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Living positive: eHealth for people with HIV and depressive symptoms

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Living positive

eHealth for people with HIV and depressive symptoms

Proefschrift

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Chapter 1

General introduction

Pete is 56 years old and has human immunodeficiency virus (HIV) for about six years. He is on medication, which is effective. However, Pete often feels tired and sad. He has told some friends that he has HIV, but they did not always respond the way he expected. He has lost some friends because of these issues, and now he is thinking of not disclosing to others that he has HIV anymore. In addition, Pete lost his job a couple of weeks ago. He was a cook at an Italian restaurant, but he was replaced by a younger cook. He misses the work he loved to do and he feels like he has failed. Pete is bothered by negative thoughts a lot and sometimes he forgets to take his HIV medication. He does not know what to do with his feelings of sadness and is thinking of discussing it with his nursing consultant in the hospital.

The case of Pete does not stand alone. Many people living with HIV (PLWH) suffer from sadness or depressive symptoms (1-3). Psychological interventions, such as cognitive behavioral therapy, were found to be effective in treating these depressive symptoms in PLWH (4-9). However, the traditional face-to-face interventions do not reach all PLWH with depressive symptoms, and experienced stigma is a barrier to seek treatment for some PLWH. Therefore, new interventions are needed that overcome these barriers, such as online interventions (eHealth). The aim of this dissertation is to evaluate the effectiveness of the eHealth intervention 'Living positive with HIV', for PLWH with depressive symptoms.

This general introduction begins with an explanation of HIV and AIDS and medical treatments for it. This is followed by a paragraph about the prevalence, risk factors, and consequences of depressive symptoms in PLWH. Thereafter, psychological interventions for depressive symptoms in PLWH are discussed. Furthermore, a description of self-help and eHealth interventions for PLWH with depressive symptoms follows. The introduction ends with the aims and outline of the dissertation.

HIV and AIDS

HIV is a virus that attacks the immune system of the human body (10). It reduces the number of cluster of differentiation 4 (CD4) cells, which keep the body protected against bacteria and viruses. As a result, the body becomes more vulnerable for infections. When the virus damages the immune system so much that the body cannot be adequately protected anymore, one may get opportunistic infections or cancers. This indicates that the person has progressed to the last stage of HIV infection: acquired immunodeficiency syndrome (AIDS) (10). If AIDS is not treated effectively, it is a fatal disease.

In the early acute phase of the HIV infection, flu-like symptoms may be experienced, such as fever, fatigue, and rash (11). However, some people do not experience symptoms at all. In the later chronic phase, many patients do not experience symptoms or only mild ones (10). Symptoms of AIDS include weight loss, fever with night sweats, prolonged diarrhea, shortness of breath, and fatigue.

Many of these symptoms belong to opportunistic infections, such as candidiasis, herpes, pneumonia, and tuberculosis (12). HIV may be transmitted via sexual behaviors, sharing needles or syringes (common among injection drug users), and during pregnancy, birth, or breastfeeding (13). HIV is still very prevalent, 36.7 million people suffer from it worldwide, and in 2016 one million people died because of HIV/AIDS (14). It was estimated that there are 22900 PLWH living in the Netherlands at the end of 2016 (15). The majority of them are men who have sex with men (MSM) (16).

More than 20 years ago, effective medication to treat HIV was developed: antiretroviral therapy (ART, also called HAART or cART). ART is a combination of at least two, but usually three, drug classes that reduce the amount of virus in the blood (17, 18). The goal of ART is to reach an undetectable viral load: such a low amount of HIV in the blood that it cannot be detected by standard tests. ART does not cure HIV, but improves the health of PLWH and slows/prevents the progression to AIDS. In addition, HIV transmission may be decreased when PLWH are on ART successfully (19, 20). For example, mother-to-child transmission decreases dramatically when ART is used (21). Because of ART, HIV has become a chronic disease instead of a disease that is related to sickness and death. However, PLWH may still suffer from physical and psychological symptoms. The symptoms that were most often reported among PLWH are pain, lack of energy, sleep difficulties, worrying, and feeling sad (22, 23).

In the Netherlands, most PLWH are on ART (15), but in other countries ART is not accessible for everyone (24). In 2014, UNAIDS set the ambitious 90-90-90 goals: 90% of PLWH are diagnosed with HIV, of which 90% are on ART, of which 90% are virally suppressed (virus level in the blood is very low or undetectable) (25). The aim is to reach the goals globally in 2020. It was found that in 2016 only Denmark and Sweden reached all goals, so there is much work to be done (26). Many PLWH do not sufficiently adhere to ART, it has been found that only 62% took their prescribed doses more than 90% of the time (27). Non-adherence may have negative consequences, such as more viral replication, HIV-related morbidity, and drug resistance (28). When many PLWH do not optimally adhere to ART, it will be difficult to reach the 90-90-90 goals (24). So, optimizing adherence should be a major focus of HIV care. During the last years, pre-exposure prophylaxis (PrEP) was developed and investigated. PrEP is antiretroviral medication that people without HIV but in a risk group (e.g. MSM) can take to prevent infection (29). PrEP was found to be effective to prevent HIV in recent studies (29-31), although adherence is also important here, and the efficacy among women cannot be confirmed yet (29).

Depressive symptoms in people with HIV

Depressive symptoms are quite common among PLWH, approximately one third of them suffers from mood disorders or clinically significant depressive symptoms (1-3). Why are depressive symptoms so prevalent among PLWH? This may be related to psychosocial factors, such as the stigma that is associated with having HIV (32), taking ART each day for the rest of one's life (33), difficulties with

coping with HIV (34), and concerns about disclosing the illness to others (35). In addition, neurobiological changes caused by the presence of HIV in the central nervous system may play a role in developing depressive symptoms (36, 37). Furthermore, depressive symptoms may already be present before HIV infection. Certain risk groups for HIV infection, such as homosexual men (38) and intravenous drug users (38, 39), have higher rates of depressive symptoms than people that do not belong to these risk groups. This may be another explanation for the high prevalence of depressive symptoms among PLWH.

Signs and symptoms of depression are the same in PLWH as in people without HIV. However, the following symptoms were found to be most common in PLWH: anhedonia, insomnia, loss of appetite, and difficulties in memory and concentration (33). Diagnosing depression in PLWH may be difficult, because some symptoms of depression overlap with symptoms of HIV or side effects of ART (33). For instance, fatigue, insomnia, and anorexia are symptoms that can be present in both HIV and depression (40, 41). Therefore, depressive symptoms may not always be recognized by physicians.

The consequences of depressive symptoms in PLWH may have a large impact as well. More specifically, depressive symptoms were found to be associated with non-adherence to ART (42). Furthermore, depressive symptoms in PLWH have an influence on quality of life. Next to an effect on mental health related quality of life of PLWH, depressive symptoms also have an effect on quality of life related to physical health, role functioning, and social functioning (43, 44). Additionally, the economic burden of PLWH with depressive symptoms is high. Costs for general medical services (e.g. inpatient and emergency services) were found to be higher for PLWH with depression than for PLWH without depression (45). Healthcare costs such as medication, inpatient and outpatient care, for PLWH with depression (or other psychiatric disease) were approximately $17,911 to $33,037 per person per year in the USA between 1995 and 2010 (45-47). Furthermore, the indirect costs due to being less productive at work because of HIV and depression are also substantial. As far as we know, there are no previous studies that investigated these indirect costs in PLWH with depression. Though, they were found to range from €1,353 per person in 2010 in Italy (48), to €19,786 per person in 2002 in Switzerland (49) for PLWH without depressive symptoms (48), and €1,782 on average per person for people with depression irrespective of HIV in Europe in 2010 (50).

Psychological interventions for people with HIV and depressive symptoms

The burden of depressive symptoms in PLWH is high on an individual and societal level. Therefore, it is important to treat depressive symptoms adequately. Many psychological interventions have been developed to reduce depressive symptoms in PLWH, such as cognitive behavioral therapy (CBT), interpersonal psychotherapy, and mindfulness. Of all interventions that were developed to treat depressive symptoms in PLWH, CBT is used most often. In CBT, unhelpful thoughts and behaviors are

adapted in order to feel better (51). Exercises are used to change dysfunctional beliefs about self or the world into more realistic, functional beliefs. Traditionally, CBT is provided face-to-face to individuals, groups, couples, or families.

Many studies have been conducted into the effectiveness of CBT. It has been found that CBT is effective in reducing depressive symptoms in PLWH (4-9). In addition, CBT may also improve quality of life (7) and ART adherence (52). Other psychological interventions, such as interpersonal psychotherapy (53, 54), peer support (8), or mindfulness (55) may also be effective in decreasing depressive symptoms in PLWH. Though, the face-to-face format of interventions has some disadvantages, such as the time it takes for patients and therapists, the stigma that may be perceived by patients, and the high costs.

Self-help and eHealth for people with depressive symptoms

As face-to-face interventions have some limitations, in the past years other treatment formats have been developed and investigated. Initially, self-help interventions for depressive symptoms have been developed. Self-help refers to a psychological intervention that a patient can work through independently from any place of preference (56). The intervention can be provided in booklet format or via other media such as audio or video. Self-help interventions can be guided (e.g. by a professional or peer) or unguided. Guidance often involves supporting the patient to work with the intervention and providing information (56). Guidance can be provided via various channels, such as telephone, e-mail, and chat. Self-help interventions, mostly CBT, were found to be effective in reducing depressive symptoms (56, 57), also in people with a physical illness (58, 59). Moreover, it has been found that guided self-help CBT was equally effective as face-to-face CBT for depressive symptoms (60). However, guidance seems important in self-help; guided self-help interventions for depression were found to be more effective than unguided interventions (57).

