Guided Internet-based intervention for people with HIV and depressive symptoms: A randomised controlled trial

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Abstract

Background: Many people living with HIV (PLWH) suffer from depressive symptoms, but some do not receive adequate treatment for it. We developed an online self-help intervention for PLWH with depressive symptoms, based on previous research. The aim of this study was to investigate the effectiveness of the intervention on depressive symptoms in PLWH.

Methods: A randomised controlled trial was conducted. PLWH with mild to moderate depressive symptoms were recruited in 23 HIV treatment centers in the Netherlands. Stratified randomization (1:1) by treatment center and sex was conducted with random number tables. The Internet-based intervention (available in Dutch and English) consisted of cognitive behavioural therapy, with minimal telephone coaching during eight weeks. The control condition consisted of weekly attention only from a coach during eight weeks and access to the intervention after the second post-test. Primary outcome was depressive symptoms, measured with the Patient Health Questionnaire-9 (PHQ-9) and the Center of Epidemiologic Studies Depression Scale (CES-D) at pretest and three post-tests (two, five, and eight months after baseline). Intention to treat analyses were conducted. This study is registered with Nederlands Trialregister, number NTR5407.

Findings: Between February 2015 and December 2015, 188 participants were randomly assigned to the intervention (n = 97) or control group (n = 91). Depressive symptoms decreased in both groups, but in the intervention group the reduction was significantly larger than in the control group (*d* = -0.56, 95% CI [-0.85, -0.27] for the PHQ-9 and *d* = -0.72, 95% CI [-1.02, -0.42] for the CES-D). This effect was found on the short term and on the long term. In the intervention group significantly more participants reached the criteria for clinically significant change in depressive symptoms than in the control group. No adverse events were reported.

Interpretation: The guided Internet-based intervention may be effective in treating depressive symptoms. Future research should focus on the effectiveness of (online) psychological interventions for PLWH with mental health problems in low- and middle-income countries.

Funding: Aids Fonds.

Introduction

Depressive symptoms are common in people living with HIV (PLWH); the prevalence is about 33%.[1] A possible consequence of depression in PLWH is reduced adherence to antiretroviral therapy (ART).[2] Although several psychological interventions have been found to effectively reduce depressive symptoms,[3,4] improve ART adherence,[5] and quality of life,[3] many PLWH do not seek treatment when they feel depressed, due to, for example, perceived stigma.[6] Internet-based interventions may help to overcome barriers to depression treatment for PLWH. In addition, they may reach more people, can be followed anonymously at preferred times and places, and may be more cost-effective. In the past years, Internet-based treatments were found to be effective in treating depression in the general population,[7] and in people with chronic somatic conditions.[8] Furthermore, face-to-face and guided Internet-based interventions for depression were found to be equally effective.[9]

Only four previous studies were conducted regarding the effectiveness of computerized/Internet treatments for depressive symptoms in PLWH.[10-13] Three of these interventions did not improve mood.[10,12,13] An online support group intervention for PLWH reduced depressive symptoms, but this study did not include a control condition.[11] The other studies investigated a metacognitive therapy and positive psychology intervention,[10] a cognitive behavioural intervention,[13] and a stress-management training.[12] An explanation for the ineffectiveness of these interventions is that they did not meet the needs of PLWH with depressive symptoms.[12,13] For example, one of the interventions was more directed at improving adherence than depression.[13] Therefore, it is necessary to develop online interventions for PLWH that effectively reduce depressive symptoms.

We designed an Internet-based treatment: Living positive with HIV.[14] It is based on a booklet self-help program for PLWH with depression.[15] The booklet was designed specifically for PLWH, to meet their needs and preferences.[16] A randomised controlled trial (RCT), showed that the booklet was effective in decreasing depressive symptoms, compared to a waiting list control condition.[15] After the RCT, the self-help booklet was adapted and converted into the current Internet-based self-help intervention. Thereafter, a focus group evaluated the intervention and it was adjusted. Subsequently a pilot study was conducted, in which twenty PLWH completed the intervention with telephone coaching. Depressive symptoms decreased after the intervention and user satisfaction was high (for more information about the pilot study, see [14]).

Aim of the current study was to investigate the effectiveness of the guided Internet-based self-help intervention in decreasing depressive symptoms in PLWH, compared to a

waiting list attention-only control condition. The effect of the intervention was examined on the short and long term (up to six months follow-up). In addition, we investigated the effect of the intervention on anxiety and the user satisfaction with the intervention.

Panel: **Research in context**

Evidence before this study

We conducted a meta-analysis regarding the effectiveness of psychosocial interventions for PLWH to improve mental health. This meta-analysis contains one Internet-based intervention for PLWH that investigated effects on mood. On August 30, 2017 the search was updated; the databases PubMed, PsycInfo, and Embase were searched by using terms related to "HIV", "Internet-based therapy", and "depression". One additional study was found. Concluding, only two Internet interventions were found for PLWH with depressive symptoms and both were not effective in improving mood.

Added value of this study

This study found that the present guided Internet-based intervention may be effective in improving depressive symptoms in PLWH, compared to an attention-only control condition. This effect remained on the long term and also anxiety was significantly reduced. Online interventions have certain advantages, such as a large reach and accessibility. In addition, this intervention is available in Dutch and English and may be adapted and used in other countries.

Implications of all the available evidence

PLWH with depressive symptoms should be referred to effective psychological treatments. Ehealth interventions are emerging and found to be equally effective as face-to-face interventions. Therefore, treatment providers may refer PLWH with depressive symptoms to an online intervention, such as the present intervention. More research into moderators, mediators, and cost-effectiveness of Internet-based interventions is needed.

