months) was 38.5 (SD= 30.1) and 41.4 (SD= 48.3) at the baseline in the intervention and control groups, respectively.

Intervention Completion Rate

Of the 28 PLHIV randomized to the intervention group, 20 (71.4%) received CBT sessions, and all PLHIV finished all CBT sessions. The homework completion rate was 81%.

Effects of the Intervention Program on Primary Outcomes

Table 2 shows the frequencies and mean (SDs) of the outcome variables at the baseline, 3-month, and 6-month follow-ups. There were no statistically significant differences in depression symptoms comparing group-based CBT to TAU, whether evaluating outcomes on the mBDI-II (21.1 ± 9.2 vs. 20.4 ± 7.7) or the HSCL-D (16.1 ± 6.7 vs. 13.6 ±7.6) at the

baseline (Table 2). However, the overall depressive symptoms by mBDI-II improved over 6-month in both the intervention and control groups (from 21.1 (SE= 9.2) to 3.8(SE=4.8)in the intervention group and from 20.4 (SE=7.7) to 11.1 (SE=8.7)in the control group). The Cohen's *d*at 6 months was - 1.0 from mBDI-II. A similar pattern was found in the HSCL-D scale; the mean (M) scores decreased from 16.1 (SE=6.7) to 3.4 (SE=5.5) in the intervention group and from 13.6 (SE=7.6) to 6.4 (SE=6.1) in the control group after the 6-month follow-up. The Cohen's *d*at 6 months was – 0.8 for HSCL-D. After the intervention, the total mBDI-II score was reduced by 11.5 to 17.6 (M= 14.6, SD= 7.5), and the total HSCL-D score was also decreased by 8.7 to 10.6 (M= 11.8, SD= 8.0) in the two intervention groups.

Table 3 describes the estimated effect of the intervention on the depressive symptoms and ART adherences by using MML. The peer-led CBT program (mBDI-II, F= 5.1, p= 0.008; HSCL-D, F= 7.8, p < 0.01) had a significant effect on the depressive symptoms. For the mBDI-II scale, the unstandardized coefficient was negative and significant at both 3-month and 6-month follow-ups (b=- 8.9, SE= 3.5, p= 0.01; b= - 8.1, SE=3.0, p= 0.007). For the HSCL-D scale, the unstandardized coefficient was negative and significant at both 3-month and 6-month follow-ups (b= - 11.1, SE= 2.9, p < 0.001; b= - 5.5, SE= 2.4, p=0.03).

Regarding the ART adherence, the mean score increased in both groups from the baseline to the6-month follow-up, and the proportion of high adherence increased both at the intervention and control groups (from 46.4% to 60.0% and from 43.6% to 60.0%, respectively) (Table 2). The Cohen's *d*at 6 months was – 0.15.The unstandardized coefficient for ART adherence was not significant at 3-month or 6-month follow-ups(b= 9.0, SE= 6.1, p= 0.15, b= 8.8, SE=5.2, p= 0.1) (Table 3).

Supplemental Table 4 describes the effect of the intervention on each component of ART adherence (4 self-reported questionnaires, PIT, pill count, and VAS). A significant intervention effect was observed on missing dose within 4-day and PIT, with positive and

significant unstandardized coefficients at the 6-month follow-up for the missing dose (b= 0.3, SE= 0.14, p= 0.04) and PIT (b= - 0.05, SE= 0.24, p= 0.04).

Effects of the Intervention Program on Secondary Outcomes

The mean CD4 count at the baseline was 383.7 (SD= 216.9) and 589.9 (SD= 344.6) for the intervention and control group, respectively (Table 2). The mean CD4 count improved in both groups at 6-month follow-up and became 578.2 (SD= 381.6) and 649.1 (SD= 309.1), respectively (Table 2). The Cohen's *d*at the 6-month follow-up was 0.4 (Table 2).The coefficient for CD4 count at 6-month follow-up was not significant (b= 135.3, SE= 135.5, p= 0.32) (Table 3).

4. Discussion

Our hypothesis was partially supported: depressive symptoms measured by mBDI-II and HSCL-D improved in the intervention group compared to the control group, with large effect size: the intervention effect was statistically significant. To the best of our knowledge, this study was the first cRCT of the effect of a peer-led cognitive behavioral therapy intervention program on improving depressive symptoms among PLHIV. Results indicated that the intervention was feasible, acceptable and was effective in reducing depressive symptoms, while improving CD4 count. The effect size for depressive symptoms estimates emphasized the large magnitude of the intervention effect, which was maintained 6-months after the baseline. The intervention program is unique because it was developed within the local context of PLHIV listening to voices from peer counselors who served as CBT providers. The program developed in this study may be useful in improving depressive symptoms of PLHIV in LMICs with low health care resources.

The intervention program significantly reduced depressive symptoms in the intervention group compared to the control group. The mean scores of the depressive symptoms (mBDI-II) decreased in the intervention group (21.1 at the baseline, 6.1 at 3-month follow-up), while the mean scores of the depression decreased less at the control group (20.4 at the baseline, 14.2 at 3-month follow-up). Similarly, the mean score at the6-month follow-up decreased more in the intervention group (3.8) than in the control group (11.1). A similar pattern was found for HSCL-D as well; the mean score of the depressive symptoms (HSCL-D) decreased sharply in the intervention group (16.1 at the baseline, 4.9 at the 3-month follow-up). In the same way, the mean score reached 3.4 at the 6-month follow-up while the control group mean score was 6.4. The effect sizes were moderate to large (-1.2 to -0.9 at 3-month; -1.0 to -0.5 at 6-month). This finding was consistent with those reported in the previous systematic review (25, 27) and RCTs conducted in the United States (28, 29,

81)using professional therapists and health care staff, with similar effect sizes. This peer-led intervention program may be effective to improve the depressive symptoms among PLHIV. The intervention group had significantly improved depression compared to the control condition, with a large and negative effect size had found in this study. The present study had quite a high effect size, which is very similar to other RCTs conducted in high resources countries like the United States (28, 81).

Several possible reasons might explain the effectiveness of a peer-led CBT program in improving depressive symptoms. First, the CBT program was developed considering the unique behavior patterns and culture of PLHIV of Myanmar. Second, the involvement of peer counselors possibly encouraged the participants to fully participate in the program, with the sessions being implemented smoothly. Peer counselors might also convince participants convinced that this program was relevant and useful for them. Third, the program was delivered in a group-based format, which was probably effective in establishing good communication and relationships between the participants and peer counselors, as well as among the participants. This could lead to a smooth and effective implementation process of the program. Therefore, the newly developed Myanmar version of the CBT program may be feasible and effective in improving depressive symptoms among PLHIV who are under treatment at ART institution in other low-resource settings/countries.

The effect size of the present intervention on ART adherence was small (Cohen's d at 6-month follow-up was -0.15) and non-significant. This finding does not support our hypothesis. ART adherence improved from the baseline to the 6-month follow-up in both groups, and the proportion of high adherence reached 60% in both groups at the 6-month follow-up. This finding was similar to one study conducted in the United States; it stated that CBT improved ART adherence in both groups; however, there was no intervention effect (28). This effect can be seen because both intervention and control groups received adherence

counseling, as in this study. However, other CBT for adherence and depression conducted in the United States and South Africa stated that the intervention had a positive effect on ART adherence(29, 81, 82).The effect of CBT on ART adherence was found when adherence counseling was not provided to the control group (29, 81, 83). In addition, the level of ART adherence was already high at the baseline in both CBT and control groups. This might be another reason for no effect of CBT on ART adherence at the 6-month follow-up. However, in this study, a significant intervention effect was found on the self-reported missing dose and PIT among components of the ART adherence. This is consistent with a previous finding that the self-reported ART adherence improved after CBT counseling in one study conducted in the United States(84). Self-reported missing dose and PIT may be a more sensitive indicator of ART adherence, while the VAS for adherence requires more complex cognitive tasks, and the proportion of returned pill count may not be necessarily an indicator of adherence. It is needed to re-examine the effect of the intervention program on ART adherence using a reliable and valid measure. Also, previous studies used one objective to identify ART adherence. It would be desirable to use a multi-method ART measure in future research on the effect of the intervention program on ART adherence (76).