In the past years, more and more computerized self-help interventions for depressive symptoms have been developed: eHealth interventions. *eHealth has been defined as the use of emerging information and communications technology, especially the Internet, to improve or enable health and healthcare (61).* Typically, eHealth interventions consist of multiple modules with text to read and assignments to complete (62). This may be accompanied by special elements, such as videos or audio files. Guidance may also be offered next to eHealth interventions. eHealth interventions have certain benefits compared to face-to-face interventions, such as a larger reach, reduced stigma due to following the intervention anonymously, the possibility to work on the intervention in a place and time of choice, and lower costs. It has been found that eHealth interventions (especially CBT) are effective in people with depressive symptoms (62-67) and in people with a chronic somatic disease with comorbid depressive symptoms (68). Again, guidance was found to be important; previous meta-

analyses have found larger effects (63, 66, 67) and less attrition (57, 66) in guided eHealth interventions compared to unguided interventions.

eHealth for people with HIV and depressive symptoms

A lot of eHealth interventions were developed and investigated for people with depressive symptoms, but only four eHealth interventions were developed for PLWH with depressive symptoms (69-72). One of these interventions was an online support group (71), which was found to be effective. However, this study did not include a control condition. The other interventions were based on metacognitive therapy and positive psychology (69), CBT to manage adherence, stress, and mood (70), and stress management (72). No effects of these interventions on mood were found. An explanation for not findings any effects may be that the interventions did not met the needs of PLWH with depressive symptoms (70, 72). For example, one of the interventions focused more on improving medication adherence than on improving depressive symptoms (70). Since eHealth interventions have certain advantages compared to face-to-face interventions, and were found to be effective for people with depressive symptoms in previous meta-analyses, more research should be conducted into eHealth interventions for PLWH to reduce depressive symptoms.

Therefore, we have developed a new eHealth intervention for PLWH with depressive symptoms: Living positive with HIV. It is based on a self-help intervention in booklet format that was developed by the same research group (73). The self-help booklet was developed after studies that investigated correlates of well-being and depressive symptoms in PLWH, and a needs assessment (34, 74, 75). The self-help booklet contains CBT and includes psychoeducation and exercises. It consists of eight lessons which can be completed in about eight weeks, in one to two hours a week. In a randomized controlled trial (RCT), it has been found that the self-help intervention was effective in decreasing depressive symptoms, compared to a waiting list control condition (76).

After the RCT, the booklet was converted into an eHealth intervention. The intervention was expanded in three ways: 1) an activation component was included in the first lesson, to stimulate participants to perform small positive activities to improve mood; 2) minimal telephone coaching with motivational interviewing was added to reduce attrition and improve motivation; and 3) the intervention was available in Dutch and English to reach more PLWH. When the eHealth intervention was finalized, a focus group of four volunteers from the Dutch HIV association was invited to evaluate the intervention. Thereafter, the intervention was adapted and a pilot study was conducted. Twenty PLWH recruited via the Dutch HIV association worked through the whole intervention, received coaching, and provided feedback. Depressive symptoms decreased significantly after following the intervention and participants evaluated the intervention positively. Now the time has come to investigate the effectiveness of the eHealth intervention in a large scale RCT. In addition, it is important

to investigate for whom the intervention is most effective and what are mediators of intervention effect? Lastly, the balance between costs and benefits is crucial, so the cost-utility of the intervention compared to attention only (control group) is investigated.

Conclusions

Depressive symptoms in PLWH are common and have a large impact on the individual and societal level. Psychological interventions, especially CBT, for PLWH with depressive symptoms were found to be effective. However, there is a need for interventions that overcome the barrier of stigma, are more flexible in terms of time and place to follow the intervention, reach more people, and are less expensive. eHealth interventions may address these needs and were found to be effective in people with depressive symptoms. Though, not much eHealth research is conducted in PLWH with depressive symptoms, while this is a group that may benefit a lot from eHealth interventions. In addition, studies into moderators and mediators of intervention effect in eHealth interventions are scarce, as are economic evaluations of eHealth interventions.

Aims and outline of this dissertation

The first aim of this dissertation is to study and provide an overview of the effectiveness of various psychosocial interventions for PLWH to improve mental health and ART adherence. The second aim is to evaluate the effectiveness of the eHealth intervention 'Living positive with HIV' for PLWH with depressive symptoms. Additionally, secondary questions regarding moderators and mediators of intervention effect and the cost-utility of the intervention compared to attention only, are investigated. The content of the chapters of the dissertation is explained below.

Chapter 2 contains a systematic review and meta-analysis on the effectiveness of psychosocial interventions for PLWH to improve mental health. The aim is to investigate the effectiveness of various psychosocial interventions, such as CBT, mindfulness, and peer support. Depression, anxiety, quality of life, and psychological well-being are the treatment outcome measures in this study. We also assess characteristics that may influence the effectiveness of an intervention (e.g. treatment provider).

Chapter 3 includes a systematic review and meta-analysis which aims to study the effectiveness of psychosocial interventions to enhance ART adherence. The effects of study characteristics and treatment characteristics on the effectiveness of interventions is also investigated.

Chapter 4 describes the study protocol for the RCT about the effectiveness of the guided online self-help intervention for PLWH with depressive symptoms. The protocol explains the research questions

of the study and the methods (e.g. content of the intervention and measurements). Chapters 5 to 8 include the results of the different research questions of the RCT.

Chapter 5 reports on the results of the RCT regarding the effectiveness of the guided Internet-based self-help intervention for PLWH with depressive symptoms, compared to a control condition that receives minimal attention only. The effects of the intervention are assessed on the short term and on the long term. Furthermore, the effect on anxiety symptoms is investigated and the user satisfaction of participants with the intervention is examined.

In **Chapter 6** possible moderators of change of the online self-help intervention 'Living positive with HIV' are studied. For whom does guided online self-help work best? Many potential moderators are investigated, e.g. demographic characteristics, HIV characteristics, and psychological characteristics.

In **Chapter 7** possible mediators of intervention effect of the guided online self-help intervention are examined. These mediators may help to identify mechanisms of change of the intervention. Possible mediators that are investigated are related to components of the intervention, for example behavioral activation and relaxation.

Chapter 8 describes the cost-utility of the guided online self-help intervention, compared to attention only. The differences between the intervention condition and the control condition regarding quality of life and healthcare and non-healthcare costs are outlined. An economic evaluation is conducted alongside the RCT and the results are reported.

Chapter 9 summarizes the results of the dissertation and discusses the findings with regard to previous research. Strengths and limitations of the studies are discussed, just as recommendations for future research and implications for clinical practice.

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Chapter 2

The benefits of psychosocial interventions for mental health in people living with HIV: A systematic review and meta-analysis

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Abstract

In this systematic review and meta-analysis we investigated the effectiveness of different psychosocial treatments for people living with HIV (PLWH) and mental health problems. Additionally, characteristics that may influence the effectiveness of a treatment (e.g., treatment duration) were studied. PubMed, PsycINFO and Embase were searched for randomized controlled trials on psychosocial interventions for PLWH. Depression, anxiety, quality of life, and psychological well-being were investigated as treatment outcome measures. Sixty-two studies were included in the meta-analysis. It was found that psychosocial interventions for PLWH had a small positive effect on mental health ($\hat{g}$ = 0.19, 95% CI [0.13, 0.25]). Furthermore, there was evidence for publication bias. Six characteristics influenced the effectiveness of a treatment for depression. For example, larger effects were found for studies with psychologists as treatment providers. To conclude, this systematic review and meta-analysis suggests that psychosocial interventions have a beneficial effect for PLWH with mental health problems.

Keywords: HIV, psychosocial intervention, mental health, depression, meta-analysis.

Resumen

En esta revisión sistemática y meta-análisis se ha investigado la efectividad de los diferentes tratamientos psicosociales para las personas viviendo con VIH (PVVIH) y con problemas de salud mental. Adicionalmente, hemos estudiado las características que pueden influir en la efectividad de un tratamiento (por ejemplo, duración del tratamiento). Como medidas de tratamiento, pruebas controladas aleatorizadas de las intevenciones psicosociales para depresión, ansiedad, calidad de vida y bienestar psicológico fueron buscadas en PubMed, PsycINFO y Embase. Sesenta y dos estudios se han incluido en el metanálisis. Hemos encontrado que intervenciones psicosociales para las PVVIH tuvieron un menor efecto positivo en la salud mental ($\hat{g}$ = 0.19, IC del 95% [0.13, 0.25]). Además, hubo evidencia de sesgo en la publicación. Seis características influyeron la efectividad del tratamiento para la depresión. Por ejemplo, hemos encontrado efectos mayores en estudios con psicólogos como proveedores del tratamiento. Concluyendo, esta revisión sistemática y meta-análisis indica que las intervenciones psicosociales tienen un efecto beneficioso para gente con PVVIH y con problemas de salud mental.

Introduction

In recent decades, due to the use of antiretroviral medication, HIV has become a chronic illness instead of a disease that rapidly leads to severe sickness and death. However, people living with HIV (PLWH) may still suffer from physical symptoms, such as pain and lack of energy (1). In addition, mental health problems such as depression and anxiety are common among PLWH (2-4). In PLWH, the prevalence rate of mood disorders or clinically significant depressive symptoms is approximately 33% (5), and the prevalence rate of anxiety disorders about 20% (6). Several psychosocial factors – such as isolation, stigma, discrimination, lack of support, and drug abuse – can contribute to feelings of depression and anxiety (4, 7). In turn, mental health problems may have various negative consequences for PLWH. For example, it has been shown that PLWH with depressive symptoms have a higher risk of poor adherence to antiretroviral therapy (ART); they are also more at risk for HIV-related morbidity and mortality (8). More specifically, in PLWH psychological factors (such as depressive symptoms and stress) have been shown to be related to immune measures, such as decreased cluster of differentiation 4 (CD4) cell count and increased viral load (9, 10). In view of the above research, it seems apparent that depression and anxiety in PLWH may decrease well-being and quality of life (11).

