Living positive: eHealth for people with HIV and depressive symptoms

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Chapter 7

Exploring mediators of a guided web-based self-help intervention for people with HIV and depressive symptoms.

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Van Luenen, S., Kraaij, V., Spinhoven, P., Wilderjans, T.F. & Garnefski, N. Exploring mediators of a guided web-based self-help intervention for people with HIV and depressive symptoms.

Abstract

Background: Cognitive behavior therapy is frequently used to treat depressive symptoms in people living with HIV. We developed an Internet-based cognitive behavioral intervention for people with HIV and depressive symptoms, which was previously found to be effective.

Objective: In the current study, potential mediators of the online intervention were investigated.

Methods: This study was part of a randomized controlled trial, in which the intervention was compared to an attention only waiting list control condition. Participants were 188 (97 in intervention group and 91 in control group) people with HIV and mild to moderate depressive symptoms recruited in HIV treatment centers in the Netherlands. The intervention consisted of online cognitive behavioral therapy for eight weeks, including minimal telephone support from a coach. Participants were assessed with online questionnaires at pretest, three times during the intervention / waiting period, and post intervention. The outcome was depressive symptoms, factors that were tested as potential mediators were changes in behavioral activation, relaxation, the cognitive coping strategies catastrophizing and positive refocusing, goal reengagement, and coping self-efficacy.

Results: Changes in behavioral activation ($p = 0.006$) and in goal reengagement ($p = 0.009$) were found to be significant mediators of the intervention effect. The mediation effect seems to occur between week 3 and 5 for behavioral activation, and between week 1 and 3 for goal reengagement. We found a return effect from depressive symptoms to goal reengagement, which could weaken the mediation effect.

Conclusions: The results suggest that changes in behavioral activation and goal reengagement may mediate the effect of the online intervention for people with HIV and depressive symptoms. The results may lead to possible mechanisms of change of the intervention and improvement of therapy outcomes.

Trial registration: Nederlands Trialregister NTR5407, September 11, 2015.

Keywords: HIV, depression, Internet, cognitive behavioral therapy, coaching, randomized controlled trial, mediators.

Introduction

Living positive with HIV is an Internet-based intervention that we have developed for people living with HIV (PLWH) and depressive symptoms (1). It has been found that this intervention was effective in treating depressive symptoms in PLWH, compared to a control group that received minimal coaching (2). However, we do not know which factors are mediators of the intervention effect. Mediators are factors that (partially) explain the relation between an independent and dependent variable. In this case, we look for treatment factors that may explain the relationship between receiving the online intervention and the decrease in depressive symptoms (3). When a mediator of intervention effect is found, it may provide us indications for possible mechanisms of change (4). A mechanism of change is defined as a process that leads to change, which may answer the important question: how does the intervention work? It is important to have more knowledge about the mechanisms of change to be able to adapt and improve the intervention in order to optimize the outcome (4). To investigate mediators of treatment outcome, at least three measurement moments are needed to establish a timeline of mediators and outcomes.

Previous research

Research on online CBT to treat depressive symptoms in PLWH is scarce. As far as we know, no studies were conducted on mediators of online CBT for depressive symptoms in PLWH. Though, potential mediators of CBT (face-to-face and online) for people with depressive symptoms in general have been investigated in the last decade. First of all, when we look at face-to-face CBT for depressive symptoms, the literature regarding changes in cognitions as a mediator is mixed. Three reviews have found that a change in cognitions was an important mediator (5-7), while another review has concluded that there is little evidence for cognitive mediation in CBT for depression (8). Therefore, the role of changing cognitions as a mediator in CBT for depressive symptoms is still unclear. Furthermore, the mediating role of behavioral factors such as changes in activation level, in CBT for depression was investigated in a review (7). Changes in behavioral factors were found to be a significant mediator in three out of six studies.

Next to mediation studies of face-to-face CBT for depressive symptoms, mediators were also investigated in online CBT for depressive symptoms. It has been found that changes in dysfunctional attitudes, a negative problem orientation (9), repetitive negative thinking (9, 10), use of cognitive skills (11), and perceived control over things in life (9, 12) were mediators in the relation between online CBT and (a decrease in) depressive symptoms. Increasing activity levels was not found to be a mediator in online CBT for depression (11). Concluding, the results regarding mediators of change of (online) CBT are mixed and should be investigated further. Additionally, many previous mediation studies

correlated across subjects changes over time – using only two measurement moments (i.e., pretest and post-test) – in two variables, which does not allow to establish a timeline of mediators and outcomes (4, 7). More research with at least three measurement moments is needed in order to establish this timeline.