The small effect size of the intervention was observed for CD4 count (Cohen's d 0.4), while the intervention effect was not statistically significant. This may be explained by a limited contribution from depressive symptoms on the HIV progression among PLHIV on ART with complete viral suppression and restored immune function(13).A greater impact of depressive symptoms on the HIV progression has been demonstrated in previous longitudinal studies with longer follow-ups(13, 14). The effect of a CBT program might be visible in a long-term follow-up.

This peer-led group-based CBT successfully improved depressive symptoms. The program also improved CD 4 count to some extent, although the intervention effect was not

significant. This study also shows that the present group-based CBT program provided by peer counselors can be implemented in low-health care resource settings like Myanmar. This program may be useful to improve depressive symptoms of PLHIV at the ART institutions. In Myanmar, it is recommended that NAP adapts this peer-led CBT program into the HIV treatment program, expecting to improve the treatment effect and the quality of life of PLHIV. It is also possible that the program can be implemented for PLHIV in other countries with limited health care resources.

This study has several limitations. First, the number of participating institutions was fewer than what we planned, despite a great effort to recruit the institutions. As described above, the major reason for not including was the newly established counseling services of the collaborator and the lower number of PLHIV at the institution. Second, the withdrawal rate was 28.5% in the intervention group and the potential contamination may have resulted in over or underestimating the effect of the intervention on the depression and ART adherence. Thirdly, approximately 43% of PLHIV from the control group were lost at follow-up and the participating PLHIV were fewer than the calculation. This may have resulted in an under or overestimate of the main outcome. However, the withdrawal and loss to follow-up happened in both groups, and PLHIV were randomized, so these potential effects are presumed to be similar in the intervention and control group. Fourth, this study relied on a self-report measure of ART adherence; however, this measure was validated and successfully used in resourced countries like Myanmar. Fifth, the findings from this study may not be generalizable to all PLHIV in Myanmar because this cRCT included only six ART institutions in the Yangon Region and MPG implemented ART institutions. The findings may not apply to other regions, or other institutions (such as NGOs or private clinics). To be a representative sample, the sample should include both NGOs and public-run ART institutions. Sixth, the small sample size raised the questions of the generalizability of the findings, and it

can also exaggerate the effects of outcomes. Seventh, two depressive symptoms scales were used in this study, and p value can be inflated. Therefore, the effect size was calculated and used in this study. Eighth, the baseline CD4 count and socio-demographic characteristics were fairly different between the intervention and control groups. This can affect the intervention effect of the study and limit the direct adjustment of outcomes. This may be due to the small number of randomization units.

Although, some limitations should be considered in this study, the newly-developed program seems feasible to be conducted in a low-resource country like Myanmar and effective in improving depressive symptoms and CD4 count among PLHIV who are receiving HIV treatment at ART institutions. However, additional supports such as psychiatric visits, and new technologies like mobile applications and psychiatric consulting through the internet might be needed to make the program more effective in the remote areas of the country. Moreover, additional cRCTs should be conducted with a greater sample size, objective measures of ART adherence, and longer follow-up.

5. Overall Conclusion

In conclusion, the findings from the current study indicated that peer-led cognitive behavioral therapy is feasible, acceptable and effective in improving depressive symptoms and CD4 count among PLHIV who are currently taking ART and have depressive symptoms. Generally the size of the treatment effects, across outcomes, was large in magnitude. This study is the first cRCT to demonstrate a positive effect on the depressive symptoms and CD4 among PLHIV.

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Figure 1 Participant flow chart