Given the impact that psychological symptoms have on the health and well-being of PLWH, it is very important to treat these symptoms. Several psychosocial interventions, such as cognitive behavioral therapy (CBT), supportive interventions, meditation, and stress management interventions, have been developed for PLWH with mental disorders. Various reviews and meta-analyses have found that these interventions are effective in reducing symptoms of depression, anxiety, and distress in PLWH (12-18). The format of these interventions may differ from a group-based or individualized format to interventions where the PLWH's partner or other family members are also involved. In addition to assessing the overall effectiveness of various psychosocial interventions, it is also important to compare interventions with each other and determine whether specific interventions stand out as the most effective to improve mental health in PLWH. With this information, more targeted treatment may be provided in the future. The interventions that seem to be the most effective could be offered first, which might improve the psychological care of PLWH. However, previous meta-analyses and reviews (12, 13, 15-18) have not compared interventions with each other to discover which specific psychosocial interventions are the most effective for PLWH with mental health problems.

Additionally, it is also meaningful to investigate whether certain characteristics may influence the effectiveness of the treatment. We can distinguish two types of characteristics that may act as moderators. The first type are characteristics of the intervention, such as treatment duration, intervention techniques, or the provider of the therapy. If we have more knowledge about the effect of treatment characteristics on the effectiveness of an intervention, this can be used to improve

existing interventions by including the most beneficial aspects when designing new interventions for PLWH with mental health problems. If we find, for example, that interventions provided online or by a psychologist are more effective than interventions provided by others (e.g., peers), it may be useful to design new interventions that are provided online or by psychologists. The second type of possible moderators are characteristics of the study, such as the sample that was used or the type of control group. These characteristics may partly explain why some studies find larger effects than others. For instance, it may be that studies with many female participants show larger effects than studies with many males. If this is the case, it may be useful to consider this aspect in future studies. As yet, not much research is available about moderators of treatment effect in PLWH. However, moderating factors were taken into account in one meta-analysis, which found that stress-management interventions for PLWH reduced anxiety symptoms. In this research, the effect of the intervention was found to be larger when they included more women, more participants with anxiety symptoms at baseline, younger participants, and made less use of medication adherence information and/or planning in an intervention (16).

Most previous meta-analyses have focused on particular psychological interventions (e.g., CBT or meditation) and mostly also on a particular outcome (such as alleviation of depression or anxiety) (12-18). However, no meta-analysis has yet investigated which psychosocial interventions are the most effective on psychological outcomes. The first aim of the present systematic review and meta-analysis was to investigate this. This meta-analysis included various psychosocial interventions for PLWH, including CBT, support interventions (e.g., peer support), interpersonal psychotherapy, stress management, mindfulness, coping improvement interventions, and family interventions. In addition, multiple outcomes were studied: depression, anxiety, quality of life, and psychological well-being. Only randomized controlled trials (RCTs) were included in the meta-analysis. As it is important to investigate moderators of intervention effect, and this was not examined in detail in previous meta-analyses, the second aim of the current meta-analysis was to carry out a moderator analysis. Since we included a lot of different intervention types and outcomes, we expected that there would be large differences between study effect sizes. A moderator analysis could give more information about which characteristics might explain these differences in results. Various possible moderators were included: intervention characteristics such as intervention duration, therapy provider, and intervention techniques (e.g., stress-management); and study characteristics such as attrition, study quality, and sample characteristics. To conclude: we investigated and provide an overview of the effectiveness for PLWH of psychosocial interventions in decreasing depression and anxiety and improving quality of life and psychological well-being. In addition, we investigated whether specific interventions stood out as having the greatest effect on these outcomes and we studied moderators of intervention effect.

Methods

Search strategy and study selection

Several strategies were used to search for relevant RCTs. First, we searched in the electronic databases PubMed, PsycINFO, and Embase on September 29, 2014. Search words included terms related to HIV/AIDS, various types of psychosocial interventions (e.g., CBT, psychotherapy), and outcomes (e.g., depression, quality of life). The search strategy with keywords can be found in Appendix A. Second, we also searched for papers in the references of available meta-analyses and reviews about the subject.

Studies were included when they met all of the following criteria: 1) RCT; 2) evaluation of a psychosocial intervention (see definition below); 3) participants in the study are HIV positive and are 18 years or older; 4) year of data collection is later than 1995 (see explanation below); 5) the outcome variables that were studied belong to one or more of the following categories: depression, anxiety, psychological well-being, or quality of life; 6) studies were written in the English language; and 7) data to calculate effect sizes was present in the paper or retrieved from the authors. Regarding the second inclusion criterion, a psychosocial intervention was operationalized as an intervention that aimed to change thoughts, emotions and/or behavior of PLWH and had a psychosocial component. Therefore, physical interventions (such as exercise), were not included in the meta-analysis. Regarding the fourth inclusion criterion, we decided to include studies that collected data later than 1995, since antiretroviral medication was developed in 1996 and consequently the future prospects of PLWH changed a lot after that period. Furthermore, the outcome domains depression, anxiety and quality of life were specified a priori. Only the outcome psychological well-being was first intended for stress-related outcomes, but this was a rather small category, so we decided to enlarge it. Positive and negative affect, psychological functioning and general mental health were examples of concepts that were included in the outcome psychological well-being. Studies that had posttraumatic stress disorder (PTSD) as an outcome were not included in the meta-analysis. Regarding the seventh criterion, authors of the included papers were contacted to retrieve data that was not available in the paper. When the authors did not respond to the requests (even after reminder e-mails) and the data to calculate effect sizes was not available, the study was not included in the meta-analysis.

The first step was the selection of studies on title and abstract, and was performed by two persons (first and fourth author). The first 100 studies were selected by both authors independently, to determine the agreement among selectors, which was substantial (19), Cohen's kappa = 0.80. Thereafter, both selected half of the remaining studies. For the second step of selecting studies, based on full text, the studies were divided among three persons (first and fourth author and a Master student in clinical psychology). The inclusion criteria, as described above, were used in the following

order to ensure a fast and equal decision: 6, 3, 1, 4, 2, 5, 7. When there was doubt about including a study, the paper was discussed with one or more of the other authors to make a decision.

Problems of multiplicity

Some decisions had to be made when multiple papers were published about the same data or when multiple measuring instruments, time points or interventions were used in one study. When there were multiple papers about the same data, the paper with the most relevant outcome data was used as the main paper. Other papers were used to add information that was not present in the main paper. In addition, when there were multiple measuring instruments for one outcome, two instruments were included in the analysis and their data was averaged. The instruments that were most validated and comparable to other studies were chosen. When there were assessments at more than one time point after the termination of the intervention, the first time point (first post-test) was included in the main analysis. Moreover, we did investigate overall differences between time points post intervention. For this analysis, time points were classified into these categories: 0-3 months post intervention, more than 3-6 months post intervention, more than 6-9 months post intervention, and more than 9 months post intervention. When two assessments occurred in one time period, both were included in the analysis and the data was averaged. At last, when there were multiple intervention and/or control conditions in a study, they were all included in the analysis and coded as intervention or control conditions. In the analysis concerning the overall effectiveness of psychosocial interventions on mental health, the data of multiple intervention conditions was averaged. To investigate which interventions and techniques were most effective in the moderator analysis, all interventions were investigated separately. Therefore, some studies were represented multiple times in this analysis. To be included as an intervention condition, the intervention should have a psychosocial component. In the control condition, people were put on a waiting list, received standard care or were in an active control condition. This last category included for example (psycho)education, support and telephone check-ups.

Data extraction and coding

We developed a protocol to extract the data from the articles. The following information was extracted from the papers: year of publication, baseline scores on outcome variables, post-treatment results, follow-up results, country of data collection, years of recruitment, study setting (inpatient; outpatient; combination), number of participants in each group, percentage attrition, percentage females, mean age, percentage MSM, percentage participants with AIDS, mean number of years with HIV, percentage participants that use ART, screening on depression (yes; no), intervention type (symptom-oriented intervention; supportive intervention; meditation intervention), intervention techniques (relaxation;

CBT; motivational interviewing; stress-management), intervention duration (total duration in hours; duration in weeks; number of sessions; duration of one session), therapy provider [psychologist/psychotherapist; counsellor (e.g., nurse, HIV specialist, social worker, trained facilitator]; peer; none (e.g., computer); other), intervention format [group; individual; combination; other (e.g., family interventions)], primary focus of intervention (mental health; no mental health), primary outcome (mental health; no mental health), theory content of intervention (theory-driven; not theory-driven), type of control group (waiting list; standard care; active control group), length of follow-up, type of analysis [intent-to-treat (ITT); no ITT], and study quality (see next paragraph).

The intervention type variable included three categories: symptom-oriented interventions, supportive interventions and meditation interventions. These categories were created post-hoc, after examining the content of the included interventions. The category symptom-oriented interventions included mostly cognitive and/or behavioral therapy, stress-management, and interpersonal therapy. Furthermore, the category supportive interventions consisted of (peer) support and psycho-education, and the category meditation interventions included interventions that incorporated mindfulness, meditation, or relaxation. Since the symptom-oriented interventions used various psychological techniques, it was further investigated whether symptom-oriented interventions that used a specific technique would have larger effects than symptom-oriented interventions that did not use this specific technique. This was investigated in the symptom-oriented interventions only, because the supportive and meditation interventions mostly did not make use of additional psychological techniques. The assessed intervention techniques were relaxation, CBT (defined as containing cognitive and/or behavioral techniques), motivational interviewing and stress-management. One symptom-oriented intervention may use multiple psychological techniques. For example, a symptom-oriented intervention may include CBT techniques and relaxation techniques. The explanation of intervention types and intervention techniques is depicted in Table 1. The variable theory content of intervention contains two categories: 1) it was described that the intervention was based on theory or a theoretical model (e.g., social cognitive theory or the health belief model) or 2) it was not described that the intervention was based on theory or a theoretical model. The type of control group was categorized as waiting list, standard care or an active control condition. Standard care included for example standard medical care and referral to mental health services when needed. The last category included for instance (psycho)education, support and telephone check-ups.