Current study

In this study, potential mediators of the effect of the online intervention Living positive with HIV on depressive symptoms were investigated. The intervention is based on CBT and contains four main components: behavioral activation, relaxation, changing negative thoughts into more balanced thoughts, and goal attainment. We statistically explored mediators for the decrease in depressive symptoms that might refer to causal mechanisms of change that may have been activated by the intervention components. The following potential mediators were investigated in the current study: changes in behavioral activation, relaxation, the cognitive coping strategies catastrophizing and positive refocusing, goal reengagement, and coping self-efficacy. We attempted to determine a temporal pattern of change: the mediators and the outcome (depressive symptoms) were investigated at pretest, three times during the intervention, and post-intervention.

Methods

Participants and procedure

This study is part of a randomized controlled trial (RCT; Nederlands Trialregister NTR5407) investigating the effectiveness of the self-help intervention 'Living positive with HIV'. More information about the procedure of the RCT can be found elsewhere (1). Nursing consultants and doctors in 23 of 26 HIV treatment centers in the Netherlands recruited participants during regular check-ups. Patients were screened with the Patient Health Questionnaire-2 (PHQ-2; (13)), and when their score was higher than zero, they were informed about the study and referred to the researchers when they were interested. Researchers called the patients and screened them on the inclusion criteria: being HIV positive for at least six months, age > 17 years, mastery of the Dutch or English language, available for the next eight weeks, having Internet and an e-mail address, 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, absence of severe cognitive impairments, not currently treated by a psychologist or psychiatrist, presence of mild to moderate depressive symptoms (determined by a Patient Health Questionnaire-9 -PHQ-9 (14)- score > 4 and < 20), absence of severe suicide ideation (determined by a score < 2 on question 9 of the PHQ-9).

When patients were eligible and agreed to participate, online informed consent was signed. Thereafter, participants completed the pretest and were randomly allocated to the intervention or control condition (waiting list and attention only from a coach). Stratified randomization by sex and HIV treatment center was performed. A random number table was used to create the sequence, which was done by an independent researcher and concealed from the main researcher. There were multiple measurement moments after randomization: three times during the intervention (lesson one, three, and five) or waiting period (week one, three, and five), a post-test when participants were finished with the intervention (experimental group) or eight weeks after pretest (control group), and a follow-up at three and six months (the last follow-up was only completed in the intervention group). In the current study, the follow-up measurements were not used in the analyses. Participants received €25 when they completed all questionnaires. The study was approved by the medical ethics committee of the Leiden University Medical Center (LUMC; nr. P14.091).

Study conditions

Guided online self-help intervention

The intervention consists of CBT and contains four main components: 1) behavioral activation: conducting small positive activities (week 1); 2) relaxation exercises (week 2); 3) changing negative cognitions into more balanced cognitions and eliciting strong and positive feelings when negative feelings are experienced (week 3 to 5); and 4) goal attainment: setting important personal goals and working on attaining them (week 6 and 7). Participants received login details for the secured website of the intervention. No changes to the intervention were made during the RCT. The intervention exists of eight lessons with psychoeducation, exercises and assignments. Participants worked approximately eight weeks on the intervention, one to two hours a week. In addition, they were called by a personal coach each week for about 15 minutes. The coach checked the well-being of the participant and discussed the progress of the intervention. Coaches used motivational interviewing to motivate participants to continue with the intervention, to minimize attrition. Coaching was provided until the participant had finished the intervention, with a maximum of ten weeks. Coaches were Master students in clinical psychology or graduates with a Master's degree in the field of psychology. Coaches received a training and followed a coaching manual. Supervision sessions with coaches and a researcher to discuss issues encountered during coaching were scheduled in the beginning of the study. There were less issues at the end of the study, therefore, they were handled via e-mail or phone. More information about the study conditions and procedures can be found elsewhere (1).

Control condition

Participants that were allocated to the control condition were put on a waiting list and received attention only from a personal coach. Telephone coaching was provided for eight weeks, approximately five minutes per week. The coach addressed the well-being of the participant, monitored depressive symptoms, and motivated the participant to keep waiting and complete questionnaires. The participant was referred to the HIV treatment center or general practitioner when the depressive symptoms worsened and became severe. After the three month follow-up, participants were invited to start with the intervention.

Assessments

All assessments were completed online and administered at pretest, week 1, 3, and 5 during the intervention/waiting period, and at post-test. The questions that were asked during the intervention/waiting period concern the symptoms that were experienced during the last week. To reduce the time to complete the questionnaires, one or two items were chosen from each questionnaire (with the chosen items being the same across measurement moments). The authors jointly determined the items that represented the concept the best. The questionnaires are explained briefly below. More information on the specific questions that were used, and the scoring can be found in Appendix 1.

Outcome measure

The outcome measure for the mediational analysis was severity of depressive symptoms. This was measured with the PHQ-2 (13), which consists of the first two questions of the PHQ-9. The construct and criterion validity of the PHQ-2 are adequate (13), and the Spearman-Brown coefficient ranged from 0.71 to 0.83 throughout the five measurement moments in the current study.