Methods

Study design

The study is an RCT including a pretest and three post-tests: two, five, and eight months after baseline (two post-tests in the control group). Patients were recruited in 23 of 26 HIV treatment centers in the Netherlands. The study was approved by the medical ethics committee of the Leiden University Medical Center (LUMC; nr. P14.091). The study protocol has been published elsewhere.[14]

Participants

There was a two-step screening on depressive symptoms. Nursing consultants and doctors in HIV treatment centers screened HIV patients initially on depressive symptoms during regular check-ups with the Patient Health Questionnaire-2 (PHQ-2).[17] When the score was > zero and the patient was interested in participating, the patient was referred to the researchers for the second screening with the Patient Health Questionnaire-9 (PHQ-9), using established cut-off scores.[18] One HIV treatment center screened patients with the Hospital Anxiety and Depression Scale (HADS),[19] as this questionnaire was already in use. Total scores > 2 and < 16 on the HADS indicated eligibility to be referred to the researchers. In addition, advertisements for the study were spread via the Dutch HIV Association (eight patients were included this way). Researchers called all interested patients to provide more information and to screen on eligibility.

Inclusion criteria were: being HIV positive for at least six months; age > 17 years; mastery of the Dutch or English language; being available for eight weeks to work on the intervention; having Internet access and e-mail address; absence of severe cognitive impairments; not currently treated by psychologist/psychiatrist; presence of mild to moderate depressive symptoms (PHQ-9 score > 4 and < 20); no use of antidepressants, or use for more than three months and no change of type or dose of antidepressants in the past three months; and absence of severe suicidal ideation (score < two on question nine concerning suicidal thoughts of the PHQ-9). Patients with severe depressive symptoms and/or suicidal ideation were referred to their general practitioner or HIV treatment center. For more information about ethical precautions see [14] When patients were willing and eligible to participate, online informed consent was signed.

Randomisation and masking

Participants were randomly allocated to one of two conditions (1:1): the Internet-based intervention or the control condition. Stratified randomisation by treatment center and sex was conducted. Random number tables were used and randomisation was performed in blocks of 12 participants per treatment center (six males and six females). The randomisation sequence was created by an independent researcher and was concealed from the main researcher. The main researcher did allocate participants to conditions, but the characters in the randomisation file were white, until assignment of a participant was carried out (then the letters of one line in

the file were made visible). Participants, researchers and coaches were not blind to the assigned condition.

Procedures

After signing informed consent, participants completed the pretest and were randomly assigned to one of two conditions. When participants completed the intervention (about eight weeks later, maximum ten weeks) they received the first post-test, and participants in the control group received the post-test after eight weeks. The second post-test was sent three months later and the third post-test (intervention group only) was sent six months after treatment completion. The participants who completed all questionnaires received €25. The last post-test of the last participant was completed in October 2016. All instruments that were used at the different time points can be found in the Appendix (p 1). The Internet-based self-help intervention consisted of CBT. Psychoeducation was alternated with exercises and assignments. The intervention was based on a self-help booklet for PLWH with depressive symptoms,[15] which was extended in three ways: 1) An activation component was added; 2) Minimal coaching with motivational interviewing was included to prevent attrition; and 3) The program was translated into English to reach more PLWH. The intervention included four main components covered in eight lessons. The first component was activation, where participants were encouraged to perform pleasant activities. The second component contained relaxation exercises. The third component included assignments to identify and change negative thoughts. The last component included goal setting and increasing confidence to attain goals. Participants received login details for the secured website of the intervention. Participants worked about eight weeks on the intervention, one to two hours a week. They received telephone coaching (see below).

Participants in the control condition were put on a waiting list and received attention only from a coach. After the second post-test participants in the control condition were invited to start with the intervention.

All participants received minimal telephone coaching. Participants in the intervention group were called by a personal coach weekly for about 15 minutes. They were asked how they were doing and how they proceeded with the intervention. Furthermore, motivational interviewing was used to prevent attrition. Formal psychotherapy was not included in the coaching, but depressive symptoms and suicidal thoughts were monitored. Coaching was offered until participants completed the intervention, with a maximum of ten weeks. After ten weeks, they could complete the intervention independently and could ask questions via e-

mail. Fourteen participants did not finish the intervention in ten weeks. Participants in the control group were also called weekly by a personal coach, for about five minutes during eight weeks. They were asked how they were doing and coaches motivated them to stay in the study. In addition, coaches monitored depressive symptoms and suicidal thoughts by asking questions about the participants' mood. When depressive symptoms or suicidal thoughts increased and became severe, this was discussed with the participant and they were referred to their general practitioner or HIV treatment center.

Coaches were Master students in clinical psychology or graduates with an MSc in Psychology. They all had followed several clinical courses during their Masters, in which they learned communication skills and therapeutic strategies. Coaches were trained by the main researcher. During the training, coaching procedures and motivational interviewing were explained and practiced. Coaches received a coaching manual with more information about motivational interviewing, the study, the procedures and content of coaching (e.g. what to do when depressive symptoms of a participant increase). In the beginning, weekly supervision sessions were arranged with all coaches and the main researcher to discuss difficulties and questions. After a few months, these supervision sessions were phased out; coaches and the researcher called or e-mailed individually when needed.

Outcomes

All assessments were completed online via a secured website, except for the PHQ-9 that was used for telephone screening. Primary outcome was depressive symptoms, as assessed with the PHQ-9,[18] (total score 0-27, higher scores indicating more symptoms) and the Center of Epidemiologic Studies Depression Scale (CES-D,[20] total score 0-60, higher scores indicating more symptoms). Both questionnaires were used to increase the strength of the findings and were recommended to be used in PLWH.[21] The secondary outcome was anxiety symptoms, as assessed with the Generalized Anxiety Disorder-7 (GAD-7,[22] total score 0-21, higher scores indicating more symptoms).

A self-designed questionnaire was used to ask about demographic characteristics and HIV information. Furthermore, medical data (e.g. viral load) was obtained from the Athena/SHM Cohort Study after consent from the participant. The ATHENA Cohort Study is maintained by the Stichting HIV Monitoring, which is supported by the Dutch Ministry of Health via the National Institute for Public Health and Environment (RIVM).