The following information was asked from the authors, when it was not available in the paper: baseline, post-treatment and follow-up data, years of recruitment, number of participants in each group, percentage attrition, percentage females, mean age, intervention duration, therapy provider, intervention format, type of control group, length of follow-up and type of analysis. The data was extracted by two persons (first author and a psychologist). Both coded a portion of the studies and 17

of the studies (27%) were coded by both authors. The intraclass correlation coefficient was calculated for the agreement on continuous variables, which was 0.99. For the categorical variables a Cohen's kappa was calculated, this was 0.72, which is substantial.

Study quality

Study quality was assessed by using two methods: the Cochrane Collaboration's tool for assessing risk of bias (20) and three criteria from a review about defining empirically supported psychological treatments (21). The Cochrane Collaboration's tool for assessing risk of bias consists of six domains. Four domains were used in this study: (1) sequence generation for allocation to conditions; (2) concealment of allocation to conditions; (3) addressing incomplete outcome data; and (4) selective outcome reporting. The domain blinding of participants and researchers was not used, because in almost all studies participants and researchers could not be blinded to the allocation to conditions. Furthermore, the domain other sources of bias was not used, because in most studies there were no other sources of bias. On each domain, a study received the judgement low risk of bias (+), high risk of bias (-) or unclear risk of bias (?) using the criteria from the tool.

Furthermore, we used three criteria from a review about defining empirically supported psychological treatments, to assess the quality of administering the intervention: (1) the availability of a treatment manual that was followed (published or designed for the study); (2) the use of a training for the therapy providers (for the study or general training); and (3) treatment integrity was checked during the study (e.g., supervision of therapy providers, recording of sessions, checking of protocol adherence). For each criterion a study received a judgement of yes (+, low risk of bias), no (-, high risk of bias), unclear (?) or not applicable (NA; e.g., when the intervention is a self-help program). Two persons (first author and a psychologist) rated the quality of the studies. Both rated a portion of the studies and 17 studies were rated by both authors to calculate their agreement. Cohen's kappa was 0.67, which is substantial.

Table 1. Intervention types and intervention techniques

Intervention types	**Intervention techniques (in symptom-oriented interventions only)**
Symptom-oriented intervention (e.g. cognitive and/or behavioral therapy, stress-management, interpersonal therapy)	Relaxation
Supportive intervention (e.g., support, psycho-education)	CBT
Meditation intervention (e.g., mindfulness, meditation, relaxation)	Motivational interviewing
	Stress-management

Moderators

The following moderators were investigated: country of data collection, first year of participant recruitment, percentage attrition, percentage females, mean age, percentage MSM, percentage participants with AIDS, mean number of years with HIV, percentage participants that use ART, screening on depression, intervention techniques, intervention duration, therapy provider, intervention format, primary focus intervention, primary outcome mental health, theory content of intervention, type of control group, type of analysis and study quality.

For the moderator analyses with continuous variables, the assumptions for meta-regression were checked (normality and linearity). None of the variables met both assumptions. Therefore, the continuous variables were transformed into categorical variables. The categorization was based on statistical and content related reasons. The variable first year of recruitment was categorized into three periods: 1996-2001, 2002-2006 and 2007-2012. The variable percentage of drop-out was separated into three categories: 0-10, 10-20 and > 20%, as was the variable percentage of females: 0-20%, 20-80 and 80-100%. The variable mean age was divided based on a median split: < 42.40 years and ≥ 42.40 years. The variable percentage MSM was divided into two categories: 0 and > 0% (because most studies had no MSM, so the median was 0%). The variable percentage of people with AIDS was separated into two categories based on a median split: < 40 and ≥ 40%, as was the variable number of years with HIV: < 10.02 years and ≥ 10.02 years and the variable percentage of people on ART: < 87 and ≥ 87%. Finally, the variable total intervention duration was divided into four categories: 1-5, 5-12, 12-18 and 18-30 hours.

Study quality was included as a moderator in the analysis. When a study met 0-2 out of seven quality criteria (0-2 times a +), the study was classified as a study with low quality. When a study met 3-4 quality criteria, the study was classified as a study with medium quality and when 5-7 criteria were met, the study was classified as a study with high quality. A rating of unclear risk of bias was scored as a high risk of bias (–) in this classification. For studies with a judgement of NA on the three criteria regarding the quality of administering the intervention, a low quality rating was given to studies which had a low risk of bias rating on 0-1 on the four other quality criteria, a medium quality rating was given to studies which had a low risk of bias on two of the other quality criteria and a high quality rating was for the studies which had a low risk of bias on 3-4 of the other quality criteria.

Data analysis

The program comprehensive meta-analysis (CMA; version 3) was used for the analysis. Hedges' *g* was calculated as a measure of effect size. Baseline, post intervention and follow-up means, standard deviations, sample sizes and/or other available data were used to calculate effect sizes (e.g., *F*, *t* or *p* values). One study (22) reported median decreases in depression scores, instead of mean decreases.

These medians were entered into CMA, because the means could not be retrieved. Also, five studies (23-27) found no differences between intervention and control conditions on one or more outcome measures, but no data was available. The effect sizes of these outcome measures of the studies were set at zero. Cohen's guidelines were applied to interpret effect sizes: 0.2 may indicate a small effect size, 0.5 may indicate a medium effect size and 0.8 may indicate a large effect size (28). Two-tailed *p*-values were used in all analyses. In CMA, a correlation between pre- and posttest should be indicated for each study. Since this correlation was rarely reported in study papers, this was set at 0.5 (as suggested by (29)). Standardized residuals were inspected to find outliers, defined as studies with standardized residuals larger than |3| (30).

A random effects model was used for the main analysis to estimate the pooled effect size of psychosocial interventions on mental health (expressed as Hedges' $\hat{g}$). Separate analyses were conducted for each outcome (depression, anxiety, quality of life, and psychological well-being), intervention type (symptom-oriented intervention, supportive intervention, and meditation intervention) and time point (0-3 months post intervention, 3-6 months post intervention, 6-9 months post intervention, and > 9 months post intervention). The random effects model was used because we assumed heterogeneity across studies. To investigate the presence and amount of heterogeneity, *Q* and I^2 were calculated. When *Q* is significant, this means that the results of the studies are probably not consistent. The amount of heterogeneity can be identified with I^2. Values of 25% indicate low heterogeneity, 50% indicates moderate heterogeneity and 75% indicates high heterogeneity (31).

For the moderator analysis, a mixed effects model was used, in which the random effects model was used to combine studies in one subgroup and a fixed effects model was used to compare across subgroups (32). In CMA, the mixed and random effects option was set to: do not assume a common among-study variance component across subgroups (do not pool within-group estimates of tau-squared).

To examine the presence of publication bias different methods were used. First, a funnel plot was created, where the standard error is plotted as a function of effect size. Studies with small standard errors (large studies in general) are displayed at the top of the plot and studies with large standard errors (small studies in general) are displayed at the bottom of the plot. When the studies are symmetrically distributed around the pooled effect size estimate, there is no indication of publication bias. When it seems that studies are missing on the lower left side, this may be an indication of publication bias (small studies with results lower than the pooled estimate are missing). Second, Egger's test of the intercept (33) was used to statistically test for publication bias. There is an indication of publication bias when the test is significant. Last, Duval and Tweedie's trim and fill analysis (34) was used to investigate whether it was necessary to impute studies in the funnel plot due to publication bias. After the imputation of missing studies, an adjusted effect size was calculated.

Results

Through electronic databases, 905 articles were identified (see flow-chart of study inclusion and exclusion in Figure 1). After removal of duplicates (228), 677 articles were screened on title and abstract. Thereafter, 197 articles were screened on full text. After this screening, 64 studies met the inclusion criteria. In addition, three studies were found in previous meta-analyses and systematic reviews. From 20 of the 67 studies, data to calculate effect sizes was not present in the paper. Therefore, the authors were contacted to obtain these data. Of 15 studies, the authors were able to provide the data, one author could not provide the data, the authors of one study did not want to be included in the meta-analysis (because study aim did not fit with the aim of the meta-analysis), and three authors did not respond. In total, 62 studies were included in the meta-analysis.

Study characteristics

The characteristics of all included studies are presented in Table 2. In total, 10,307 participants were randomized to intervention and control conditions (range 12-936; *k* = 62). Drop-out (the percentage of participants that did not complete the first posttest) ranged from 0 to 55%, with a mean of 18% (*SD* = 11.93; *k* = 58). Seven studies (7/60) included only males and 13 included only females, the percentage of females in the included studies was 44% on average (*SD* = 34.54). The mean of the mean age of participants across studies was 42.01 years (*SD* = 5.98, range of the mean: 26.00-59.00 years, *k* = 54). The mean percentage of MSM in the studies that reported on it was 31% (*SD* = 38.27; *k* = 22). Across the studies that documented it, the mean percentage of people with AIDS was 45% (*SD* = 28.59; *k* = 15) and the mean duration of HIV was 9.81 years (*SD* = 3.59, range of the mean: 0-18 years; *k* = 28). Most participants in the studies that reported on it used ART, the mean percentage of people that used it is 76% (*SD* = 34.28; *k* = 28). For some characteristics, the number of studies that reported on it was very low. Therefore, these results should be interpreted with caution.