Potential mediators

Activation

Behavioral activation was measured by a sum score of two items from the subscale activation of the Behavioral Activation for Depression Scale (BADS) (15). The psychometric properties of the Dutch BADS are adequate (16), and the Spearman-Brown coefficient of the two items ranged from 0.79 to 0.84 throughout the five measurement moments in the current study.

Relaxation

Relaxation was measured with one self-designed item concerning difficulty to relax. The reliability of this instrument could not be calculated, because it consisted of only one item.

Cognitive coping: catastrophizing and positive refocusing

The subscales catastrophizing and positive refocusing of the Cognitive Emotion Regulation Questionnaire short version (CERQ-short) (17) were adopted to measure the use of these cognitive coping strategies when thinking about having HIV. The subscales consist of two items each. The psychometric properties of the CERQ-short are adequate (17). In the current study the Spearman-Brown coefficient ranged from 0.84 to 0.94 throughout the five measurement moments for the catastrophizing subscale, and from 0.72 to 0.81 throughout the five measurement moments for the positive refocusing subscale.

Goal reengagement

One item of the Goal Disengagement and Goal Reengagement Scale (GDGRS) (18) was used to measure goal reengagement. For the current study, the item was specifically reformulated to measure goal reengagement in relation to having HIV. The reliability of the total instrument was previously found to be satisfactory (18).

Coping self-efficacy

A sum score of two self-designed items was used to measure self-efficacy to cope with having HIV. The items were based on the Generalized Self-Efficacy Scale, which has good reliability and validity (19). The Spearman-Brown coefficient of the two items in the current study ranged from 0.75 to 0.92 throughout the five measurement moments.

Statistical analysis

The mediation analyses were conducted with the PHQ-2 score as dependent variable (Y), Group (intervention and control) as independent variable (X), and activation, relaxation, the cognitive coping strategies catastrophizing and positive refocusing, goal reengagement, and coping self-efficacy as potential mediators (M). Note that the PHQ-2 and all six mediator questionnaires were administered at all five measurement moments (pre-test, week 1, 3, 5, and post-test).

The mediation analyses were performed in three steps. In step 1 all potential mediators were entered separately into a multilevel structural equation model (MSEM (20)). An MSEM model was chosen because Group (X) does not change over time (level 2: between subjects-level), whereas PHQ-2 (Y) and the mediator (M) scores do change over time (level 1: within subjects-level). As Group (X) is constant over time, only mediation at the between level can take place. To test this, MSEM computes the product term $a \times b$ and evaluates its significance, with a being the between effect from X to M, and b the between effect from M to Y. Mediation is present when the product term significantly differs

from zero. The significant mediators that were found were thereafter all together included in a single model in order to investigate which mediation effects remain significant after controlling for the other mediators in the model. The analysis in step 1 was repeated for the per protocol sample, as a sensitivity analysis. The per protocol sample included participants in the intervention group that finished at least the first five lessons of the intervention, and participants in the control group that received at least five telephone calls from the coach.

In step 2 an explorative analysis was conducted to investigate when the mediating effect(s) exactly occurred (i.e., in between which two measurement moments). To this end, for the significant mediators encountered in step 1, the same MSEM model was fitted as in step 1, however using different combinations of measurement moments. In particular, the timing of the mediation effect(s) was investigated by comparing for each measurement moment an MSEM model including only the measurements up to that moment (including the measurement moment in question) to an MSEM model including only subsequent measurement moments. For example, for week 1, an MSEM model including the pretest and week 1 was compared to an MSEM model including week 3, week 5, and the post-test. The first measurement moment for which in both associated MSEM models mediation is present, was considered as the moment when the mediation occurred.

In step 3 return effects from the dependent variable to the significant mediators identified in step 1 (i.e., from Y to M) were studied. When return effects are present, this may indicate that the mediation effect is less strong. Return effects were investigated by means of a bivariate autoregressive latent trajectory analysis (ALT (21, 22)). In order to get a good fitting but not too complex ALT model (which generalizes well), some constraints on the parameters were imposed. In particular, for each variable, parameters representing auto-regressive paths were set equal to each other, with the same being true for cross-lagged parameters. Further, for each variable, residual variances for each measurement moment were kept equal (except for the first measurement moment as prescribed by the predetermined model parameterization, see (21)). Finally, time-specific correlations between residuals were set equal over time. To determine whether the ALT model fitted well to the data, the following model fit indices were evaluated: root mean square error of approximation (RMSEA) with its 90% confidence interval (CI), comparative fit index (CFI) and Tucker Lewis Index (TLI). The model has a good fit when the RMSEA value is below 0.06, when the 90% CI for RMSEA has an upper bound < 0.08 and a lower bound > 0.05, and when the CFI and TLI values are higher than 0.95 (23, 24). The analyses were based on full information maximum likelihood (FIML) techniques, which means that all available data - including participants with partially missing data - was used. $\alpha = 0.05$ was used for significance testing. All analyses were conducted in MPlus version 7.31.