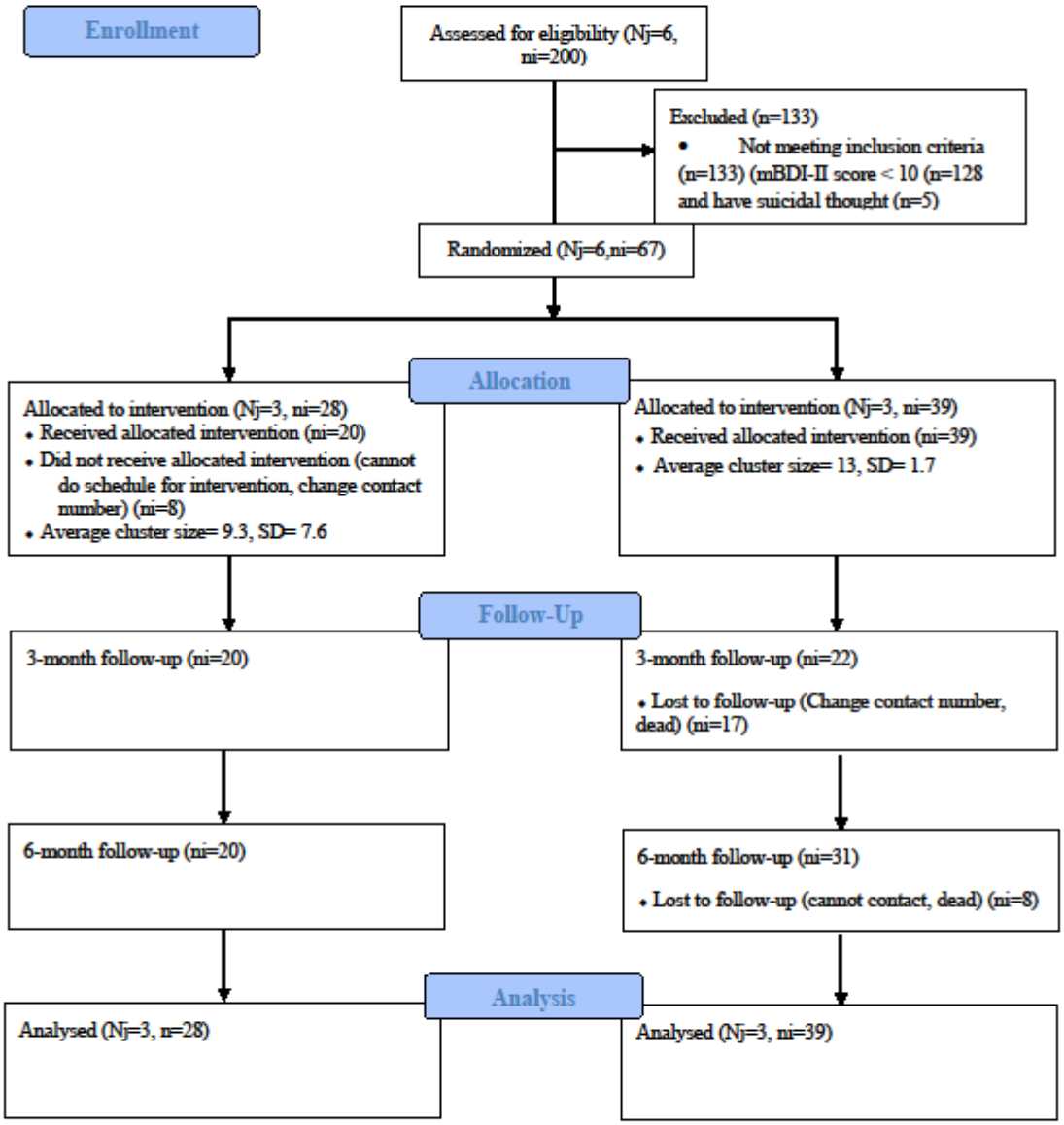


Table 1 Characteristics of PLHIVs at the baseline

Individual level variables	Intervention Nj = 3 (ni = 28 PLHIV)		Control Nj = 3 (ni = 39 PLHIV)	
	n or mean	% or SD	n or mean	% or SD
Age	38.8	9.9	32.8	9.3
Gender				
Male	9	32.1	18	46.2
Female	19	67.9	21	53.8
Ethnicity				
Bamar	25	89.3	36	84.6
Ethnic/Others	3	10.7	6	15.4
Marital status				
Single	2	7.1	13	33.3
Married	25	89.3	20	51.3
Widowed/Divorced	1	3.6	6	15.4
Education				
Primary school	7	25.0	5	12.8
Middle school	10	35.7	8	20.5
High school	6	21.4	14	35.9
Graduate/Postgraduate	5	17.9	12	30.8
Lifetime alcohol use	8	28.6	16	41.0
Lifetime substance use	1	3.6	1	2.6
Lifetime smoking	11	39.3	12	30.8
ART duration (months)	38.5	30.1	41.4	48.3

Table 2 Mean (SD) and frequencies of outcomes at the baseline, 3-month and 6-month follow-up in the intervention and control groups

Outcome	Intervention						Control						Effect size	
	Baseline (ni = 28)		3-month follow-up (ni = 20)		6-month follow-up (ni = 20)		Baseline (ni = 39)		3-month follow-up (ni = 22)		6-month follow-up (ni = 31)		3-month	6-month
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	d	d
Depression														
BDI-II	21.1	9.2	6.1	7.7	3.8	4.8	20.4	7.7	14.2	10.6	11.1	8.7	-0.9	-1.0
HSCL-D	16.1	6.7	4.9	5.5	3.4	5.5	13.6	7.6	13.5	8.8	6.4	6.1	-1.5	- 0.8
ART adherence	1.4	0.6	1.5	0.6	1.6	0.5	1.3	0.7	1.3	0.7	1.6	0.6	0.15	- 0.15
CD4 count	383.7	216.9	-	-	578.2	381.6	589.9	344.6	-	-	649.1	309.1	-	0.4

Note: ART adherence as categorical variable (Number, percent) –Low (2 (7.1%), 1 (5.0%), 0 (0%)), Medium (13 (46.4%), 8 (40%), 8 (40%)), High (13 (46.4%), 11 (55%), 12 (60%) for 3-month and 6-month follow-ups at intervention group, Low (4 (10.3%), 2 (9.1%), 1 (3.3%)), Medium (18 (46.2%), 11 (50%), 11 (36.7%)), High (17 (43.6%), 9 (40.9%), 18 (60%)) for 3-month and 6-month follow-ups at control group

Table 3 Effect of the intervention program on the outcomes using linear mixed model

	Intervention effect b (unstandardized coef.)	SE	95% CI	p value
BDI-II				
Baseline *vs* 3-month follow-up	- 8.9	3.5	- 16.0 – -1.9	0.01
Baseline *vs* 6-month follow-up	- 8.1	3.0	- 14.0- -2.2	0.007
Overall (df = 2)				0.009
HSCL-D				
Baseline *vs* 3-month follow-up	- 11.1	2.9	- 16.9– - 5.3	<0.001
Baseline *vs* 6-month follow-up	- 5.5	2.4	- 10.2– - 0.8	0.03
Overall (df = 2)				0.001
ART adherence				
Baseline *vs* 3-month follow-up	9.0	6.1	- 3.4 – 21.3	0.15
Baseline *vs* 6-month follow-up	8.8	5.2	- 1.7 – 19.3	0.1
Overall (df = 2)				0.1
CD4 Count				
Baseline *vs* 6-month follow-up	135.3	135.5	- 134.4–405.1	0.32
Overall (df = 2)				0.32

Supplementary Table 1 – Elements of intervention program

Session	Activities	Purpose
Session 1- Introduction, What is depression? Importance of ART adherence, Worksheet - pay closer attention on the thoughts	Consent form, Ice breaker, Introduction and set the ground rules of the group; discuss about depression and important of ART adherence, start and close the section with relaxing meditation	Develop the trust between Counselors and the participants, non-judgment and confidentiality, Understanding depression and ART adherence
Session 2- Taking stock and getting start to fight back depression, Worksheet - Personal Experiment	Open with relaxing meditation, and check-in; one week experiences sharing, use a few examples to understand personal experiment, close with re-cap, reflection session within group and close with relaxing meditation	Review how depression affects the health and lifestyle, choose two to three steps to get moving in a positive direction, make a specific plan to try out these steps during next week
Session 3- Continue to do the personal experiment	Open with relaxing meditation, and check-in; review about previous week activities, experiences and homework, use a number of different stories to create a context and frame a personal action plan to fight depression (to know blocks and problems, how to overcome in next week); close with re-cap, reflection session within group and close with relaxing meditation	Review the personal action plan, to identify what plan work for you and what didn't, to know any good experiences from personal action plan, learn roadblocks, and problems, to create new personal experiments to try out in the next week
Session 4- Adding it up and continuing personal experiment	Open with relaxing meditation, and check-in; review about previous week activities, experiences and homework, discuss and experiences sharing of blocks and problems of personal action plan, story activity to solve blocks and problems, set small specific goals for next four-week activities, close with relaxing meditation	Participants examine the personal action plan's blocks and problems, and assist to find ways to overcome these, Encourage participants to set the realistic and small specific goals as personal activity for next few weeks

Session 5- Standing at a distance (Learn the pattern of own thinking)	Open with relaxing meditation, and check-in; review about previous week activities, discuss the stories to know how to look up negative thoughts and learn how to overcome these, pick up one or two own negative thoughts to take a step back	Activity target to understand stress and depression and way to react; encourage participants to pick out common negative thoughts to learn thinking changes
Session 6- Ignoring the evidence	Open with relaxing meditation, and check-in; review previous week exercises and discuss personal experiences over step back, talk about how negative thoughts seem true when you ignore positive information, find out the some example of participants' ignoring evidences, elaborate the story examples to find the way to control negative thoughts, plans ways to catch the own ignoring evidence for next week, close with relaxing meditation	Participants will explore their experiences of stepping back common negative thoughts, learn how they ignoring the good evidence, look more detail to thinking changes
Session 7- Challenging your negative thoughts	Open with relaxing meditation, and check-in; review about previous week activities; learned about own negative thoughts, learn some methods for challenging negative thoughts through different examples, talk about the toughest negative thoughts, plan how participants will use some methods to challenge negative thoughts over the next week	Participants evaluate their own negative thoughts, and ignoring the evidence, and try out various ways to challenge their own negative thoughts

Session 8- Creating a self-care plan	Open with relaxing meditation, and check-in; review about previous week activities, discuss the progress over the course of this program, identify the worked best method and set the specific and realistic goals for continuing the progress, talks about the ways to monitor how you are doing and early to notice when the things get rough, plan for a long-term self-care plan, and write down all these ideas	Participants review what has helped them most in the last few weeks, choose the best plan to continue in the long term, look ahead the situations that may be difficult or problems for them, Create their own written personal plan to help keep depression under control in future