The majority of studies was conducted in the USA and Canada (*k* = 46). Other countries of data collection were China, Iran, Kenya, Nigeria, South Africa, Switzerland, Tanzania, Thailand, The Netherlands, Uganda, and Vietnam. One study recruited participants in the USA and Mexico and one study in South Africa, Puerto Rico, and the USA. The years of participant recruitment ranged from 1996 to 2013 (*k* = 57). The majority of studies was conducted in an outpatient setting (58/62), only two studies were conducted in an inpatient setting and two studies combined inpatients and outpatients. Ten studies (10/62) incorporated the presence of depressive symptoms as an inclusion criterion. In the majority of studies (54/62), mental health (i.e., depression, anxiety, quality of life, or psychological well-being) was a primary outcome measure. Depression was measured in 47 studies, anxiety in 22, quality of life in 19, and psychological well-being in 25 studies. Some studies (31/62) used an active

control condition, 9 studies used a waiting list condition, and 22 studies had a standard care control condition. Furthermore, more than half of the studies (32/51) used an ITT analysis, and included one or more follow-up assessments (40/62); 22 studies had one follow-up, 16 studies had two follow-ups, one study had three follow-ups, and one study had four follow-ups. The timing of follow-ups ranged from 1 to 17 months after treatment completion.

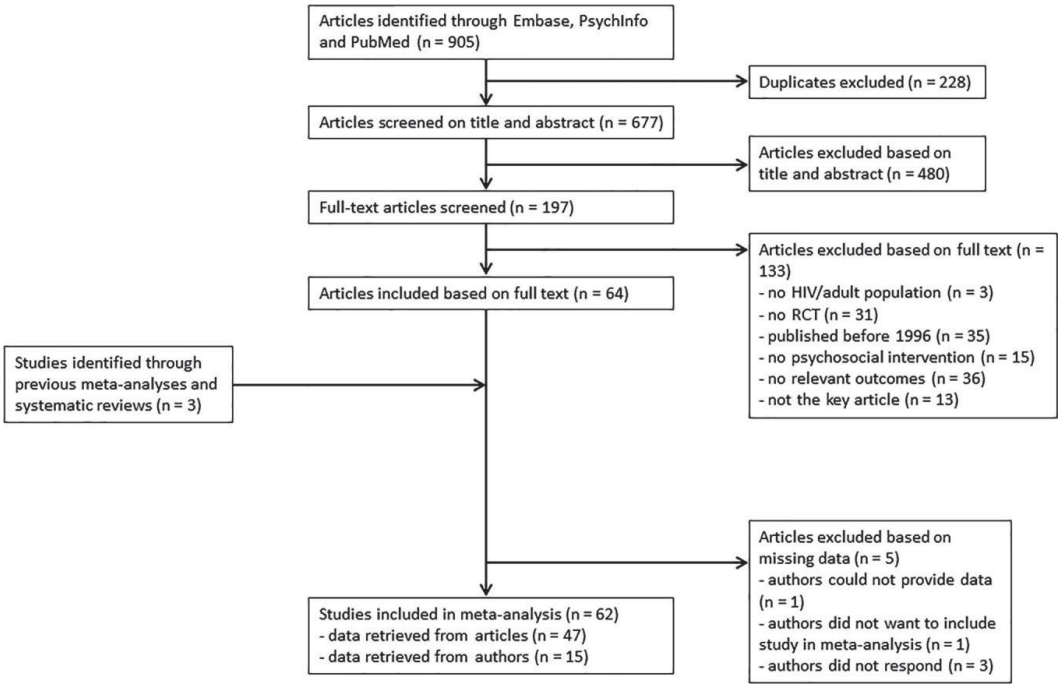


Figure 1. Flow chart of study inclusion and exclusion

Table 2. Characteristics of the included studies

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Balfour et al., 2006 (35)	Canada 2000-2004	*N* = 27, PLWH diagnosed with depression	NR	NR	N: Supportive Therapy for Adherence T: Supportive intervention P: Psychologist; D: 5 h; S: Individual	Standard care	Depression: CES-D	-	0	Yes
Berger et al., 2008 (36)	Switzerland 2003-2004	*N* = 104, PLWH on ART	43.96	14	N: Cognitive behavioral stress management T: Symptom-oriented intervention (CBT, relaxation, stress-management) P: Psychotherapist; D: 24 h; S: Group	Standard care	Depression: HADS Anxiety: HADS Quality of life: MOS-HIV	6 and 12 months	26	Yes
Boivin et al., 2013a (37)	Uganda 2008-2010	*N* = 71, mothers with HIV	33.69	100	N: Mediational intervention for sensitizing caregivers T: Supportive intervention P: Field trainer; D: 26 h; S: Individual	Active control group: information	Depression: HSCL-25 Anxiety: HSCL-25	-	17	NR
Boivin et al., 2013b (38)	Uganda 2008-2010	*N* = 109, mothers with HIV	NR	100	N: Mediational intervention for sensitizing caregivers T: Supportive intervention P: Field trainer; D: 26 h; S: Individual	Active control group: information	Depression: HSCL-25 Anxiety: HSCL-25	-	0	Yes
Bormann et al., 2006 (39)	USA 2003-2004	*N* = 93, PLWH for more than 6 months	42.9 (6.84)	81	N: Spirtual mantram repetition T: Meditation P: Nurse; D: 10 h; S: Group & individual	Active control group: information and discussion	Depression: CES-D Anxiety: STAI Quality of life: Q-LES-Q Well-being: PSS, FACIT-SpEx	3 months	20	Yes

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Brazier et al., 2006 (23)	Canada 2000	*N* = 62, PLWH	NR	NR	N: The art of living with HIV program T: Meditation P: NR; D: NR; S: Group	Standard care	Quality of life: MOS-HIV Well-being: MHI, DSI	-	24	NR
Brown et al., 2011 (40)	USA 2009	*N* = 60, females with HIV	44.7 (8.80)	100	N: Computerized stress management training T: Symptom-oriented intervention (CBT, relaxation, motivational interviewing, stress-management) P: Computer; D: 2 h; S: Individual	Waiting list	Depression: CES-D, BSI Anxiety: BSI, POMS Well-being: PSS, HIV-related life-stressor burden questionnaire	-	2	NR
Carrico et al., 2006 (41)	USA 1998-2004	*N* = 130, gay/bisexual men with HIV	41.6 (8.60)	0	N: Cognitive behavioral stress management T: Symptom-oriented intervention (CBT, relaxation, stress-management) P: Psychologist; D: 22.5 h; S: Group	Active control group: information	Depression: POMS	-	25	Yes
Carrico et al., 2009 (42)	USA 2000-2002	*N* = 936, PLWH that had unprotected sex	39.8	21	N: Healthy living project: CBT T: Symptom-oriented intervention (CBT) P: NR; D: 22.5 h; S: Individual	Waiting list	Depression: BDI Anxiety: STAI Quality of life: SF-36 Well-being: PSS	7.5 and 12.5 months	20	Yes
Chan et al., 2005 (43)	China NR	*N* = 16, males with HIV	38.15 (8.03)	0	N: Group CBT T: Symptom-oriented intervention (CBT, relaxation, stress-management)	Waiting list	Depression: CES-D Quality of life: SF-36	-	19	No

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
					P: Psychologist; D: 14 h; S: Group					
Chang et al., 2007 (44)	USA 2003-2004	*N* = 119, PLWH that suffer from HIV-related symptoms	45.5 (7.5)	15	N: Relaxation during acupuncture treatment T: Meditation P: Tape; D: 10.5 h; S: Individual	Standard care	Quality of life: MOS-HIV, FAHI	-	33	NR
Chhatre et al., 2013 (45)	USA 2011	*N* = 22, PLWH on ART	49.9 (5.7)	18	N: Transcendental meditation T: Meditation P: Certified instructor; D: 28 h; S: Group	Active control group: information	Depression: CES-D Quality of life: SF-36, FAHI Well-being: PSS	-	9	No
Côté & Pepler, 2002 (46)	Canada 1996-1998	*N* = 90, males with HIV	40	0	N1: Cognitive coping skills intervention T1: Symptom-oriented intervention (CBT) N2: Expression of emotions intervention T2: Supportive intervention P: Nurse; D: 1.25 h; S: Individual	Waiting list	Well-being: PANAS	-	NR	No
Duncan et al., 2012 (47)	USA 2006-2008	*N* = 76, PLWH with distress	48.06 (7.93)	16	N: Mindfulness based stress reduction T: Meditation P: Mindfulness teacher; D: 30 h; S: Group & individual	Standard care	Depression: BDI Well-being: PSS, PANAS	3 months	14	Yes
Eller et al., 2013 (48)	South Africa, Puerto Rico, USA	*N* = 222, PLWH with depression	43.15 (9.59)	42	N: HIV/AIDS symptom management manual T: Supportive intervention	Active control group: information	Depression: depressive	2 months	18	NR