Results

Participants

In the HIV treatment centers, 3642 patients were screened on depressive symptoms. Of these, 445 were screened by the researchers and 188 patients were included in the study. Patients were 1:1 randomized to the intervention group (n = 97) and the control group (n = 91). Note that due to the stratified randomization the intervention group contains a few more participants than the control group. The post-test was completed by 75 participants (77%) of the intervention group and 77 participants (85%) of the control group. Figure 1 displays for each group separately the flow of participants through the study in terms of PHQ-2.

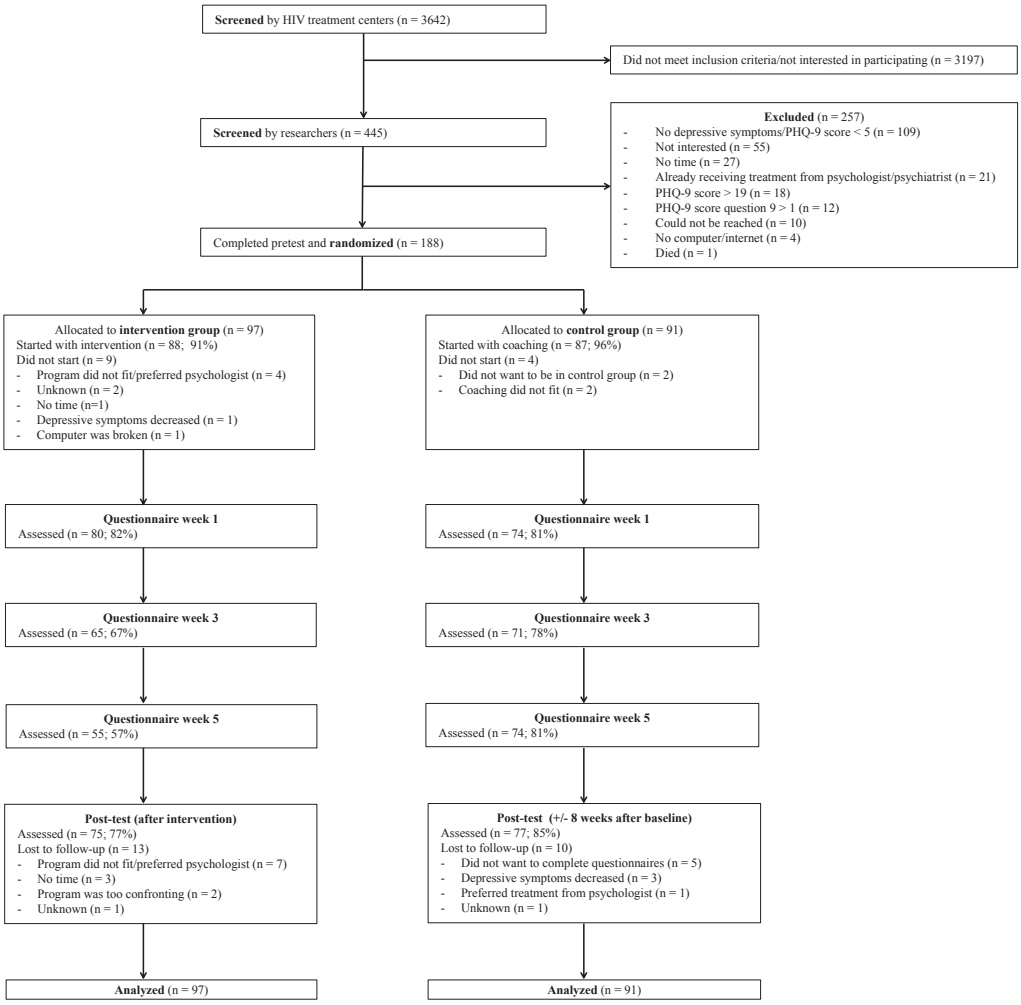

Figure 1. Flow of participants through the study.

Twenty-two participants (12%) in the study were female and 166 (88%) were male. The average age of participants was 46.30 years old (*SD* = 10.63). Thirty-two participants (17%) were heterosexual, 144 (77%) homosexual and 12 (6%) bisexual. Most participants had a medium education (n = 77; 41%) or a high education (n = 69, 37%), and a minority a low education (n = 42; 22%). Participants had HIV for 9.87 years on average (*SD* = 6.58). Twenty-three participants (12%) had AIDS and 165 (88%) did not have AIDS, and 184 participants (98%) used ART and 4 (2%) did not use ART. More information on the baseline characteristics of the sample can be found elsewhere (2). Mean scores on the questionnaires at different time points can be found in Table 1.