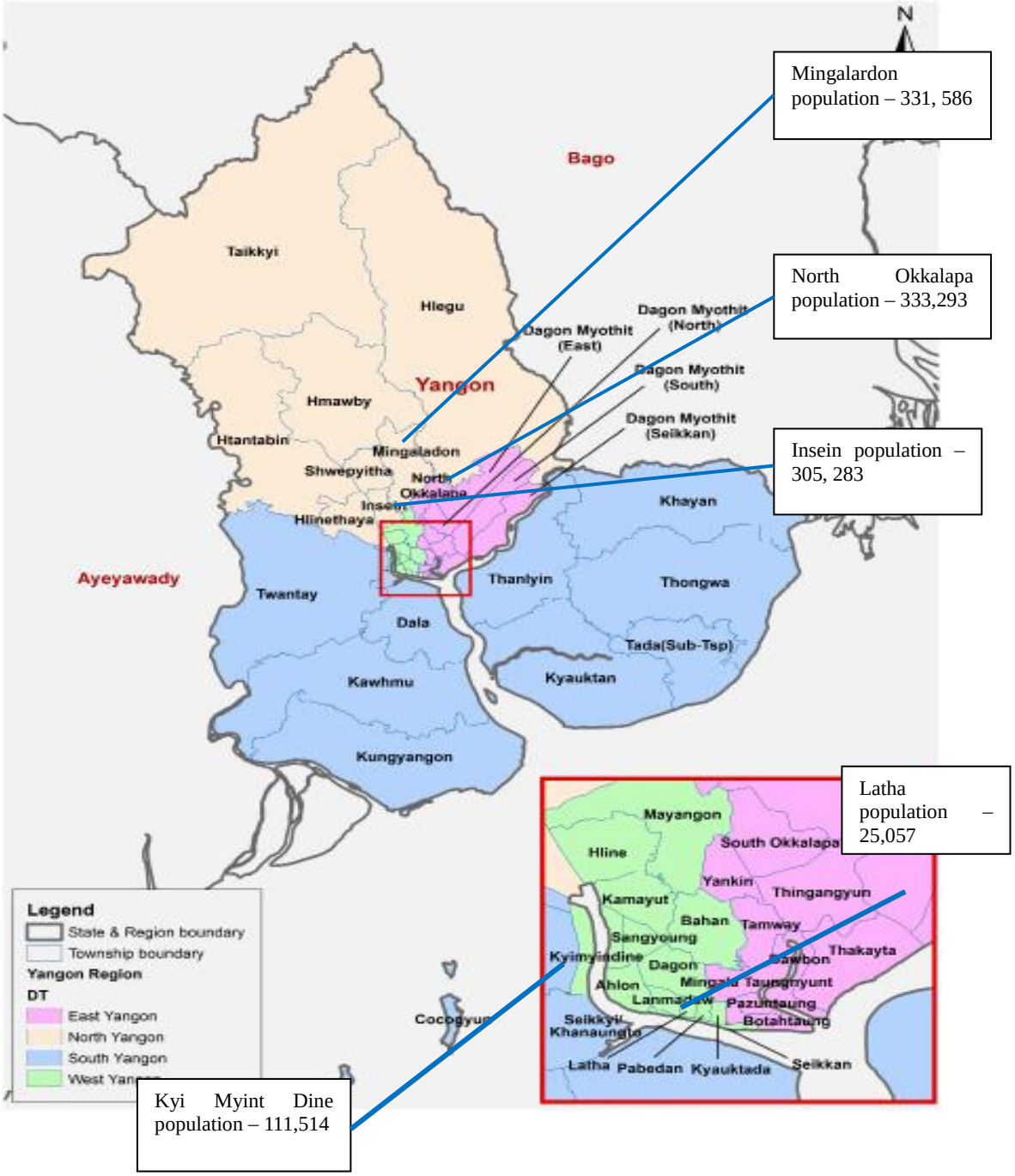
Supplementary Table 2 - Adherence Assessment

Self-reporting	No to all questions	Yes to 1 question	Yes to 2 or more questions
VAS	95% or more	75 – 94%	Less than 75%
PIT – Clients know the ----	Dose, time, and instructions	Dose and time	Dose only or confused
Pill Count	95% or more	75 – 94%	Less than 75%
Overall Adherence	**High**	**Moderate**	**Low**

Supplementary Table 3– Peer counselors' specification

Name	**Age**	**Education**	**ART Counseling Experiences at MPG (years)**	**CBT**
Counselor 1	40	University	2	No experience
Counselor 2	36	High school	2	No experience
Counselor 3	26	Graduate	2	No experience
Counselor 4	37	High school	8	No experience
Counselor 5	49	Graduate	1	No experience
Counselor 6	42	High School	1	No experience

Supplementary Figure 1 – Geographical location and population of selected area



70.9% of population – 15 – 64 years

Supplemental table 4 - Effect of CBT for ART Adherence item by item

	Intervention effect b (Unstandardized coef.)	SE	p value
Self-reported Adherence Q1			
Baseline *vs* 3-month follow-up	-0.22	0.18	0.22
Baseline *vs* 6-month follow-up	0.08	0.15	0.59
Overall (df = 2)			0.18
Self-reported Adherence Q2			
Baseline *vs* 3-month follow-up	-0.23	0.15	0.13
Baseline *vs* 6-month follow-up	-0.27	0.14	0.06
Overall (df= 2)			0.14
Self-reported Adherence Q3			
Baseline *vs* 3-month follow-up	-0.81	0.53	0.13
Baseline *vs* 6-month follow-up	0.3	0.14	0.04
Overall (df = 2)			0.06
Self-reported Adherence Q4			
Baseline *vs* 3-month follow-up	-0.35	0.16	0.03
Baseline *vs* 6-month follow-up	-0.19	0.14	0.18
Overall (df = 2)			0.08
Pill identification test			
Baseline *vs* 3-month follow-up	0.05	0.21	0.81
Baseline *vs* 6-month follow-up	-0.05	0.24	0.04
Overall (df = 2)			0.04
Pill count			
Baseline *vs* 3-month follow-up	-0.35	0.18	0.06
Baseline *vs* 6-month follow-up	0.1	0.18	0.60
Overall (df = 2)			0.06
Visual Analog Scale			
Baseline *vs* 3-month follow-up	-11.15	10.65	0.30
Baseline *vs* 6-month follow-up	6.48	8.28	0.44
Overall (df = 2)			0.04

Appendix 1: **Certificate of Informed Consent**

I have been invited to participate in research of ART adherence and depression program. I understand that it will involve question regarding depression, ART medicine taking details, and 8 sessions of cognitive behavioral therapy and 3 follow-up visits. I have been informed that the risks are minimal and may include some psychological distress. I am aware that there may be no benefit to me personally and that I will not be compensated beyond travel expenses. I have been provided with the name of a researcher who can be easily contacted using the number and address I was given for that person.
I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I provide consent voluntarily to participate as a participant in this research and understand that I have the right to withdraw from the research at any time without in any way affecting my services that get from Myanmar Positive Group (MPG).

Name of Participant ----------

Signature of Participant ----------
Date (dd/mm/yyyy) ----------

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness ----------

Signature of witness ----------
Date (dd/mm/yyyy) ----------

Appendix 2: Questionnaires for the intervention study

Please read to interviewee:

During this interview, you will asked about some personal information including whether you have experienced a variety of potentially stressful life events, and whether you have had problems with feelings or behaviors over the past two weeks. I will also ask about the medication currently you are taking. Remember that I will not write down your name with these answers – all of the information you give us will be kept private and will not be concerned to your name.

Direction for interviewer: If the client refuses to answer a question or does not know the answer to a question, cross out the whole row for that question with one line.