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
	2005-2007				P: Self-help; D: NR; S: Individual		symptom intensity and frequency			
Erlen et al., 2001 (49)	USA 1998	*N* = 20, people with AIDS	42.05	20	N: Life review T: Symptom-oriented intervention P: Nurse; D: 6 h; S: Individual	Standard care	Depression: CES-D Quality of life: Ferrans and Powers Quality of Life Index	3 and 12 months	NR	NR
Fife et al., 2008 (50)	USA NR	*N* = 80, PLWH	NR	30	N: A psychosocial education model T: Symptom-oriented intervention (stress-management) P: NR; D: 8 h; S: Other (with partner)	Active control group: telephone support	Depression: PANAS Anxiety: PANAS Well-being: PANAS	3 months	33	No
Gayner et al., 2012 (51)	Canada 2004-2007	*N* = 117, males with HIV	43.79 (7.08)	0	N: Mindfulness based stress reduction T: Meditation P: Social worker & psychologist; D: 30 h; S: Group	Standard care	Depression: HADS Anxiety: HADS Well-being: PANAS	8 months	12	Yes
Heckman & Carlson, 2007 (52)	USA 1999-2002	*N* = 299, PLWH	43.10	30	N1: Telephone coping improvement group T1: Symptom-oriented intervention (CBT) N2: Telephone information support group T2: Supportive intervention P: Practitioner; D: 12 h; S: Group	Standard care	Depression: BDI Quality of life: FAHI Well-being: SCL-90, HIV-related life stressor burden scale	4 and 8 months	14	Yes

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Heckman et al., 2011 (53)	USA 2004-2007	*N* = 295, PLWH with depressive symptoms, age > 49 years	55.30 (4.80)	33	N1: Coping improvement group T1: Symptom-oriented intervention (stress-management) N2: Interpersonal support group T2: Supportive intervention P: Social worker & psychologist; D: 18 h; S: Group	Active control group: telephone check-ups and individual therapy when needed	Depression: GDS	4 and 8 months	17	Yes
Heckman et al., 2013 (54)	USA 2008-2010	*N* = 361, PLWH with depressive symptoms, age > 49 years	59.00 (5.10)	39	N1: Telephone coping effectiveness training T1: Symptom-oriented intervention (CBT, stress-management) N2: Telephone supportive-expressive group T2: Supportive intervention P: Therapist; D: 18 h; S: Group	Standard care	Depression: GDS	4 and 8 months	8	Yes
Hersch et al., 2013 (55)	USA 2010-2011	*N* = 168, PLWH on ART	46.34 (9.84)	24	N: Life steps intervention T: Symptom-oriented intervention (CBT, relaxation, stress-management) P: Computer; D: NR; S: Individual	Waiting list	Well-being: HIV/AIDS stress scale, PANAS	3 and 6 months	9	Yes
Ironson et al., 2013 (56)	USA 2004-2009	*N* = 244, PLWH in mid-range of illness	42.80 (8.80)	39	N: Augmented trauma writing T: Symptom-oriented intervention P: Self-help; D: 2 h; S: Individual	Active control group: daily event writing	Depression: HAM-D	6 and 12 months	12	Yes

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Jensen et al., 2013 (57)	USA 2000-2004	*N* = 72, females with HIV	31.27 (8.41)	100	N: Cognitive behavioral stress management T: Symptom-oriented intervention (CBT, relaxation, stress-management) P: Psychologist; D: 22.5 h; S: Group	Active control group: psycho-education	Depression: BDI Well-being: FACIT-SpEx	6 months	NR	Yes
Kaaya et al., 2013 (58)	Tanzania 2001-2004	*N* = 331, pregnant women with HIV	26.00	100	N: Counselling T: Supportive intervention P: Social worker/nurse; D: NR; S: Group	Standard care	Depression: HSCL-25	-	43	No
Kalichman et al., 2005 (59)	USA 1999-2000	*N* = 125, PLWH that had sex with noncon-cordant sex partners	NR	30	N: Healthy relationships intervention T: Symptom-oriented intervention (CBT, stress-management) P: NR; D: 10 h; S: Group	Active control group: information and support	Depression: BDI Anxiety: BSI Well-being: HIV-related stress	3 and 6 months	35	No
Klein et al., 2013 (60)	USA 2011	*N* = 175, African American females with HIV	40.70 (8.50)	100	N: Women involved in life learning from other women T: Symptom-oriented intervention (relaxation, stress-management) P: Computer; D: 2 h; S: Individual	Active control group: information and discussion	Well-being: Willow Stress Scale	-	4	Yes
Kraaij et al., 2010 (61)	The Nether-lands 2008	*N* = 73, PLWH	49.48 (8.15)	11	N1: CBT self-help T1: Symptom-oriented intervention (CBT, relaxation) N2: Computerized structured writing	Waiting list	Depression: HADS	-	25	No

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
					T2: Symptom-oriented intervention P: Self-help; D1: 16 h; D2: 2 h; S: Individual					
Lechner et al., 2003 (62)	USA NR	*N* = 330, women with AIDS	39.60 (7.14)	100	N: Cognitive behavioral stress management + expressive/supportive therapy T: Symptom-oriented intervention (CBT, relaxation, stress-management) P: Psychologist; D: 20 h; S: Individual	Active control group: psycho-education	Quality of life: MOS-HIV	-	18	Yes
Li et al., 2010 (63)	Thailand 2007	*N* = 507, PLWH	37.40 (6.60)	67	N: Behavioral intervention T: Symptom-oriented intervention (stress-management) P: Nurse/counsellor; D: 18 h; S: Group	Standard care	Quality of life: MOS-HIV	6 months	2	NR
Lovejoy, 2012 (64)	USA 2009-2010	*N* = 100, PLWH that had unprotected sex, age > 44 years	53.80 (4.90)	46	N1: Motivational Interviewing (1 session) T1: Symptom-oriented intervention (motivational interviewing) N2: Motivational Interviewing (4 sessions) T2: Symptom-oriented intervention (motivational interviewing) P: Psychologist; D1: 0.81 h; D2: 2.72 h; S: Group	Active control group: encouraged to obtain information and support	Depression: DASS Anxiety: DASS Well-being: DASS	3 months	8	Yes

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
McCain et al., 2008 (65)	USA 2000-2004	*N* = 387, PLWH	42.20	40	N1: Cognitive behavioral relaxation T1: Symptom-oriented intervention (CBT, relaxation, stress-management) N2: Tai Chi Training T2: Meditation N3: Spirtual growth T3: Meditation P: Investigator; D: 15 h; S: Group	Waiting list	Quality of life: FAHI	6 months	NR	Yes
Miles et al., 2003 (66)	USA 1997-2000	*N* = 109, African America females with HIV	35.50 (8.49)	100	N: Maternal self-care symptom management T: Supportive intervention P: Nurse; D: NR; S: Individual	Standard care	Depression: CES-D, POMS Anxiety: POMS, HIV worry scale Quality of life: MOS-HIV	5 months	32	Yes
Miller et al., 2005 (67)	USA 1999-2000	*N* = 12, PLWH	39.42 (9.75)	25	N: Supportive-affective group experience T: Supportive intervention P: Mediators; D: 18 h; S: Group	Active control group: sent self-help materials	Depression: BDI Anxiety: STAI state Well-being: SWS; DDS	-	25	No
Mitrani et al., 2012 (68)	USA 2003-2007	*N* = 126, females with HIV and substance use diagnosis	42.60 (7.50)	100	N: Structural Ecosystems Therapy T: Symptom-oriented intervention (CBT) P: Social worker; D: 5.2 h; S: Other (family)	Active control group: information	Depression: BSI, SIGH-AD Anxiety: BSI, SIGH-AD Well-being: PSS	4 and 8 months	8	Yes

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Murphy et al., 2002 (69)	USA 1999-2000	*N* = 52, PLWH with adherence problems	39.00 (6.88)	12	N: CBT for adherence T: Symptom-oriented intervention (CBT) P: NR; D: NR; S: Group & individual	Standard care	Depression: CES-D, RAND mental health inventory Anxiety: health-related anxiety, RAND mental health inventory	3 months	37	No
Murphy et al., 2011 (70)	USA 2007-2009	*N* = 80, mothers with HIV	37.40 (6.80)	100	N: Teaching, Raising and Communicating with Kids program T: Supportive intervention P: Social worker; D: 3.25 h; S: Group	Standard care	Depression: RAND mental health inventory Anxiety: RAND mental health inventory Quality of life: SF-36	5 and 8 months	14	Yes
O'Leary et al., 2005 (71)	USA 2000-2001	*N* = 811, males with HIV that had sex with male partners whose HIV status was seronegative or unknown	41.00 (7.90)	0	N: Peer-led behavioral intervention T: Supportive intervention P: Peer; D: 18 h; S: Group	Active control group: information and discussion	Depression: BSI Anxiety: BSI	6 months	15	No

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Olley, 2006 (72)	Nigeria NR	*N* = 67, PLWH	27.40 (8.10)	56	N: Psycho-education T: Supportive intervention P: NR; D: 4 h; S: Individual	Active control group: discussion and support	Depression: BDI Anxiety: CCEI	1 month	7	NR
Pacella et al., 2012 (73)	USA 2005-2008	*N* = 66, PLWH with PTSD and on ART	46.37 (6.30)	37	N: Prolonged exposure T: Symptom-oriented intervention (CBT) P: Psychologist; D: 17.5 h; S: Individual	Active control group: telephone check-ups	Depression: CES-D Well-being: PTCI	3 months	29	Yes
Peltzer et al., 2012 (74)	South Africa 2010	*N* = 152, PLWH with adherence problems	36.90 (6.50)	65	N: Medication adherence intervention T: Supportive intervention P: Counsellor; D: 3 h; S: Group	Standard care	Depression: BDI	3 months	3	NR
Petersen et al., 2014 (75)	South Africa 2012-2013	*N* = 76, PLWH diagnosed with depression	37.59 (10.36)	74	N: Group-based interpersonal psychotherapy T: Symptom-oriented intervention (CBT) P: HIV specialist; D: 8 h; S: Group	Standard care	Depression: PHQ-9 Anxiety: HSCL-25	-	55	No
Ransom et al., 2008 (76)	USA 2006-2007	*N* = 79, PLWH with depression	44.40 (8.60)	16	N: Telephone interpersonal psychotherapy T: Symptom-oriented intervention P: Psychologist; D: 5 h; S: Individual	Standard care	Depression: BDI Well-being: OQ	-	16	Yes
Rao et al., 2009 (24)	USA 2006-2007	*N* = 79, PLWH	42.00 (10.00)	25	N: Art therapy T: Symptom-oriented intervention P: Art therapist; D: 1 hr; S: Individual	Active control group: videotape	Anxiety: STAI state	-	4	No