Mediation analysis step 1

Table 2 shows the results of the mediation analysis based on MSEM in which all mediators are investigated separately. Changes in BADS and GDGRS were found to be significant mediators. Subsequently, these two mediators were together included in a single model. Changes in BADS remained a significant mediator when changes in GDGRS was controlled for (*a x b*: 0.25, *SE* = 0.10, *p* = 0.01), whereas changes in GDGRS was not a significant mediator anymore when changes in BADS was controlled for (*a x b*: 0.15, *SE* = 0.09, *p* = 0.10). Correlations between BADS and GDGRS varied across measurement moments (range from *r* = 0.07, *p* = 0.39 to *r* = 0.54, *p* < 0.001). The mediation analysis was repeated on the per protocol sample and the results were similar as for the whole sample. For illustrative purposes, Figure 2 displays the course of PHQ-2, BADS, and GDGRS scores over time in both groups. The intervention group shows a stronger reduction in PHQ-2 score over time than the control group, and at the same time BADS scores and GDGRS scores increase more over time in the intervention group than in the control group.

Table 1. Mean scores on the questionnaires at different time points. Data are provided as *M* (*SD*).

Characteristic	Intervention group	Control group
Depressive symptoms (PHQ-2[a]) pretest	3.10 (1.47)	2.78 (1.26)
Week 1	2.13 (1.41)	2.27 (1.55)
Week 3	1.66 (1.20)	2.24 (1.56)
Week 5	1.24 (1.25)	2.05 (1.59)
Post-test	1.53 (1.41)	2.38 (1.59)
Behavioral activation (BADS[b]) pretest	4.78 (3.15)	4.58 (3.05)
Week 1	5.90 (2.74)	5.30 (2.88)
Week 3	6.52 (2.88)	5.35 (2.82)
Week 5	7.35 (2.31)	5.78 (2.74)
Post-test	7.57 (2.99)	5.46 (3.07)
Relaxation pretest	1.62 (0.60)	1.69 (0.68)
Week 1	1.66 (0.57)	1.74 (0.62)
Week 3	1.97 (0.59)	1.80 (0.65)
Week 5	2.13 (0.70)	1.81 (0.61)
Post-test	2.05 (0.66)	1.86 (0.70)
Catastrophizing (CERQ-short[c]) pretest	3.80 (2.36)	3.37 (1.74)
Week 1	3.44 (1.77)	3.61 (2.10)
Week 3	3.05 (1.58)	3.38 (2.04)
Week 5	2.75 (1.21)	3.24 (1.68)
Post-test	2.92 (1.75)	3.16 (1.69)
Positive refocusing (CERQ-short[c]) pretest	6.39 (2.23)	6.37 (2.03)
Week 1	6.13 (1.89)	5.96 (1.85)
Week 3	6.32 (1.96)	5.90 (1.97)
Week 5	6.91 (1.96)	6.39 (2.05)
Post-test	7.04 (2.17)	6.07 (2.19)
Goal reengagement (GDGRS[d]) pretest	3.15 (0.86)	2.97 (0.82)
Week 1	3.42 (0.79)	3.12 (0.81)
Week 3	3.55 (0.75)	3.10 (0.94)
Week 5	3.71 (0.79)	3.26 (0.97)
Post-test	3.55 (0.79)	3.08 (0.99)
Coping self-efficacy pretest	7.08 (1.78)	7.24 (1.66)
Week 1	7.51 (1.59)	7.15 (1.78)
Week 3	8.03 (1.60)	7.14 (1.83)
Week 5	8.11 (1.40)	7.53 (1.69)
Post-test	7.93 (1.65)	7.20 (1.72)

[a] PHQ-2 = Patient Health Questionnaire-2, [b] BADS = Behavioral Activation for Depression Scale, [c] CERQ-short = Cognitive Emotion Regulation Questionnaire short version, [d] GDGRS = Goal Disengagement and Goal Reengagement Scale.

Table 2. Mediation effects of six potential mediators (tested separately) with Group as independent variable and PHQ-2[a] score as dependent variable, based on MSEM[b] analysis on data containing all 5 measurement moments.

Potential mediator	*a x b*[c]	*SE*	*p*
Behavioral activation (BADS[d])	0.31	0.11	0.006[e]
Relaxation	0.05	0.08	0.55
Catastrophizing (CERQ-short[f])	-0.005	0.06	0.92
Positive refocusing (CERQ-short[f])	0.10	0.08	0.17
Goal reengagement (GDGRS[g])	0.29	0.11	0.009[e]
Coping self-efficacy	0.12	0.08	0.13

[a] PHQ-2 = Patient Health Questionnaire-2, [b] MSEM = multilevel structural equation model, [c] coefficient for the product term testing the mediation effect, [d] BADS = Behavioral Activation for Depression Scale, [e] $p < .05$, [f] CERQ-short = Cognitive Emotion Regulation Questionnaire short version, [g] GDGRS = Goal Disengagement and Goal Reengagement Scale.