1. Demographic Information

DI.1	Sex (0) Male (1) Female	0			1	
DI.2	Completed Age in years					
DI.3	Current marital status: (0) Single (1) Married (2) Widowed (3) divorced	0	1	2	3	
DI.4	What is the highest level of education you have completed? (0) No formal education (1) Primary (1-4 standard) (2) Middle (5-8 standard) (3) High school (9-10 standard) (4) Graduate/Post-graduate	0	1	2	3	4
DI.5	What is your primary ethnic group? (0) Bamar (1) Ethnic group (2) Others	0		1		2

2. Assessment of Mental Health Symptoms

2.1 Beck Depression Inventory II

This questionnaire consists of 21 groups of statements. Please listen each group of statements carefully and then pick out the one statement in each group that best describes the way you been feeling during the **Previous Two Weeks** including today. Circle the number (0, 1, 2 or 3) beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (changes in sleeping pattern) or Item 18 (changes in appetite).

BD I1.	Sadness 0) I do not feel sad 1) I feel sad much of the time 2) I am sad all the time 3) I am so sad or unhappy that I can't stand it	0	1	2	3

BDI2.	Pessimism 0) I do not discourage about my future 1) I feel more discourage about my future than I used to be 2) I do not expect things to work out for me 3) I feel my future is hopeless and will only get worse	0	1	2	3
BDI 3.	Past failure 0) I do not feel like a failure 1) I have failed more than I should have 2) As I look back, I see a lot of failures 3) I feel I am a total failure as a person	0	1	2	3
BDI 4.	Loss of pleasure 0) I get as much pleasure as I ever did from the things I enjoy 1) I don't enjoy things as much as I used to 2) I get very little pleasure from the things I used to enjoy 3) I can't get any pleasure from the things I used to enjoy	0	1	2	3
BDI 5.	Guilty feelings 0) I do not feel particularly guilty 1) I feel guilty over many things I have done or should have done 2) I feel quite guilty most of the time 3) I feel guilty all the time	0	1	2	3
BDI 6.	Punishment feelings 0) I do not feel I am being punished 1) I feel I may be punished 2) I expect to be punished 3) I feel I am being punished	0	1	2	3
BDI 7.	Self-dislike 0) I feel the same about myself as ever 1) I have lost confidence in myself 2) I am disappointed in myself 3) I dislike myself	0	1	2	3
BDI 8.	Self-criticalness 0) I do not criticize or blame myself more than usual 1) I am not critical of myself than I used to be 2) I would myself for all of my faults 3) I blame myself for everything bad that happens	0	1	2	3

BDI 9.	Suicidal thoughts or wishes 0) I do not have any thought of killing myself 1) I have thoughts of killing myself, but I would not carry them out 2) I would like to kill myself 3) I would kill myself if I had the chance	0	1	2	3
BDI 10.	Crying 0) I do not cry any more than I used to 1) I cry more than I used to 2) I cry over every little thing 3) I feel like crying, but I cannot	0	1	2	3
BDI 11.	Agitation 0) I am no more restless or wound up than usual 1) I feel more restless or wound up than usual 2) I am so restless or agitated that it is hard to stay still 3) I am so restless or agitated that I have to keep moving or doingsomething	0	1	2	3
BDI 12.	Loss of interest 0) I have not lost interest in other people or activities 1) I am less interested in other people or things than before 2) I have lost most of my interest in other people or things 3) It is hard to get interest in anything	0	1	2	3
BDI 13.	Indecisiveness 0) I make decisions about as well as ever 1) I find it more difficult to make decisions than usual 2) I have much greater difficult in making decisions than I used to 3) I have trouble making any decisions	0	1	2	3
BDI 14.	Worthlessness 0) I do not feel I am worthless 1) I do not consider myself as worthwhile and useful as I used to 2) I feel more worthless as compared to other people 3) I feel utterly worthless	0	1	2	3

BDI 15.	Loss of energy 0) I have as much energy as ever 1) I have less energy than I used to have 2) I do not have enough energy to do very much 3) I do not have enough energy to do anything	0	1	2	3
BDI 16.	Changes in sleeping pattern 0) I have not experienced any change in my sleeping pattern 1) a. I sleep somewhat more than usual b. I sleep somewhat less than usual 2) a. I sleep a lot more than usual b. I sleep a lot less than usual 3) a. I sleep most of the day b. I wake up 1-2 hours early and cannot get back to sleep	0	1	2	3
BDI 17.	Irritability 0) I am no more irritable than usual 1) I am more irritable than usual 2) I am much more irritable than usual 3) I am irritable all the time	0	1	2	3
BDI 18.	Changes in appetite 0) I have not experienced any change in my appetite 1) a. My appetite is somewhat less than usual b. My appetite is somewhat greater than usual 2) a. My appetite is much less than before b. My appetite is much greater than usual 3) a. I have no appetite at all b. I crave food all the time	0	1	2	3
BDI 19.	Concentration difficulty 0) I can concentrate as well as ever 1) I cannot concentrate as well as usual 2) It is hard to keep my mind on anything for very long 3) I find I cannot concentrate on anything	0	1	2	3

BDI 20.	Tiredness or fatigue 0) I am no more tired or fatigued than usual 1) I get more tired or fatigued more easily than usual 2) I am too tired or fatigued to do a lot of things I used to do 3) I am too tired or fatigued to do most of the things I used to do	0	1	2	3
BDI 21.	Loss of interest in sex 0) I have not noticed any recent change in my interest in sex 1) I am less interested in sex than I used to be 2) I am much less interested in sex now 3) I have lost interest in sex completely	0	1	2	3

2.2 Mental health problems

The following questions ask about how things have been for you in the Last Two Weeks. Some of the questions relate to how people sometimes feel after experiencing a hurtful or terrifying event in their lives. When you answer each question, I would like you to thin back just over the Last Two Weeks.

In the past two weeks, how often has each of the problems occurred?		None of the time	A little of the time	Most of the time	Almost all of the time
MH. 1	In the last 2 weeks, how often have you had recurring thoughts or memories about the stressful event?	0	1	2	3
MH. 2	In the last 2 weeks, how often have you felt emotionally upset when something reminded you of the stressful event?	0	1	2	3
MH. 3	In the last 2 weeks, how often have you avoided thoughts and feelings related to past stressful events; Did not want to hear about past scary events?	0	1	2	3
MH. 4	In the last 2 weeks, how often have you avoided places and activities that are safe that remind you of the past stressful event?	0	1	2	3
MH. 5	In the last 2 weeks, how often have you felt as if you were going crazy; feel like you become crazy?	0	1	2	3
MH. 6	In the last 2 weeks, how often have you felt that you were the only one who has suffered these events?	0	1	2	3
MH.	In the last 2 weeks, how often have you felt sad; unhappy?	0	1	2	3

7					
MH.8	In the last 2 weeks, how often have you felt no interest in things/less interest in daily activities; no more interest in work; do not want to work?	0	1	2	3
MH.9	In the last 2 weeks, how often have you felt lonely?	0	1	2	3
MH.10	In the last 2 weeks, how often have you felt tired, low in energy or slowed down?	0	1	2	3
MH.11	In the last 2 weeks, how often have you worried too much about things; worried?	0	1	2	3
MH.12	In the last 2 weeks, how often have you been thinking too much?	0	1	2	3
MH.13	In the last 2 weeks, how often have you felt disappointed; disappointed?	0	1	2	3
MH.14	In the last 2 weeks, how often have you felt nervousness or shakiness inside?	0	1	2	3
MH.15	In the last 2 weeks, how often have you felt stress?	0	1	2	3

Calculate the criteria score for this person

A	Write the number of questions the person answered in this box (MH.1- 15) ---------- →	
B	Total scores for MH.1 to MH.15 ---------- →	
If the person refused some questions, calculate the average score for the questions the person answered. Then, replace the refused items with this average. Calcualte the average by adding the total for all answered questions and dividing by the number of answered questions. For example, if someone refused question MH.1 and the total score of MH.2 to MH.15 is "28" then divide 28 by 14. The average is "2". Replace MH.1 with the average "2", and the new total score is "30".		