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Rotherham-Borus et al., 2012 (25)	USA 2005-2006	*N* = 339, mothers with HIV	40.20 (8.20)	100	N: Family CBT T: Symptom-oriented intervention (CBT) P: NR; D: 28 h; S: Other (group and family)	Waiting list	Well-being: BSI	6 and 12 months	8	Yes
Safren et al., 2009 (77)	USA 2002-2004	*N* = 45, PLWH with depression and on ART	NR	16	N: CBT for adherence and depression T: Symptom-oriented intervention (CBT, relaxation, motivational interviewing) P: Psychologist; D: 8.68 h; S: Individual	Active control group: single session about adherence	Depression: BDI, HAM-D Well-being: CGI	3 and 9 months	7	Yes
Safren et al., 2012 (78)	USA 2005-2008	*N* = 89, PLWH with depression and substance use disorder	46.85 (7.15)	39	N: CBT for adherence and depression T: Symptom-oriented intervention (CBT, relaxation, motivational interviewing) P: Psychologist; D: 6.64 h; S: Individual	Active control group: single session about adherence	Depression: BDI, MADRS Well-being: CGI	3 and 9 months	9	Yes
Sarna et al., 2008 (22)	Kenya 2003-2004	*N* = 234, PLWH that started with ART	37.15 (7.90)	64	N: Adherence intervention T: Supportive intervention P: Nurse; D: NR; S: Individual	Active control group: counselling	Depression: BDI	5.5 and 11 months	15	NR
SeyedAlinaghi et al., 2012 (79)	Iran 2008-2010	*N* = 245, PLWH	35.10 (6.50)	31	N: Mindfulness based stress reduction T: Meditation P: Psychologist; D: 25.75 h; S: Group	Active control group: information and support	Depression: SCL-90 Anxiety: SCL-90	3, 6, 9 and 12 months	29	No

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Shuter et al., 2014 (80)	USA 2012-2013	*N* = 138, PLWH interested in quitting smoking	45.62 (9.91)	43	N: Positively smoke free on the web T: Symptom-oriented intervention P: Computer; D: 2 h; S: Individual	Active control group: advice and brochure	Depression: CES-D Anxiety: GAD-7 Well-being: PSS	2.5 months	9	Yes
Sikkema et al., 2004 (81-84)	USA 1997-1999	*N* = 267, PLWH that lost a loved one to AIDS	40.10 (7.02)	35	N: CBT T: Symptom-oriented intervention (CBT, stress-management) P: Therapist; D: 18 h; S: Group	Standard care	Depression: SCL-90, HAM-D Anxiety: SCL-90, HAM-A Quality of life: FAHI	4, 8 and 12 months	12	No
Simoni et al., 2007 (85)	USA 2000-2002	*N* = 136, PLWH on ART	42.60 (8.90)	45	N: Peer support T: Supportive intervention P: Peer; D: 12 h; S: Group & individual	Standard care	Depression: CES-D	3 months	23	No
Simoni et al., 2013 (86)	USA/Mexico 2009-2011	*N* = 40, PLWH with depressive symptoms and adherence problems	46.00 (10.60)	28	N: CBT for adherence and depression and electronic pillbox T: Symptom-oriented intervention (CBT, relaxation, motivational interviewing) P: Psychologist; D: 9 h; S: Individual	Standard care	Depression: BDI, MADRS	3 months	15	Yes
Stein et al., 2007 (26)	USA 2001-2004	*N* = 177, PLWH with depressive symptoms	40.30 (7.40)	44	N: Telephone family intervention T: Supportive intervention P: Social worker, psychologist, nurse; D: 2.6 h; S: Other (with partner)	Waiting list	Depression: BDI	-	10	No

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
Szapocznik et al., 2004 (87)	USA 1996-1999	*N* = 209, African American mothers	36.00 (8.00)	100	N1: Structural Ecosystems Therapy T1: Symptom-oriented intervention (CBT) N2: Attention condition T2: Supportive intervention P: Counsellor, social worker, therapist; D1: 12.45 h; D2: 5.74 h; S1: Other (family); S2: Individual	Standard care	Depression: BSI Anxiety: BSI	9 months	8	Yes
Van Tam et al., 2012 (88)	Vietnam 2008-2009	*N* = 275, PLWH that started with ART	NR	32	N: Peer support for adherence T: Supportive intervention P: Peer; D: NR; S: Individual	Active control group: adherence counselling	Quality of life: WHOQOL-HIVBREF	-	17	No
Vidrine et al., 2006 (89)	USA 2004	*N* = 95, PLWH interested in quitting smoking	42.80 (8.10)	22	N: Telephone counselling for smoking cessation T: Symptom-oriented intervention (CBT) P: Counsellor; D: NR; S: Individual	Active control group: advice and self-help	Depression: CES-D Anxiety: STAI state	-	16	NR
Webel, 2010 (90)	USA 2008	*N* = 89, females with HIV	47.00 (8.16)	100	N: HIV symptom management T: Symptom-oriented intervention (CBT, relaxation) P: Peer; D: 14 h; S: Group	Active control group: self-help manual	Quality of life: HIV/AIDS targeted quality of life instrument	1.75 months	48	Yes
Weber et al., 2004 (27)	Switzerland NR	*N* = 60, PLWH on ART	NR	17	N: CBT	Standard care	Well-being: SCL-90	-	12	NR

Authors and year of publication	Country and recruitment period[a]	*N* after randomization and sample description[b]	Mean age (*SD*)	Female (%)	Intervention: name (N)[c], type (T)[d] (techniques)[e], provider (P)[f], duration (D)[g], setting (S)[h]	Control group	Outcomes and measures[i]	Follow-up	Drop-out (%)[j]	ITT[k]
					T: Symptom-oriented intervention (CBT) P: Psychotherapist; D: NR; S: Individual					
Williams et al., 2005 (91)	USA 2001-2003	*N* = 58, people with advanced AIDS	45.09 (2.22)	21	N1: Meditation T1: Meditation N2: Meditation and massage T2: Meditation P1: Meditation teacher; P2: Meditation teacher and massage therapist; D1: 8.5 h; D2: 18.5 h; S: Group & individual	C1: active control group: provision of mental health services; C2: active control group: massage	Quality of life: MVQOLI	17 months	29	Yes
Williams et al., 2008 (92)	USA 2003-2006	*N* = 164, males with HIV and experience of childhood sexual abuse	43.50 (8.00)	0	N: Sexual Health Intervention for Men T: Symptom-oriented intervention (CBT) P: Trained male facilitator; D: 12 h; S: Group	Active control group: information and discussion	Depression: CES-D	3 and 6 months	16	No
Williams et al., 2013 (93)	USA 2007-2011	*N* = 117, African American males with HIV that had unprotected sex	46.60 (8.30)	0	N: Enhanced sexual health intervention for men T: Symptom-oriented intervention (CBT, stress-management) P: Trained male facilitator; D: 12 h; S: Group	Active control group: information	Depression: BDI	6 months	27	No

[a] *NR* not reported in paper, [b] N after randomization and sample description. With *ART* = antiretroviral therapy; *PLWH* = people living with HIV; *PTSD* = posttraumatic stress disorder, [c] *N* name of the intervention. With *CBT* = cognitive behavioral therapy, [d] *T* type of intervention, [e] Intervention techniques in symptom-oriented interventions. With *CBT* = cognitive behavioral techniques, [f] *P* provider intervention, [g] *D* duration intervention, [h] *S* setting intervention.

[i] Outcomes and measures. With *BDI* = Beck Depression Inventory, *BSI* = Brief Symptom Inventory, *CCEI* = Crown Crisp Experiential Index, *CES-D* = Center for Epidemiologic Studies Depression scale, *CGI* = Clinical Global Impression, *DASS* = Depression Anxiety Stress Scales, *DDS* = Death Distress Scale, *DSI*: = Daily Stress Inventory, *FAHI* = Functional Assessment of HIV infection, *FACIT-SpEx* = Functional Assessment of Chronic Illness Therapy Spiritual Well-being-Expanded, *GAD-7* = Generalized Anxiety Disorder 7, *GDS* = Geriatric Depression Scale, *HADS* = Hospital Anxiety and Depression Scale, *HAM-A* = Hamilton Anxiety Rating Scale, *HAM-D* = Hamilton Depression Scale, *HSCL-25* = Hopkins Symptom Checklist, *MADRS* = Montgomery-Asberg Depression Rating Scale, *MHI* = Mental Health Index, *MOS-HIV* = Medical Outcomes Study HIV Health Survey, *MVQOLI* = Missoula-VITAS Quality of Life Index, *OQ* = Outcomes Questionnaire, *PANAS* = Positive and Negative Affect Schedule, *PHQ-9* = Patient Health Questionnaire 9, *POMS* = Profile of Mood States, *PSS* = Perceived Stress Scale, *PTCI* = Posttraumatic Cognitions Inventory, *SCL-90* = Symptom Checklist 90, *SF-36* = Short Form Health Survey, *SIGH-AD* = Structured Interview Guide for the Hamilton Anxiety and Depression Subscales, *STAI* = Spielberger State-Trait Anxiety Inventory, *SWS* = Spiritual Well-being Scale, *Q-LES-Q* = Quality of Life Enjoyment and Satisfaction Questionnaire.

[j] Drop-out refers to the percentage of participants that did not complete the first posttest, [k] *ITT* = Intent-To-Treat analysis.