User satisfaction was measured with a self-designed questionnaire at the first post-test. In the intervention group, participants were asked to give a grade for the intervention (0-10) and

whether they would recommend the intervention (yes, maybe, no). In both groups, participants were asked to give a grade for the coach (0-10).

Statistical analysis

A power analysis with the program Power Analysis and Sample Size Software (PASS)[23] was performed. With an estimated effect size of 0·50 (based on the RCT on the effectiveness of the self-help booklet [15]), an alpha of 0·05, a power of 0·80, and an expected dropout of 15% at the first post-test, 150 participants had to be included. We aimed to include 200 participants, since we expected attrition during follow-up. For more information about the power analysis, see.[14]

All analyses were conducted in SPSS version 23 and an α of 0·05 was used for significance testing. Differences between dropouts and completers of the intervention/study were investigated with χ^2 tests and ANOVA's. The analyses were based on intention to treat (ITT).

Longitudinal multilevel regression analyses (LMRA)[24] were conducted to investigate differences between groups in depressive and anxiety symptoms from pretest to post-tests. Time and Group were included as fixed effects and slopes for Time and the intercept were included as random effects. Pretest, first post-test and second post-test were included in the between-group analyses. Pretest and three post-tests of the intervention group were included in the within-group analyses to examine the long-term effects of the intervention. Maximum likelihood estimation was used to estimate the effects in the model. It was examined which covariance structure provided the best fit; the variance components option was chosen for the between-group analyses and the heterogeneous autoregressive option was chosen for the within-group analyses. Additionally, a per protocol analysis was performed, with participants that completed at least five lessons of the intervention (indicated by self-report); using this minimum ensured that at least three out of four main intervention components were actually followed. The effect of HIV treatment center on the random intercept was investigated exploratory, by adding treatment center as an extra level in the analysis.

Cohen's d was used as effect size. For the between-group effect sizes mean change scores of the control group were subtracted from mean change scores of the intervention group and divided by the pooled standard deviation at pretest of the raw scores.[25] For the effect size of Time (long term effect of the intervention), we used the formula b/SD.[25] The standard deviation of the raw scores of the intervention group at pretest was used. Effect sizes were calculated by using the estimated values from the LMRA. The formula that was described by

de Zeeuw et al. [26] was used to calculate the standard error of the between-group effect size and subsequently 95% CI's of effect sizes.

Clinically significant change, deterioration, and number needed to treat (NNT) from pretest to the first post-test were examined for the PHQ-9 and the CES-D. First, a reliable change index was calculated for each individual to determine improvement; pretest score was subtracted from first post-test score and divided by the standard error of difference between the two scores.[27] To calculate the standard error of difference, test-retest reliability (r_{xx}) was used: r_{xx} = 0·84 for the PHQ-9[18] and the CES-D. When the reliable change index was < -1·96, this indicated improvement. Second, recovery was calculated by examining whether a cut-off point for depression (10 on the PHQ-9[28] and 22 on the CES-D[29]) was crossed at the first post-test. Recovery was only calculated for participants that scored above this cut-off at pretest (clinical cases), because participants that scored below this cut-off at pretest already reached the criterion.[27] Third, it was calculated whether a participant both improved and recovered for participants that scored above the cut-off at pretest. Then, the criteria for clinically significant change according to Jacobson and Truax,[27] were reached. Fourth, deterioration was calculated, which was indicated by a reliable change index > 1.96. Last, NNT was calculated by using the percentages of participants that reached the criteria for clinically significant change. Clinically significant change, deterioration, and NNT were calculated on the per protocol sample by using the raw data.

This study is registered with Nederlands Trialregister (NTR5407).

Role of the funding source

The funder had no role in study design, data collection, analysis, and interpretation, or writing the report. The corresponding author had full access to all data and authors SVL, NG, PS, and VK had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the flow of participants through the study. Between February 2015 and December 2015, 3642 PLWH were screened for depressive symptoms in HIV treatment centers, of whom 445 were subsequently screened by the researchers. In total, 188 participants were included in the study; 97 in the intervention group and 91 in the control group. In the control group, 77 participants (85%) completed the first post-test and 67 (74%) completed the second post-test. Forty-six participants (51%) started with the intervention after the waiting period. In the intervention group, 88 participants (91%) started with the

intervention, 75 (77%) completed the first post-test, 64 (66%) completed the second post-test and 60 (62%) completed the third post-test. The participants in the intervention group that dropped out (i.e. did not complete the first post-test), all stopped before they completed the fifth lesson. Reasons for dropping out can be found in Figure 1. There was no significant difference between groups in proportion of participants that did not complete the first post-test. In addition, no significant differences were found on any of the baseline characteristics between participants that did complete and did not complete the first post-test.

Table 1 shows the baseline characteristics. A majority of the participants was male, approximately 46 years old, homosexual, and had followed medium or high education. On average, participants had the HIV diagnosis for about ten years and used ART. Participants in the intervention group were called by the coach 6·38 times on average (*SD* = 2·59), and in the control group 6·23 times on average (*SD* = 2·18), with no differences between groups ($t(183{\cdot}94) = 0{\cdot}43$, $p = 0{\cdot}67$). There was a difference between groups in the total average duration of calls per participant: 90·74 minutes (*SD* = 60·32) in the intervention group and 60·52 minutes (*SD* = 42·30) in the control group ($t(172{\cdot}47) = 4{\cdot}00$, $p < 0{\cdot}0001$).