MH.16	In the past 2 weeks, how often have you had thoughts of wanting to hurt or kill yourself; want to commit suicide?	0	1	2	3
MH.17	In the past 2 weeks, how often have you had thoughts of wanting to hurt or kill others?	0	1	2	3

3. ART adherence

Treatment was initiated on (dd/mm/yyyy) / /

Duration of treatment Months/years

Being telling the clients that, *Most people with HIV have many pills to take at different times during the day. Many people find it hard to always remember to take their pills. It is important for me to understand how you are really doing with your medication. Don't worry about telling me if you don't always take all your doses. I need to know what is really happening, not what you think I want to hear.*

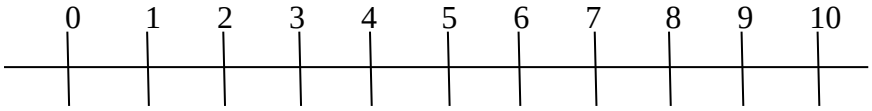
3.1 Self-reporting

Please mark the client's response to the following questions

Question	**Yes**	**No**
Do you sometimes find it difficult to remember to take your medicine?		
When you feel better, do you sometimes stop taking your medicine?		
Thinking back over the past four days, have you missed any of your doses?		
Sometimes if you feel worse when you take the medicine, do you stop taking it?		

3.2 Visual Analogue Scale (VAS)

Ask the client to think back over the past four days and identify the times when she or he either missed a dose or took it at the wrong time. Show the client a copy of this visual analogue scale, or an unmarked enlarged version. While placing your finger on the appropriate place, tell the client that if he or she would point to 0 – in the meantime, you move your finger to 0. Now give the client an opportunity to point out their level of adherence. The health care worker then marks the visual analogue scale. If the scale is marked off at 4, then the percentage adherence would be 40 percent.



Score %

3.3 Pill Identification Test (PIT)

Ask the client to inspect each container and its content. He or she should then tell you the name of the medication, number of pills to take per dose, the times he or she takes the medication, and whether there are any additional instructions.

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Judged correct (Y/N)	

3.4 Pill count

Did the client return the medication container? Yes* No

*If Yes, check that the client only used medication from this container since the date of their last visit. If leftover medication had been used or an emergency prescription obtained, then the calculation will be invalid – omit and move to adherence assessment.

% Adherence = $\frac{\text{Dispensed - Returned}}{\text{Expected to be taken}}$ * 100 $\frac{\square - \square}{\square}$ * 100 = ____ %

Adherence Assessment

Component	Category 1	Category 2	Category 3
Self-reporting	No to all questions	Yes to 1 question	Yes to 2 or more questions
VAS	95% or more	75 – 94%	Less than 75%
PIT – Clients know the ----	Dose, time, and instructions	Dose and time	Dose only or confused
Pill Count	95% or more	75 – 94%	Less than 75%
Overall Adherence	**High**	**Moderate**	**Low**

4. Viral load

Testing was done on (dd/mm/yyyy) ____/____/____

Test result ____

5. Assessment of Alcohol and Substance use

Alcohol			
AL.1	In your life, have you ever drunk alcohol (e.g beer, wine, etc)?	No 0	Yes 1
If "No", Please skip to substance.			
AL.2	In the past three months, have you ever drunk alcohol (e.g beer, wine, etc)?	No 0	Yes 1
Substance			
SB.1	In your life, have you ever used substances (e.g heroin, methamphetamine, yama, yaba, ice, etc)?	No 0	Yes 1
If "No", Please skip to smoking.			
SB.2	In the past three months, have you ever used substances (e.g heroin, methamphetamine, yama, yaba, ice, etc)?	No 0	Yes 1
Smoking			
SM.1	In your life, have you ever smoked (e.g cigarette, cheroot, smokeless tobacco chewing)?	No 0	Yes 1
If "No", please skip the following.			
SM.2	In the past three months, have you ever smoked (e.g cigarette, cheroot, smokeless tobacco chewing)?	No 0	Yes 1

Thank you!

Appendix 3: Ethical approval letter, The University of Tokyo

（医）

審査番号	11908

西暦　2018年04月18日

審　査　結　果　通　知　書
実　施　許　可　通　知　書

倫理委員会の設置者、実施機関の長
東京大学大学院医学系研究科・医学部長　殿

倫理委員会委員長
東京大学大学院医学系研究科・医学部倫理委員会
疫学・観察等研究倫理委員会

赤林　朗

審査依頼のあった件についての審査結果を下記のとおり通知いたします。

記

研究課題名	HIVとうつ病の人々に対する抗レトロウィルス療法のアドヒアランスと抑うつに対する認知行動療法の効果 ：ランダム化比較試験
審査結果	■承認する　□条件付きで承認する　□変更を勧告する　□承認しない □該当しない　□既承認事項の取り消し
審査事項 （審査資料）	＜新規案件＞ ■研究の新規実施 ＜継続案件＞ □研究に関する変更 □その他（　　）
審査区分	■委員会審査（審査日：西暦2018年04月09日） □迅速審査（審査日：西暦　　年　月　日）
指摘事項および 理由・条件等	
備考	

研究責任者　　川上 憲人　殿

依頼のあった研究に関する審査事項について上記のとおり決定しましたので通知いたします。
倫理委員会での審査結果が承認となりましたので、研究の実施を許可いたします。

西暦　2018年04月18日

倫理委員会の設置者、実施機関の長
東京大学大学院医学系研究科・医学部長
宮園　浩平（公印省略）

Appendix 4: Ethical approval letter, Department of Medical Research, Ministry of Health and Sport, Myanmar

The Government of the Republic of the Union of Myanmar
Ministry of Health and Sports
Department of Medical Research
No. 5, Ziwaka Road, Dagon Township, Yangon 11191
Tel : 95-1-375447, 95-1-375457, 95-1-375459 Fax : 95-1-251514

ERC Number: 017817
Approval Number: Ethics/DMR/2018/061
Date of Approval: 17 May, 2018 (valid up to 16 May, 2019)

Project Title: **Effect of cognitive behaviour therapy for antiretroviral therapy adherence and depression among people who living with HIV and depressive symptoms: a randomized controlled trial**

Principal Investigator: **Dr. Khine Lae Win**
The University of Tokyo, Japan

Items Approved:

1. Full Proposal Version 2 Dated 11 May, 2018
2. Informed consent forms (Myanmar and English) Version 2 Dated 11 May, 2018
3. Study area(s) – Kyimyindine STD, North Okkalapa STD, Latha STD, Insein General Hospital, San Pya Hospital, East Yangon General Hospital, Mingalardon Hospital and Wai Bar Gi Hospital
4. Investigators' CV Dated 11 May, 2018

The Ethics Review Committee on Medical Research Involving Human Subjects, Department of Medical Research, Ministry of Health and Sports approves to conduct the proposed research project as it is in full compliance with the Declaration of Helsinki, Council for International Organizations of Medical Sciences guidelines and International Conference on Harmonisation in Good Clinical Practice guidelines.

The principal investigator should be aware that there might be site monitoring visits at any time from ERC team during project implementation and should provide full cooperation to the team.