Mediation analysis step 2: timing of mediation effects

Table 3 shows the timing of the mediation effects of the significant mediators in step 1. The results show that for changes in BADS the mediation effect is not significant when the pretest, week 1 and week 3 measurements are combined. However, the mediation effect is significant when the week 5 and post-test measurements are combined. Therefore, it seems likely that the BADS mediation effect occurs between week 3 and week 5. For changes in GDGRS, the results are almost similar. The mediation effect is not significant when the pretest and week 1 measurements are combined and is significant when the week 3, week 5, and post-test measurements are combined. Hence, it seems likely that the GDGRS mediation effect occurs between week 1 and week 3.

Mediation analysis step 3: return effects

Table 4 presents the results of the analysis on return effects from the dependent variable to the mediators. The values of the fit indices (RMSEA, CFI, and TLI) indicate that the model has an acceptable to good fit. The results show that there is no return effect from the PHQ-2 to the BADS, but there is a return effect from the PHQ-2 to the GDGRS. However, the standardized coefficient (β) for the effect of the GDGRS on the PHQ-2 (β = -0.20) is higher -in absolute value- than the β for the effect of the PHQ-2 to the GDGRS (β = -0.13). This suggests that the mediation effect is larger than the return effect.

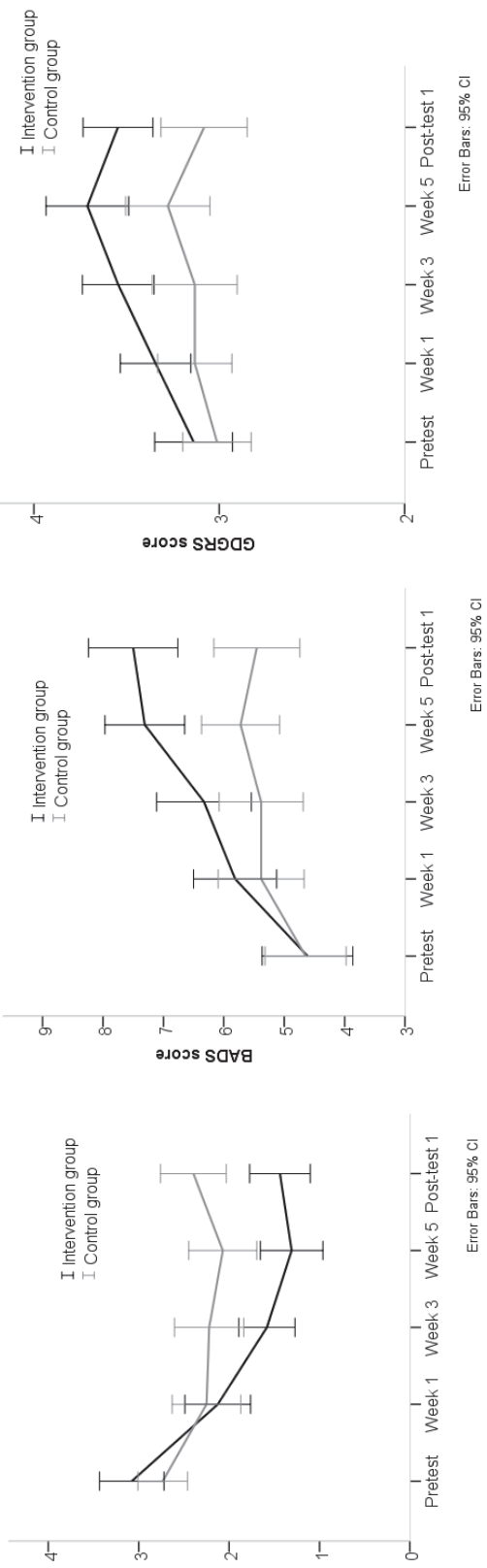

Figure 2. Course of the mean PHQ-2 score, BADS score, and GDGRS score over time for both groups.

Table 3. Timing of mediation effects: comparison of the mediation effect in MSEM[a] models fitted to data containing different sets of measurement moments to investigate when the mediation effect occurs.

Combination of measurement moments	BADS[b] *a x b*[c]	BADS[b] SE	BADS[b] *p*	GDGRS[d] *a x b*[c]	GDGRS[d] SE	GDGRS[d] *p*
Pretest	0.03	0.06	0.66	0.06	0.04	0.17
Week 1 – post-test	0.44	0.13	0.001[e]	0.43	0.14	0.003[e]
Pretest – week 1	0.10	0.10	0.30	0.20	0.12	0.09
Week 3 – post-test	0.59	0.16	< 0.001[e]	0.50	0.18	0.005[e]
Pretest – week 3	0.20	0.11	0.08	0.19	0.10	0.04[e]
Week 5 – post-test	0.69	0.20	< 0.001[e]	0.60	0.27	0.03[e]
Pretest – week 5	0.23	0.11	0.04[e]	0.22	0.10	0.02[e]
Post-test	0.52	0.15	< 0.001[e]	0.24	0.10	0.02[e]

[a] MSEM = multilevel structural equation model, [b] BADS = Behavioral Activation for Depression Scale, [c] coefficient for the product term testing the mediation effect, [d] GDGRS = Goal Disengagement and Goal Reengagement Scale, [e] $p < .05$.