Figure 2 presents the mean scores on the PHQ-9, CES-D, and GAD-7 over time in both groups (also in Table in Appendix, p 2) and Table 2 presents the results of the mixed model analyses where groups were compared in the change in depressive and anxiety symptoms over time. For the PHQ-9 and the CES-D, there was a significant effect of Time x Group: the reduction in depressive symptoms from pretest to post-test 1 was significantly larger in the intervention group than in the control group. The effect sizes for the differences in PHQ-9 and CES-D scores between conditions at post-test 1 (corrected for baseline) were *d* = -0·56, 95% CI [-0·85, -0·27] for the PHQ-9 and *d* = -0·72, 95% CI [-1·02, -0·42] for the CES-D. Furthermore, there was a significant effect of Time: depressive symptoms decreased from pretest to post-test 1 in both groups. For the GAD-7, there was no significant effect of Time, but there was an effect of Time x Group: the reduction of anxiety symptoms from pretest to post-test 1 was significantly larger in the intervention group than in the control group (*d* = -0·75, 95% CI [-1·05, -0·45]. There were no effects of Time or Time x Group from post-test 1 to post-test 2. The effect sizes for the differences in PHQ-9, CES-D and GAD-7 scores between conditions at post-test 2 (corrected for baseline) were somewhat smaller than at post-test 1 (*d* = -0·46, 95% CI [-0·75, -0·17] for the PHQ-9, *d* = -0·47, 95% CI [-0·76, -0·18] for the CES-D, and *d* = -0·56, 95% CI [-0·85, -0·27] for the GAD-7.

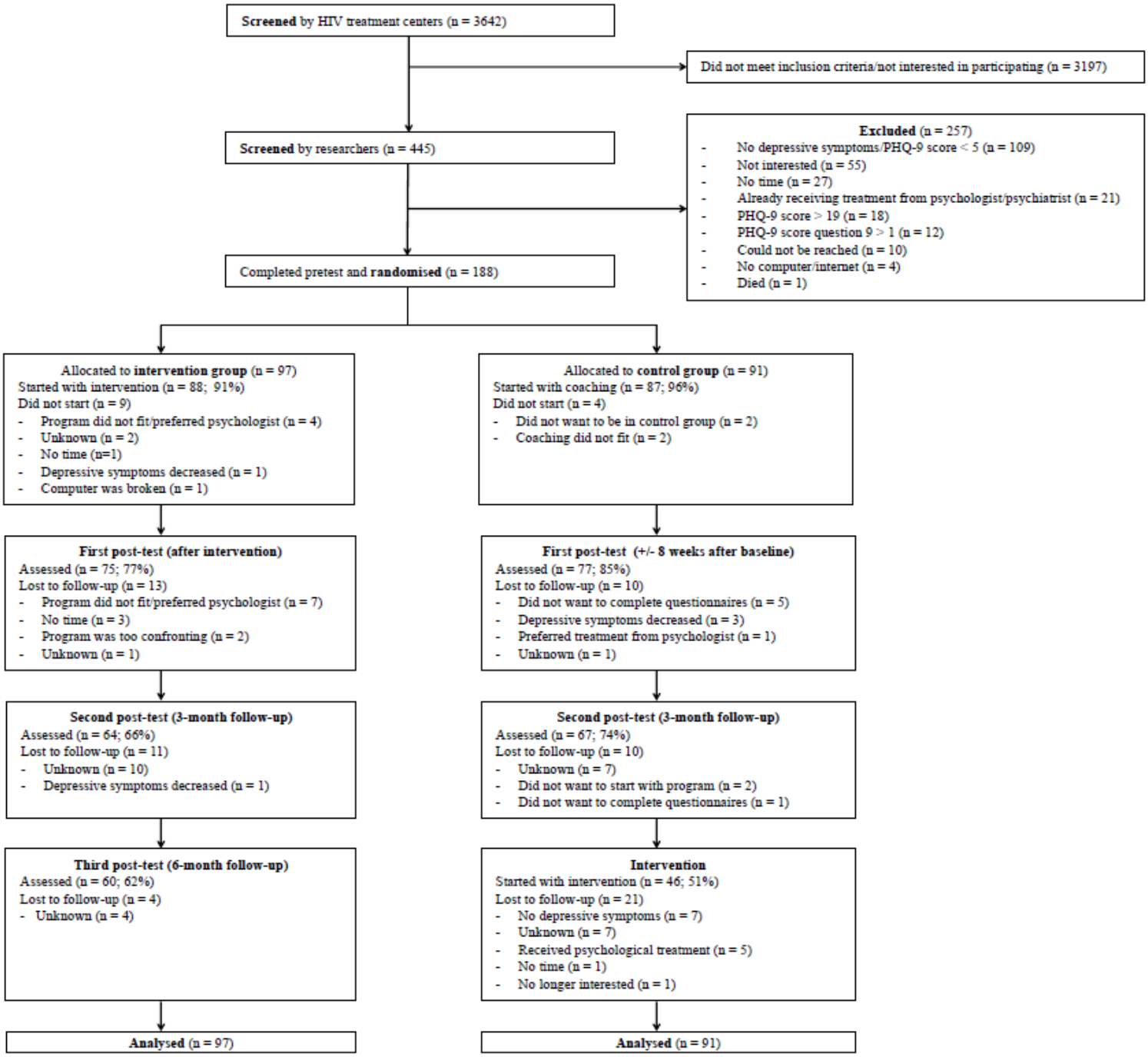

Figure 1. Trial profile.