Prof. Pe Thet Khin
Chairperson
Ethics Review Committee
Department of Medical Research

IORG Number: IORG0007357 FWA Number: FWA00018816 IRB Number: IRB00008835

Appendix 5: CONSORT checklist for a cluster randomized trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[i,ii]	See table 2	P.2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	P. 3-7
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	P.8
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	P. 9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**N/A**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	P. 9-10
	4b	Settings and locations where the data were collected		P. 9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	P. 10-13
Outcomes	6a	Completely defined	Whether outcome measures	P. 13-

		pre-specified primary and secondary outcome measures, including how and when they were assessed	pertain to the cluster level, the individual participant level or both	16
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**N/A**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	P. 15-16
	7b	When applicable, explanation of any interim analyses and stopping guidelines		**N/A**
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		P. 16
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	P. 16
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	P. 16
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	Replace by 10a, 10b and 10c	P.16

		interventions		
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	P. 16
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	P. 16
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	P. 10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		P. 16
	11b	If relevant, description of the similarity of interventions		N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	P. 17
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		P. 17
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	P. 19& Figure 1

		intended treatment, and were analysed for the primary outcome		
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	P. 19& Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up		P. 19
	14b	Why the trial ended or was stopped		N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	P. 19, 20 Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	P. 20-21 Table 2, 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		P. 21 Table 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		NA

Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[iii])		N/A
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		P. 25, 26
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	P. 26
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		P. 23-26
Other information				
Registration	23	Registration number and name of trial registry		P. 9
Protocol	24	Where the full trial protocol can be accessed, if available		N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		N/A

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Effect of cognitive behavior therapy for depression and antiretroviral therapy adherence among people living with HIV in Myanmar: study protocol for a cluster randomized controlled trial

Introduction

Depressive symptoms are significant problem and frequent among individuals with chronic medical illnesses and particularly for people living with HIV (PLHIV). PLHIV are increased risk for major depression the prevalence of major depression was nearly two times higher in PLHIV than in people who do not have HIV in comparison (Ciesla & Roberts, 2001; Yu et al., 2009). Depressive symptoms in PLHIV have been related to more rapid decrease in CD4 count, faster increase in HIV viral load and progressive to AIDS (Ironson et al., 2005; Leserman et al., 2002).

In the treatment of HIV, high levels of adherence to antiretroviral therapy (ART) are necessary to maximize the treatment outcomes. However, depressive symptoms were associated with the ART non-adherence among PLHIV (DiMatteo, Lepper, & Croghan, 2000; Gonzalez, Batchelder, Psaros, & Safren, 2011; Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Li, Ji, Ding, Tian, & Lee, 2012; Seth et al., 2014; Uthman, Magidson, Safren, & Nachega, 2014). Moreover, Improvement in depression was associated with good in ART adherence and while worsening in depression is associated with active drug use (Springer, Chen, & Altice, 2009).

Systematic reviews, (Crepaz et al., 2008) conducted cognitive behavioral intervention for PLHIV's mental health and immune functioning, and concluded that depressive symptom was improved by cognitive behavioral intervention (Crepaz et al., 2008; Himelhoch, Medoff, & Oyeniyi, 2007). The majority of cognitive behavior intervention was group psychotherapy,

counseling, coping effectiveness training, and emotional expression and delivered by professional psychologist and psychiatric (Crepaz et al., 2008; Himelhoch et al., 2007). Moreover, cognitive behavioral therapy (CBT) to depression and ART adherence has been effective to improve ART adherence and depressive symptoms among PLHIV (Himelhoch et al., 2013; Safren et al., 2009; Safren et al., 2012). However, most of the studies are conducted in developed countries and there is limited study for cognitive behavior therapy for depression and ART adherence among PLHIV in developing countries like Myanmar.

Therefore, the following aim and objectives are set to develop and test cognitive behavioral therapy for adherence and depression as applied to ART adherence among PLHIV.

Objectives

(1) To test the effectiveness of cognitive behavioral therapy (CBT) for ART adherence and depression among people living with HIV and depressive symptoms in Yangon, Myanmar

Hypothesis

The hypothesis of this study is that those who are assigned to cognitive behavioral therapy (CBT) for depression and ART adherence have decreased depressive symptoms (primary outcome),better adherence (primary outcome), and improved immunological outcome (CD4 count) than the comparison group (usual counseling for HIV, ART) over six months follow-up period.

Trial design

This study will be a two-arm, parallel-group cRCT. The randomization procedure will be implemented at the cluster (institution) level. The institutions will be randomly assigned to an intervention (CBT) or a control (treatment as usual, TAU). After the completion of a baseline study, the institutions will be randomized using 1:1 ratio. The randomization will be conducted based on the stratum of the institution (hospital site or team site); and non-blinded.

Measurements will be collected at the institution and participants' level, and analysis of the effectiveness of the intervention programe will be conducted at the participants' level taking into account of the cluster (institution) level effects. The study protocol was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN-CTR, ID = UMIN000031442).

2. Methods

Participants

This cRCT will include participants who registered as PLHIV at Myanmar Positive Group (MPG) in Yangon. Participants are taking ART and health services at different centers; divided as Hospital and Team based center. The services and manpower are different between Hospitals and Team sites. Therefore, the cluster level is at center where they take services. The participants will takea face-to-face interview on mBDI-II, ART adherence and suicidal thought and experience. The eligible criteria for the participants in this study are:

1) being HIV positive and on ART for more than one month
2) Age 18 years and older at study entry
3) having sufficient knowledge of Myanmar language
4) available for the next 10 weeks to work on intervention

The participants who have the following criteria will be excluded:

1) declined to participate in this study

The participants who have BDI-II score greater than 10 at screening and no suicidal thought and experiences will select for the intervention. Not to miss the sub-threshold depressive participants, BDI-II score greater than 10 was set as cutoff score to include in this study (Hobkirk et al., 2015). In addition, psychological treatments like CBT have significant effect on the sub-threshold depression (Cuijpers, Smit, & van Straten, 2007).

Procedure

Figure 1 shows a participant flow chart for this study. We will recruit the participants from MPG. We will contact the participants who getting services at different centers (eight centers) through the counselors of MPG and invite to them to participate in this study. After full explanation of study purposes and procedure, participants will have two opportunities to give written informed consent to participate in this study. At the initial screening, participants need to provide informed consent form to answer the screening question (mBDI-II, Adherence and suicidal thought). At the initial screening, the expected response rate is 80%, therefore, about 300 participants will expect to agree and participate. After participants complete the baseline survey, participants who meet the criteria will contact to participate in the intervention. The centers will be allocated randomly to the intervention or control. For those who agree to provide the informed consent will conduct cognitive behavior therapy (CBT) program for further 8 to 10 weeks. Assignment to intervention group (CBT)orcontrol group (usual Counseling) will be concealed from both CBT therapist and participants until the conclusion of the first counseling visit. The post-survey will conduct (mBDI-II, adherence, and CD4 count, service satisfaction question) within one month after completion the program (3-month follow-up) and 6-month follow-up survey will conduct both in the intervention and control groups.

Intervention& Control:

Group based CBT is a structured, manualized 8-session program adapted from a previously established manual (Furukawa et al., 2012; J, 2008).The program is rewritten into Burmese to fit with Myanmar people who have HIV and depressive symptoms. The client manual which will be used by both clients and counselors contains all the materials to be covered in each session with the space to write down his or her feeling and examples. The trainer manual with detailed example and theoretical background is also prepared. The

trainers and the clients will share one book; called “Weekly Activity Book” and that will contain homework worksheets and daily ART status calendar that stated by the clients. This book will reflect the daily activity results, self-monitoring results of the clients. For the quality control of the intervention, the manual in Burmese will set for the whole intervention and this manual will modify by two health professionals who are expert in psychiatric field.