Table 4. Results of the analysis on return effects from the dependent variable (PHQ-2[a]) to the mediators.

Mediator	*b*[b] Y → M (SE)	*β*[c] Y → M (SE)	*p*	RMSEA[d]	90% CI RMSEA[d] (lower, upper)	CFI[e]	TLI[f]
BADS[g]	-0.12 (0.10)	-.06 (0.05)	0.24	0.06	(0.04, 0.09)	0.94	0.94
GDGRS[h]	-0.08 (0.03)	-.13 (0.06)	0.02[i]	0.06	(0.03, 0.08)	0.95	0.94

[a] PHQ-2 = Patient Health Questionnaire-2, [b] *b* = unstandardized coefficient, [c] β = standardized coefficient (using STDYX standardization), [d] RMSEA = Root Mean Square Error of Approximation, [e] CFI = Comparative Fit Index, [f] TLI = Tucker Lewis Index, [g] BADS = Behavioral Activation for Depression Scale, [h] GDGRS = Goal Disengagement and Goal Reengagement Scale, [i] $p < .05$.

Discussion

This study investigated potential mediators of a guided Internet-based intervention for PLWH with depressive symptoms, compared to a control group that received attention only. Changes in behavioral activation and goal reengagement were found to be significant mediators of the intervention effect. For changes in behavioral activation, the mediation effect seemed to occur between week 3 and 5 of the intervention and for changes in goal reengagement the mediation effect seemed to occur between

week 1 and 3. The mediation effect of changes in behavioral activation seemed to be stronger than the effect of changes in goal reengagement since goal reengagement was not a significant mediator anymore when the model was controlled for behavioral activation. Moreover, a return effect (from the dependent variable to the mediator) was found for goal reengagement and not for behavioral activation.

In a review about CBT for depression, changes in behavioral activation were found to be a significant mediator in three out of six studies (7). More specifically, when only high quality studies were examined, three out of four studies concluded that changes in behavioral factors were a significant mediator. This is in line with our findings. However, a previous study into Internet CBT for depression investigated changes in behavioral activation as a mediator and has found that it was not a significant mediator of the intervention effect (11). An explanation for the difference in results between our study and this previous study may be the difference in timing of the intervention components and measurement moments. That is, the component behavioral activation was offered early in our intervention and late in the other intervention. We included three measurement moments during the intervention period in our study and there was only one measurement moment during the intervention in the previous study, and at that moment behavioral activation was not offered yet. Therefore, it is not surprising that no mediation effect of behavioral activation was found in the previous study. It is important to include multiple measurement moments of the dependent variable and possible mediators during the intervention period, in order to determine a timeline of the effects of mediators and outcome. As far as we know, changes in goal reengagement as a mediator of intervention effect for (online) CBT for depression was not investigated previously. More research is needed regarding the mediating role of changes in behavioral activation and goal reengagement in online CBT for depressive symptoms.

The current study was conducted to find mediators of the intervention effect, which may provide us with suggestions for possible mechanisms of change underlying the intervention. Since changes in behavioral activation and goal reengagement were found to be mediators of the intervention, they may suggest possible mechanisms of change. It was previously found that reward processing and avoidance may be possible mechanisms of change of behavioral activation (25-27). That is, specific components of the intervention may activate these mechanisms, e.g. by activating participants, avoidance of (positive) activities may be reduced. In turn, this may lead to a reduction in depressive symptoms. However, it was previously found that there is no 1-to-1 relation between offering certain components of the intervention and the change in corresponding mediators (8, 28). For example, it was found that negative thinking decreased after CBT but also after behavioral activation. So, even when the focus was not on changing negative thoughts in the behavioral activation

treatment, they did decrease (28). More research should be conducted into the relation between offering certain components of the intervention and the change in corresponding mediators.

Goal reengagement and behavioral activation as components of the intervention are related, as both are trying to increase the amount of (positive) activities to improve one's mood. In addition, in interventions that include behavioral activation, goal setting is often included as a first step of activation (29, 30). Since behavioral activation and goal reengagement are related, it may not be surprising that the timing of the mediation effects did not correspond to the timing of the related intervention components. The mediation effect of changes in behavioral activation occurred approximately three weeks after the component was introduced, and the mediation effect of changes in goal reengagement occurred approximately four weeks before the component was introduced. This is also in line with previous findings regarding the weak relation between offering a certain intervention component and a change in the corresponding mediator (8, 28).