Table 1.
Baseline characteristics of the intervention and control group

Characteristic	Intervention group (n = 97)	Control group (n = 91)	Total sample (n = 188)
Age (years), *M* (*SD*)	45·53 (10·32)	47·12 (10·94)	46·30 (10·63)
Sex, n (%)			
Male	85 (88%)	81 (89%)	166 (88%)
Female	12 (12%)	10 (11%)	22 (12%)
Nationality, n (%)			
Dutch	80 (83%)	78 (86%)	158 (84%)
Other	10 (10%)	8 (9%)	18 (10%)
Dutch and other	7 (7%)	5 (5%)	12 (6%)
Education, n (%)			
Low	20 (21%)	22 (24%)	42 (22%)
Medium	44 (45%)	33 (36%)	77 (41%)
High	33 (34%)	36 (40%)	69 (37%)
Marital status, n (%)			
Married or cohabiting	41 (42%)	44 (48%)	85 (45%)
Single or living without partner	56 (58%)	47 (52%)	103 (55%)
Sexual orientation, n (%)			
Heterosexual	19 (20%)	13 (14%)	32 (17%)
Homosexual	73 (75%)	71 (78%)	144 (77%)
Bisexual	5 (5%)	7 (8%)	12 (6%)
Use of psychotropic medication, n (%)			
No	85 (88%)	81 (89%)	166 (88%)
Yes	12 (12%)	10 (11%)	22 (12%)
Time since HIV diagnosis (years), *M* (*SD*) [a]	9·35 (6·46)	10·41 (6·70)	9·87 (6·58)
Diagnosis of AIDS, n (%)			
No	88 (91%)	77 (85%)	165 (88%)
Yes	9 (9%)	14 (15%)	23 (12%)
CD4, *M* (*SD*)[b]	726 (290)	647 (280)	690 (287)
Viral load, n (%)[c]			
Undetectable (< 50)	59 (88%)	59 (86%)	118 (87%)
Detectable (≥ 50)	8 (12%)	10 (14%)	18 (13%)
Use of ART, n (%)			
Yes	94 (97%)	90 (99%)	184 (98%)
No	3 (3%)	1 (1%)	4 (2%)

Note. [a] = available for 187 participants; [b] = available for 86 participants; [c] = available for 136 participants; ART = antiretroviral therapy; CD4 = cluster of differentiation 4.

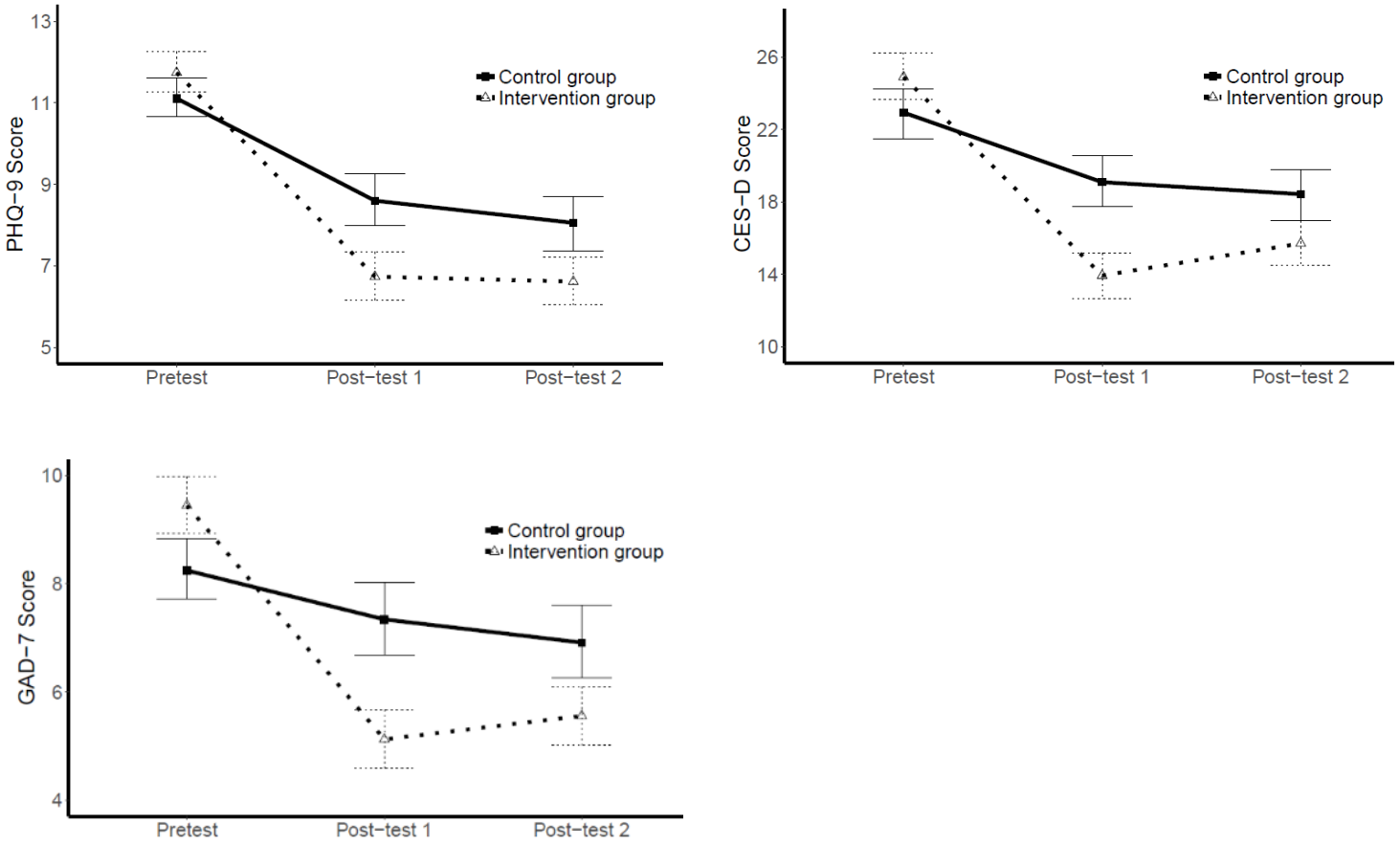

Figure 2. Estimated scores on the PHQ-9, CES-D and GAD-7 over time in both groups.