Each session is designed to complete within 30 to 45 minutes, however, the actual length depends to participants and counselor’s assessment and need. Session are meant to happen at weekly intervals but it can be space for up to two weeks depends on participant’s and counselor’s schedule. Each session star with a brief review of previous session and the homework. The initial session includes psycho education of the CBT model, motivational interviewing and adherence. Session 2-4 focuses on the increasing pleasant activities through personal experiments. Session 5-7 focuses on problem identifying, and challenging negative thoughts. In session 8, the participants and the counselors together review the cognitive and behavioral skills that learned in the program and create the self-care plan for self-monitoring, identification, and preparing for the high risk situation.

The counselors who provide the CBT will be the peer counselor who trained to provide psychosocial support to people living with HIV and at least 1 year experience as a counselor. We will invite one psychiatric who have experience on providing motivational interview and counseling, make five-day training for counselors. After the training, we will do the role plays and revise again for the actual intervention. In addition, to assure the quality of CBT, counselors will monitor by researcher, psychiatric throughout the intervention and do the regular discussion for progress and difficulties. All the intervention will held at the place of MPG office. The other group (a control group) will receive only the regular counseling section regarding HIV, and ART.

Outcomes:

The study will be conducted by individual interviews using the structured questionnaire for the screening. All questionnaires will translate into the local (Myanmar) language by one health professional who has full understanding of HIV, drug use, depression and the culture of Myanmar. Back translation will be done by two health professional who have not connected with this study.

Primary outcomes: Adherence is defined as the extent to which a person takes a medication according to medical prescription, inclusive of timing, dosage and consistency and in term of right doses, right time and following the dietary recommendation(Aye, Puckpinyo, & Peltzer, 2017; Chaiyachati KrH Ogbuiji O, 2014). The primary outcome will be the ART adherence and it will measure by multi-method tool (four methods)(Steel Gavin, 2007). These are self-reporting, visual analogue scale (VAS), pill identification test (PIT), and pill count. After combing all these questions, ART adherence will divide into three groups; high, moderate and low. Adherence will assess at baseline as well as at the end of intervention, one month, three month and six month after intervention.

The another primary outcome; depressive symptoms will assess using Beck's Depressive Inventory II (BDI-II) scale, 21 items questionnaire from Beck Institute of Cognitive Therapy and Research, and which have been validated in the psychiatric outpatients and coefficient alpha was 0.91 (Beck, Steer, Ball, & Ranieri, 1996). For each item, the participants will ask about how often they experienced the symptoms related to depression during the previous two weeks. Individual items are scored on 0-3. Total scores for depressive symptoms range from 0 to 63 and where higher scores indicate greater depressive symptoms.

International Depressive symptom Scale (IDSS); mental health symptoms part will be used in this study to measure the depressive symptoms. IDSS mental health symptoms part consists of 15 items and that have been validated in the primary health care clinic attendees in

Myanmar and coefficient alpha was 0.92 (Haroz et al.). For each item, the participants will ask about how often they experiences the symptoms related to mental health during the previous two weeks. Individual items are scored on 0 “none of the time” to 3 “Almost all of the time”. Total score for symptoms range from 0 to 45, and the higher score indicates more mental health problems.

Secondary outcome: The viral load will record from each participant as one of the secondary variable and it will use as the continuous variable.

Demographic variables: Background characteristics such as sex, age, race, marital status, education and occupation status, income and expenditure per month will assess in this study. Their drug use history and methadone maintenance therapy will also assess.

Sample size:

The required sample size was calculated according to the guidelines on the Consolidated Standards of Reporting Trials (CONSORT) for cluster RCTs (Campbell, Elbourne, Altman, & group, 2004) taking into account the intra-class correlations (ICC) nested by ART dispensing sites (Table 1). Sample size in the cluster randomized controlled trial should be multiplied by the design effect (1+[m-1] ρ), where m is the average cluster size and ρ is ICC. In the previous study of Sub-Saharan Africa, ICC for mental health status measured by SF8 among people living with HIV attending at HIV clinic was 0.054 (95% CI 0.029, 0.119)(Zhang J. et al., 2014). For another primary outcome; ART adherence, ICC was 0.042 (95% CI 0.022, 0.096) (Zhang J. et al., 2014).Therefore, the estimated ICC for the primary outcome for this study was set to 0.054 and cluster size was set to 4. An effect size of intervention program for individual depressive symptoms was estimated base on the previous meta-analysis (Crepaz et al., 2008), and the effect size (d) of cognitive behavioral intervention for depressive symptoms among PLHIV was 0.22. The effect size (d) of depression and antiretroviral therapy adherence association among PLHIV was 0.18

(Gonzalez, J. S et al., 1999). The required sample size ranges between 58 to 99 PLHIV and from 4 ART centers they will recruit in the case of alpha error probability of 0.05, power of the test 0.90 (Table 1). G*Power V.3.1.9.2 was used to determine the sample size in this study.

Table 1 Sample size calculation for cRCT

Article	Effect size (d) (95% CI)	Required sample size	Design effect	Required sample size for cluster RCT
Gonzalez, J. S et al., 1999	0.18 (0.13, 0.24)	61	1.162	98.82
Crepaz et al., 2008	0.22 (-0.04, 0.49)	50	1.162	58.1

Randomization

The eight ART dispensing sites will be randomized to intervention or control group. The randomization will be stratified into two strata based on urban or suburb because intervention effect might be different based on educational factor; it has been proven that urban people have more higher education and good literacy rate (Myanmar Demographic Health Survey 2015-16). From each strata, either intervention or control group will randomly selected. Lottery randomization will do for the randomization and this randomization will be done by the one who does not involve in the research. The randomization result will register by research assistant on the present of the research team.

Data collection technique:

Pretested structured interview questionnaires will be used for data collection.Face-to-face interviewing method will be applied by two trained interviewers.The questionnaires will consist of variables indicating the socio-demographic factors, client's factors upon health care services and ART adherence, knowledge about HIV and ART, depressive symptoms.

Data Analysis

Repeated measures (General linear models – GLM) will be used for pre-post

assessment of adherence and depression. Significant p value is < 0.05 at 95% confidence interval and two tailed. The data will enter and analyze with SPSS 16.0 (SPSS, Inc., Chicago, IL).

3. Ethical Consideration

All participants will be explained objectives, benefits, adverse effects and uses of this study. The voluntary written inform consent will be taken from all participants before starting the interview. Trainers will monitor the well-being of the participants in both intervention and control group. Each week during intervention and at the time of interview, they will ask how the participant is doing. When the depressive symptoms worsen or suicidal thoughts will be happened, the trainers will discuss with the participants. If necessary, the trainers can refer the participants to the out-patient unit of general hospitals. The trainers can discuss with the researchers and psychiatrics. When a participant is referred for more intensive treatment to psychiatrics, the participants may continue with the study, but the referral will be added as a covariate in the analysis to control the effect on outcome. All participants will be assured for confidentiality. All participants will be assure for withdraw from the research anytime and it will not affect the treatment. Ethical approval will be taken from Research Ethic Committee of The University of Tokyo and Research Ethical Committee of Department of Medical Research (Lower Myanmar) for the local site.

4. Expected Benefits

By doing this study, the effective of cognitive behavioral therapy for ART adherence and depression can develop for people living with HIV (PLHIV). This data will be useful for the further long term intervention program for PLHIV in developing countries like Myanmar. In addition, this study can be useful for the policy formation of HIV control programin Myanmar.

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