No other significant mediators of intervention effect were found. This means that changes in relaxation, coping self-efficacy, and the cognitive coping strategies catastrophizing and positive refocusing were no significant mediators. In most previous reviews (5-7) changes in cognitions were found to be mediators of CBT for depression, but one review found no evidence for changes in cognitions as a mediator (8). In the current study, changes in cognitions were not measured, but changes in the use of cognitive coping strategies was included. This may be comparable to a change in cognitions, but changes in the use of cognitive coping strategies were not found to be mediators. These cognitive coping strategies were addressed in the intervention and also did improve in the intervention group. However, the use of these strategies also improved in the control group. Future studies may investigate changes in cognitions as a mediator of intervention effect.

Strengths and limitations

Some strengths and weaknesses of this study may be identified. An important strength was that a temporal pattern of change was investigated because multiple measurement moments were included during the intervention period. Many previous mediation studies only included a pretest and a post-test, which is not sufficient to demonstrate a timeline and 'real' mediation effects (4). In addition, multiple mediators were investigated that corresponded to components of the intervention. Another strength was that advanced state of the art statistical analyses were used: MSEM and ALT. Furthermore, all available data was used in the analyses, so participants with some missing measurement moments were not totally excluded from the analyses. Last, return effects from the dependent variable to the mediators were investigated, to study the strength of the mediation effects. A weakness of this study is that the measurement of some mediators included the use of self-designed questionnaires with only a few items. The reliability of these questionnaires was mostly adequate, but

the validity needs to be investigated. Only a few items were used, because the questionnaires were administered multiple times and it should not take too much time to complete them. Another weakness was that there was much drop-out during the study. However, the drop-out rate was comparable to other studies regarding the effectiveness of Internet interventions (31, 32). No differences in demographic and HIV specific characteristics (e.g. duration of HIV) were found between drop-outs and completers in the current study (2), so probably attrition bias was not a problem. Finally, a selection of mediators was investigated in the current study. Other mediators may also have an effect and may be assessed in future studies.

Future research

In future studies, mediators may be more elaborately assessed with validated questionnaires with more items. Attrition may be prevented by using techniques that were previously suggested, such as inducing hope for benefits of the intervention and reducing time barriers by using habit-forming strategies (33). Other potential mediators may be investigated, such as changes in worrying. Additionally, it is important to study what the mechanisms of change of the intervention are. This is a challenge to investigate, as the relation between intervention components, mediators, and mechanisms of change is weak. As a first step, dismantling studies may be conducted, where each component of the intervention is provided to a different group of participants, and will be compared to a group that receives the complete intervention (4). In this way, it can be investigated which components may be related to changes in specific mediators. Furthermore, manipulation of a proposed mechanism of change may be conducted to study the effects on the outcome (4).

Conclusion

To conclude, potential mediators of a guided Internet-based intervention for PLWH with depressive symptoms were studied. The intervention was previously found to be effective in decreasing depressive symptoms, compared to a control group receiving attention only. We found that changes in behavioral activation and goal reengagement were significant mediators of the intervention effect. The mediation effect of changes in behavioral activation seemed to be stronger than for changes in goal reengagement. The mediators that were found in this study may suggest possible mechanisms of change of the intervention. More research into these mechanisms of change is needed to find out how the intervention works. The outcomes of these studies may be used to optimize the intervention and help decrease depressive symptoms among PLWH even more effectively.

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Appendix

Appendix 1. Items and scoring of the questionnaires

Depressive symptoms (PHQ-2)

Over the last week, how often have you been bothered by any of the following problems? Score from 0 (not at all) to 3 (nearly every day).

1 Little interest or pleasure in doing things.

2 Feeling down, depressed, or hopeless.

Activation (BADS)

Please indicate to what extent the following statements apply to you over the past week. Score from 0 (not at all) to 6 (completely).

1 I engaged in a wide and diverse array of activities.

2 I am content with the amount and types of things I did.

Relaxation

Please indicate which answer is most appropriate to you over the past week. Score 1 (yes), 2 (sometimes), 3 (no).

1 Is it difficult for you to relax?

Cognitive coping: catastrophizing and positive refocusing (CERQ-short)

Please read the sentences below and indicate how often you had the following thoughts over the past week. Score from 1 ((almost) never) to 5 ((almost) always).

1 I keep thinking about how terrible it is that I have HIV.

2 I continually think how horrible it is to have HIV.

3 I think of pleasant things that have nothing to do with having HIV.

4 I think of something nice instead of having HIV.

Goal reengagement (GDGRS)

We will ask you to click the answer to the statement that you think best suits you during the past week. Score from 1 (totally disagree) to 5 (totally agree).

1 If I have to stop pursuing an important goal in my life because I have HIV I start working on other new goals.

Coping self-efficacy

Click the answer that is most applicable to you over the past week. Score from 1 (totally disagree) to 5 (totally agree).

1 I am confident that I can deal with having HIV.

2 Whatever happens in relation to having HIV, I'll figure it out.

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