Table 2.
Results of the mixed model analyses comparing the intervention group with the control group in the change in depressive and anxiety symptoms over time

Measure and time point	Time effect				Time x group effect			
	b*	*SE* b	*t*†	*p* value	b*	*SE* b	*t*†	*p* value
PHQ-9								
Pretest to post-test 1	-2·51	0·56	-4·48	<0·0001	-2·50	0·80	-3·14	0·002
Post-test 1 to post-test 2	-0·54	0·55	-0·98	0·33	0·42	0·79	0·53	0·59
CES-D								
Pretest to post-test 1	-4·21	1·11	-3·81	0·0002	-6·76	1·57	-4·31	<0·0001
Post-test 1 to post-test 2	-0·66	1·11	-0·59	0·55	2·44	1·59	1·53	0·13
GAD-7								
Pretest to post-test 1	-0·90	0·51	-1·77	0·08	-3·42	0·72	-4·75	<0·0001
Post-test 1 to post-test 2	-0·43	0·52	-0·83	0·41	0·86	0·73	1·17	0·24

Note. CES-D = Center for Epidemiologic Studies Depression Scale; GAD-7 = Generalized Anxiety Disorder 7; PHQ-9 = Patient Health Questionnaire 9; * b is the unstandardised coefficient; † t is the t-test statistic.

In addition, the long term effects of the intervention were investigated. Table 3 presents the results of the mixed model analyses that investigated the effect of the intervention on depressive and anxiety symptoms on the short and long term (intervention group only). A significant effect of Time was found on all outcomes: symptoms decreased from pretest to post-test 1 and remained low on post-test 2 and 3. There was no effect of Time from post-test

1 to post-test 2 and from post-test 2 to post-test 3. Within-group effect sizes were medium from pretest to post-test 1 and around zero from post-test 1 to post-test 2 and from post-test 2 to post-test 3.

Table 3.
Results of the mixed model analyses investigating the effects of the intervention on depressive and anxiety symptoms on the short term and on the long term (intervention group only)

Measure and time point	Time effect				
	b*	***SE* b**	***t*†**	***p* value**	***d* (95%CI)**
PHQ-9					
Pretest to post-test 1	-3·75	0·41	-9·17	<0·0001	-0·79 (-1·02, -0·56)
Post-test 1 to post-test 2	-0·30	0·37	-0·80	0·43	-0·06 (-0·26, 0·14)
Post-test 2 to post-test 3	0·20	0·46	0·44	0·66	0·04 (-0·16, 0·24)
CES-D					
Pretest to post-test 1	-7·56	0·84	-9·03	<0·0001	-0·72 (-0·94, -0·50)
Post-test 1 to post-test 2	0·60	0·74	0·81	0·42	0·06 (-0·14, 0·26)
Post-test 2 to post-test 3	0·02	0·91	0·02	0·99	0·002 (-0·20, 0·20)
GAD-7					
Pretest to post-test 1	-2·63	0·38	-6·91	<0·0001	-0·56 (-0·77, -0·34)
Post-test 1 to post-test 2	0·04	0·34	0·12	0·91	0·01 (-0·19, 0·21)
Post-test 2 to post-test 3	-0·22	0·42	-0·53	0·60	-0·05 (-0·25, 0·15)

Note. CES-D = Center for Epidemiologic Studies Depression Scale; GAD-7 = Generalized Anxiety Disorder 7; PHQ-9 = Patient Health Questionnaire 9; * b is the unstandardised coefficient; † t is the t-test statistic.

We examined the effect of HIV treatment center in an unconditional means model with three levels. The intraclass correlation was estimated, and it was around zero in all models. This means that there was no effect of treatment center, therefore we did not include it in the analyses. Furthermore, the per protocol analyses confirmed the findings of the ITT analyses and are therefore not reported.

Improvement, recovery, clinically significant change, deterioration, and NNT on the first post-test can be found in the Appendix (p 3). In the intervention group, significantly more participants improved (reliable change index < -1·96) than in the control group; χ^2 (1) = 8·73, p = 0·003 for the PHQ-9 and χ^2 (1) = 12·07, p = 0·001 for the CES-D. For the participants that scored above the cut-off for depression on pretest, it was examined whether they scored below the cut-off on post-test 1. Sixty-two percent of the participants scored above the cut-off on the PHQ-9 at pretest and were considered clinical cases and 55% scored above the cut-off on the CES-D. Significantly more of these participants recovered in the intervention group than in the control group; χ^2 (1) = 7·71, p = 0·005 for the PHQ-9 and χ^2 (1) = 11·41, p = 0·001 for the CES-D. On the PHQ-9, significantly more participants reached the criteria for clinically significant change (both recovery and improvement) in the intervention group than in the control group, χ^2 (1) = 7·72, p = 0·005, and the same applies to the CES-D, χ^2 (1) = 15·65, p < 0·0001. Deterioration was rare, with no significant differences between groups: χ^2 (1) = 1·35, p = 0·25 for the PHQ-9 and χ^2 (1) = 3·42, p = 0·06 for the CES-D. The NNT was 3·30 for the PHQ-9 and 2·20 for the CES-D.

Most participants were satisfied with the intervention, the overall grade was 7·34 out of 10 (*SD* = 1·62, n = 74). Fifty five participants (74%) would definitely recommend others to follow the intervention, 18 (24%) would maybe recommend it and one participant (2%) would not recommend the intervention. The coach was evaluated with a 7·62 out of 10 (*SD* = 1·52, n = 146). Participants in the intervention group (*M* = 7·92, *SD* = 1·31) evaluated the coach more positively than participants in the control group (*M* = 7·32, *SD* = 1·66; *t*(144) = 2·43, *p* = 0·02). No adverse events were reported.

Discussion

We found that a guided Internet-based self-help intervention had a medium-sized effect in decreasing depressive symptoms in 188 PLWH, compared to an attention-only control condition. Significantly more participants in the intervention condition than in the control condition showed clinically significant change. In addition, anxiety symptoms decreased after the intervention, compared to the control group. Finally, user satisfaction was high. The results of this study are important, since only four previous studies investigated the effectiveness of computerized/Internet interventions for PLWH and three found no effect of the intervention on mood.[10,12,13] This is the first RCT that showed that an Internet-based intervention for PLWH can significantly reduce depressive symptoms. The current study adds to the literature that found that online interventions for depression could be effective for the general population,[7] and for people with a chronic somatic disease.[8] The between-group effect sizes that we found for depressive symptoms on the first post-test were somewhat larger than was found in previous research, e.g. [7,8] Furthermore, the long term effect of the intervention on mental health was found to be enduring. However, the follow-up period in the present study was six months in the intervention group (and three months in the control group), so longer follow-up measurements are necessary.

The control group also improved, participants appreciated the coaching, and coaches received high grades. The weekly attention may lead to a decrease in depressive symptoms, as also suggested by others.[30] Furthermore, the coach also seemed important in the intervention group. As participants were satisfied with the coaching and it was feasible with Master students in clinical psychology and graduates, this form of coaching can be used when implementing the intervention. Additionally, nurses in HIV treatment centers may be trained to provide the coaching to increase scalability.

The current study had important strengths and weaknesses. A strength was the design: an RCT with a large sample covering 23 of 26 HIV treatment centers throughout the

Netherlands. In addition, the intervention was designed specifically for PLWH and provided online, which has advantages compared to face to face treatment. And the intervention is available in Dutch and English and could be translated into other languages, and used in other countries. Moreover, results of PHQ-9 and CES-D questionnaires were comparable, this increases confidence in the results. Finally, ITT analyses were conducted.

A first limitation is that the dropout was quite high: 19% at the first post-test. However, Internet-based interventions often have a comparable high dropout.[7,8] In the current study no baseline differences were found between dropouts and completers, which indicates that no specific characteristics were related to dropout and that the results may be generalised. Second, only self-report measures were used, instead of other measures such as interviews which can be used for diagnostic purposes. However, a diagnosis of depression was not an inclusion criterion in the current study and interviews would have been time consuming. Third, it is possible that participants in the intervention group met participants in the control group and shared experiences. However, since participants lived throughout the country we expect that these chances were small. Fourth, waiting list control conditions may inflate the effects of interventions in studies and it is possible that this also occurred in the current study. Though, this study used an attention only waiting list control condition, which was more active than only waiting. This may have reduced the inflation. Fifth, the intervention was developed by the researchers. However, we did everything we could to avoid contact with participants after allocation to conditions. Independent replication of this study is recommended. Lastly, our findings may not be generalisable to all PLWH in the Netherlands, more research is necessary.

For future research, it is important to investigate moderators and mediators of treatment effect; to find out for which subgroups this intervention is the most optimal and what the working mechanisms of the intervention are. In addition, it is also valuable to investigate the cost-effectiveness of the intervention. Furthermore, the intervention may be implemented and the effectiveness and implementation should be studied, also on the long term. Finally, as HIV is very prevalent in other parts of the world (e.g. Africa), the intervention may be adapted to the local culture of these countries and its effectiveness may be investigated there.

To conclude, this RCT found that the guided Internet-based intervention Living positive with HIV may be effective in decreasing depressive symptoms on the short and long term, up to six months. Additionally, anxiety reduced after the intervention, and the intervention and the coach were mostly positively evaluated. This new, online intervention may be a meaningful enhancement to psychological care for PLWH with depressive symptoms. There

is evidence now that implementation of the intervention including coaching may be justified in the Netherlands.

Contributors

NG and VK designed the study and wrote the research proposal, received funding for the study, and developed the intervention. The study was set up in practice by SVL, NG, PS, and VK. SVL screened and included patients, organized the data collection, and analysed the data together with statisticians. SVL, NG, PS, and VK composed the manuscript. The Medical Study Group was involved in screening patients in treatment centers, and read and approved the final version of the manuscript.

Declaration of interests

This study was supported by the Aids Fonds (file number 2013027). We declare no competing interests.

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References

1. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005; **58**: 175-89.
2. Gonzalez JS, Batchelder AW, C P, Safren SA. Depression and HIV/AIDS treatment nonadherence: A review and meta-analysis. *J Acquir Immune Defic Syndr* 2011; **58**: 181-7.
3. van Luenen S, Garnefski N, Spinhoven P, Spaan P, Dusseldorp E, Kraaij V. The Benefits of Psychosocial Interventions for Mental Health in People Living with HIV: A Systematic Review and Meta-analysis. *AIDS Behav* 2018; **22**: 9-42.
4. Crepaz N, Passin WF, Herbst JH, et al. Meta-analysis of cognitive-behavioral interventions on HIV-positive persons' mental health and immune functioning. *Health Psychol* 2008; **27**: 4-14.
5. Spaan P, van Luenen S, Garnefski N, Kraaij V. Psychosocial interventions enhance HIV medication adherence: A systematic review and meta-analysis. *J Health Psychol* 2018, published online February, 8. DOI: 10.1177/1359105318755545.
6. Heckman TG, Heckman B, Kochman A, Sikkema KJ, Suhr J, Goodkin K. Psychological symptoms among persons 50 years of age and older living with HIV disease. *Aging & mental health* 2002; **6**: 121-8.
7. Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin Psychol Rev* 2012; **32**: 329-42.
8. van Beugen S, Ferwerda M, Hoeve D, et al. Internet-Based Cognitive Behavioral Therapy for Patients With Chronic Somatic Conditions: A Meta-Analytic Review. *J Med Internet Res* 2014; **16**: e88.
9. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. *Cogn Behav Ther* 2018; **47**: 1-18.
10. Drozd F, Skeie LG, Kraft P, Kvale D. A web-based intervention trial for depressive symptoms and subjective well-being in patients with chronic HIV infection. *AIDS Care* 2014; **26**: 1080-9.
11. Mo PK, Coulson NS. Online support group use and psychological health for individuals living with HIV/AIDS. *Patient Educ Couns* 2013; **93**: 426-32.
12. Brown JL, Vanable PA, Carey MP, Elin L. Computerized stress management training for HIV+ women: a pilot intervention study. *AIDS Care* 2011; **23**: 1525-32.
13. Hersch RK, Cook RF, Billings DW, et al. Test of a web-based program to improve adherence to HIV medications. *AIDS Behav* 2013; **17**: 2963-76.
14. van Luenen S, Kraaij V, Spinhoven P, Garnefski N. An Internet-based self-help intervention for people with HIV and depressive symptoms: study protocol for a randomized controlled trial. *Trials* 2016; **17**: 1-12.
15. Kraaij V, van Emmerik A, Garnefski N, et al. Effects of a cognitive behavioral self-help program and a computerized structured writing intervention on depressed mood for HIV-infected people: a pilot randomized controlled trial. *Patient Educ Couns* 2010; **80**: 200-4.
16. Kraaij V, van der Veek SM, Garnefski N, Schroevers M, Witlox R, Maes S. Coping, goal adjustment, and psychological well-being in HIV-infected men who have sex with men. *AIDS Patient Care STDS* 2008; **22**: 395-402.
17. Kroenke K, Spitzer RL, Williams JBW. The Patient Health Questionnaire-2 - Validity of a two-item depression screener. *Med Care* 2003; **41**: 1284-92.
18. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 - Validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606-13.
19. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; **67**: 361-70.

20. Radloff LS. The CES-D scale a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977; **1**: 385-401.
21. Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV Infected Patients: a Review. *Current Psychiatry Reports* 2015; **17**: 11.
22. Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder - The GAD-7. *Arch Intern Med* 2006; **166**: 1092-7.
23. Hintze J. NCSS and PASS (number cruncher statistical systems). Kaysville, Utah; 2004 [cited 2017 September, 4]. Available from: www.NCSS.com.
24. Stoel RD, van Den Wittenboer G, Hox J. Analyzing longitudinal data using multilevel regression and latent growth curve analysis. *Metodologia de las Ciencias del Comportamiento* 2003; **5**: 21-42.
25. Feingold A. A regression framework for effect size assessments in longitudinal modeling of group differences. *Rev Gen Psychol* 2013; **17**: 111-21.
26. de Zeeuw EL, Tak EC, Dusseldorp E, Hendriksen IJ. Workplace exercise intervention to prevent depression: a pilot randomized controlled trial. *Mental Health and Physical Activity* 2010; **3**: 72-7.
27. Jacobson NS, Truax P. Clinical significance - A statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991; **59**: 12-9.
28. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *Can Med Assoc J* 2012; **184**: E191-E6.
29. Haringsma R, Engels G, Beekman A, Spinhoven P. The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. *Int J Geriatr Psychiatry* 2004; **19**: 558-63.
30. Popp L, Schneider S. Attention placebo control in randomized controlled trials of psychosocial interventions: theory and practice. *Trials* 2015; **16**: 1-3.

Appendix

Supplementary Table 1.
Overview of assessments during the study

Assessment	Screening HIV treatment centers	Screening researchers	Pretest	Post-test 1	Post-test 2	Post-test 3[1]
PHQ-2 or HADS	X					
PHQ-9		X	X	X	X	X
CES-D			X	X	X	X
GAD-7			X	X	X	X
Demographics and HIV questionnaire			X			
User satisfaction				X		

Note. [1] Not sent to participants in the control group; CES-D = Center of Epidemiologic Studies Depression Scale; GAD-7 = Generalized Anxiety Disorder-7; HADS = Hospital Anxiety and Depression Scale; PHQ-2 = Patient Health Questionnaire-2; PHQ-9 = Patient Health questionnaire-9.

Supplementary Table 2.
Estimated means and standard deviations on the PHQ-9, CES-D and GAD-7 over time in the intervention and control group

Measure and time point	Intervention group (n = 97)		Control group (n = 91)	
	M	***SD***	***M***	***SD***
PHQ-9				
Pretest	11·74	2·49	11·11	2·37
Post-test 1	6·73	3·00	8·60	3·12
Post-test 2	6·62	3·03	8·06	3·17
Post-test 3[a]	7·18	3·45		
CES-D				
Pretest	24·91	5·93	22·94	6·48
Post-test 1	13·94	6·39	19·09	7·05
Post-test 2	15·71	6·39	18·43	7·05
Post-test 3[a]	16·26	7·22		
GAD-7				
Pretest	9·44	2·59	8·24	2·90
Post-test 1	5·12	2·77	7·34	3·27
Post-test 2	5·55	2·77	6·91	3·27
Post-test 3[a]	5·69	3·18		

Note. [a] = Intervention group only; CES-D = Center for Epidemiologic Studies Depression Scale; GAD-7 = Generalized Anxiety Disorder 7; PHQ-9 = Patient Health Questionnaire 9.

Supplementary Table 3.

Improvement, recovery, clinically significant change, deterioration, and NNT on the PHQ-9 and the CES-D on the first post-test in both groups

Condition	Improvement, n (%)		Baseline clinical case, n (%)		Recovery, n (%)		Clinically significant change, n (%)		Deterioration, n (%)		NNT	
	PHQ-9	CES-D	PHQ-9	CES-D	PHQ-9	CES-D	PHQ-9	CES-D	PHQ-9	CES-D	PHQ-9	CES-D
Intervention	33 (52%)	30 (47%)	40 (62%)	37 (57%)	29 (74%)	27 (75%)	25 (64%)	24 (67%)	1 (1%)	0 (0%)	3·30	2·20
Control	21 (27%)	15 (19%)	56 (62%)	49 (54%)	21 (45%)	15 (37%)	16 (34%)	9 (22%)	4 (5%)	4 (5%)		

Note. CES-D = Center for Epidemiologic Studies Depression Scale; NNT = number needed to treat; PHQ-9 = Patient Health Questionnaire 9.

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