Intervention characteristics

The description of intervention characteristics was based on all interventions, so eight studies (46, 52-54, 61, 64, 87, 91) were represented twice in this analysis and one study (65) was represented three times, because multiple interventions were investigated in these studies. The letter m will be used to indicate the number of interventions. Regarding intervention types (see Table 1), a majority of the interventions were symptom-oriented (41/72), the rest were supportive (20/72), or meditation interventions (11/72). Regarding techniques used in symptom-oriented interventions (*m* = 41), CBT techniques were used in 29 interventions, relaxation techniques in 14, stress-management techniques in 16, and finally motivational interviewing techniques in 6 interventions. Almost two-thirds of the interventions (47/72) were focused on one of our outcome measures (depression, anxiety, quality of life, or psychological well-being). Studies that investigated interventions that were not focused on one of our outcome measures, were often aimed at medication adherence or sexual risk behavior, and sometimes at coping, disclosure, general health, family functioning, posttraumatic stress disorder symptoms, or smoking. A majority (44/72) of the interventions were theory-driven and 28 interventions were not theory-driven. Concerning the duration of the interventions, the total length ranged from 1 to 30 hours (*m* = 62), with a mean of 12.63 (*SD* = 8.46). The duration of the intervention in weeks ranged from 1 to 54 (*M* = 12.20, *SD* = 13.27, *m* = 66) and the number of sessions ranged from 1 to 48 (*M* = 9.92, *SD* = 8.62, *m* = 67). The average length of one session was 1.37 hour (*SD* = 0.66, range 15 minutes to 3 hours, *m* = 63). Providers of the interventions were psychologists/psychotherapists (18/65), counsellors (e.g., nurses, 29/65), peers (4/65), none (e.g., computer interventions, 9/65), and other (e.g., investigators, 5/65). The format of the intervention was either individual (31/72), group (30/72), a combination of individual and group (6/72), or other (e.g., family interventions, 5/72).

Quality of the included studies

The quality ratings of the studies are presented in Table 3. The first quality criterion, regarding the sequence generation for allocation to conditions, was reported in more than half of the studies (32/62), in the other studies it was unclear. The criterion about the concealment of allocation to conditions was often not reported, only 13 studies mentioned it, in the other studies it was unclear. Incomplete outcome data (the third criterion) was adequately addressed in half of the studies (31/62, e.g., with an ITT analysis), in 20 studies it was not adequately addressed and in 11 studies this was not clear. For most studies (58/62) there was no study protocol available, so the criterion of selective outcome reporting was unclear, only four studies had a rating of low risk of bias on this criterion.

Eight studies investigated an intervention without a provider (e.g., computer or self-help interventions). These studies were not coded on the quality of the administered intervention. In 36 of the 54 studies a treatment manual was available and followed and in 18 studies this was not described.

Trained providers were used in 36 of the 54 studies, in 17 studies this was unclear and one study explained that they did not make use of trained providers. Finally, in 31 of the 54 studies treatment integrity was checked and in 23 studies this was not described. A summary of the ratings on all quality criteria is presented in Figure 2. Regarding the overall quality classification, most studies were classified as low (24/62) or medium (28/62) quality. Only 10 studies were classified as high quality. None of the studies met all quality criteria, but five studies met all except one criterion.

Intervention effectiveness

The overall effect of psychosocial interventions on mental health outcomes was Hedges' $\hat{g}$ = 0.19, 95% CI [0.13, 0.25], $p < 0.001$ (see Figure 3). Thus, psychosocial interventions may have a positive effect on mental health, compared to a control condition. However, the effect size was small. Standardized residuals were inspected to identify outliers (studies with standardized residuals |3|), but none were found.

Table 4 shows the overall effect of psychosocial interventions on mental health and the effect sizes for each outcome, intervention type and time point separately. It shows that the pooled effect sizes for depression and psychological well-being were larger ($\hat{g}$ = 0.21 and $\hat{g}$ = 0.20) than those for anxiety and quality of life ($\hat{g}$ = 0.09 and $\hat{g}$ = 0.13). Furthermore, heterogeneity was moderate and significant for the outcomes depression and psychological well-being and smaller and not significant for anxiety and quality of life. Therefore, we decided to conduct the moderator analysis only on the outcomes depression and psychological well-being. Results are presented for the moderator analyses on depression and differences with the moderator analyses of psychological well-being will be discussed.

The results regarding intervention type (categories: symptom-oriented intervention, supportive intervention, and meditation intervention; Table 4) show that each intervention type had a pooled effect size of approximately $\hat{g}$ = 0.20. The analysis on time points shows that the first and third time point had pooled effect sizes of $\hat{g}$ = 0.18, while the second ($\hat{g}$ = 0.13) and last ($\hat{g}$ = 0.08) time point had smaller pooled effect sizes. The pooled effect size of the last time point was not significant and it should be noted that it was based on only nine studies. In sum, the overall effect of psychosocial interventions on mental health outcomes was small ($\hat{g}$ = 0.19).

Table 3. Quality of the included studies

Study	Sequence generation	Allocation concealment	Incomplete outcome data	Selective outcome reporting	Availability of treatment manual	Use of training for therapy providers	Treatment integrity was checked	Quality classification[a]
Balfour et al., 2006	+	+	+	?	+	+	?	High
Berger et al., 2008	+	+	+	+	+	+	?	High
Boivin et al., 2013a	?	?	?	?	?	+	+	Low
Boivin et al., 2013b	?	?	+	?	?	+	+	Medium
Bormann et al., 2006	+	?	+	?	+	?	+	Medium
Brazier et al., 2006	+	?	-	?	?	?	?	Low
Brown et al., 2011	+	?	+	?	**NA**	**NA**	**NA**	Medium
Carrico et al., 2006	+	?	+	?	+	?	+	Medium
Carrico et al., 2009	+	?	+	?	+	?	+	Medium
Chan et al., 2005	?	?	-	?	+	?	?	Low
Chang et al., 2007	+	+	+	?	**NA**	**NA**	**NA**	High
Chhatre et al., 2013	?	?	-	?	?	+	?	Low
Côté & Pepler, 2002	?	?	-	?	+	?	+	Low
Duncan et al., 2012	+	?	?	?	?	+	?	Low
Eller et al., 2013	?	?	?	?	**NA**	**NA**	**NA**	Low
Erlen et al., 2001	?	?	?	?	?	+	+	Low
Fife et al., 2008	?	?	-	?	+	?	+	Low

Study	Sequence generation	Allocation concealment	Incomplete outcome data	Selective outcome reporting	Availability of treatment manual	Use of training for therapy providers	Treatment integrity was checked	Quality classification[a]
Gayner et al., 2012	+	+	+	?	+	?	?	Medium
Heckman & Carlson, 2007	?	?	+	?	+	?	+	Medium
Heckman et al., 2011	+	?	+	?	+	?	+	Medium
Heckman et al., 2013	+	?	+	?	+	-	+	Medium
Hersch et al., 2013	?	?	+	?	**NA**	**NA**	**NA**	Low
Ironson et al., 2013	?	?	+	?	**NA**	**NA**	**NA**	Low
Jensen et al., 2013	?	?	+	?	+	+	+	Medium
Kaaya et al., 2013	+	+	-	?	?	+	?	Medium
Kalichman et al., 2005	+	+	-	?	+	?	+	Medium
Klein et al., 2013	+	+	?	?	**NA**	**NA**	**NA**	Medium
Kraaij et al., 2010	+	?	-	?	**NA**	**NA**	**NA**	Low
Lechner et al., 2003	?	?	-	?	+	+	+	Medium
Li et al., 2010	?	?	?	?	+	+	?	Low
Lovejoy, 2012	+	+	+	?	+	+	+	High
McCain et al., 2008	+	+	+	?	+	+	?	High
Miles et al., 2003	+	?	+	?	?	+	+	Medium
Miller et al., 2005	?	?	-	?	?	+	?	Low

Study	Sequence generation	Allocation concealment	Incomplete outcome data	Selective outcome reporting	Availability of treatment manual	Use of training for therapy providers	Treatment integrity was checked	Quality classification[a]
Mitrani et al., 2012	?	?	+	?	+	+	+	Medium
Murphy et al., 2002	+	?	-	?	+	?	?	Low
Murphy et al., 2011	?	?	+	?	+	?	?	Low
O'Leary et al., 2005	+	?	-	?	+	+	?	Medium
Olley, 2006	?	?	?	?	+	?	?	Low
Pacella et al., 2012	?	?	+	?	+	+	+	Medium
Peltzer et al., 2012	+	?	?	?	+	?	?	Low
Petersen et al., 2014	+	?	-	?	+	+	+	Medium
Ransom et al., 2008	?	?	+	?	+	+	+	Medium
Rao et al., 2009	?	?	+	?	?	?	?	Low
Rotherham-Borus et al., 2012	?	?	+	+	+	+	+	High
Safren et al., 2009	?	?	+	?	+	?	+	Medium
Safren et al., 2012	?	?	+	?	+	+	+	Medium
Sarna et al., 2008	+	+	?	?	?	+	+	Medium
SeyedAlinaghi et al., 2012	+	?	-	+	+	+	?	Medium
Shuter et al., 2014	+	?	+	+	**NA**	**NA**	**NA**	High
Sikkema et al., 2004	?	?	-	?	+	+	+	Medium

Study	Sequence generation	Allocation concealment	Incomplete outcome data	Selective outcome reporting	Availability of treatment manual	Use of training for therapy providers	Treatment integrity was checked	Quality classification[a]
Simoni et al., 2007	+	+	-	?	?	+	+	Medium
Simoni et al., 2013	+	+	+	?	+	+	+	High
Stein et al., 2007	?	?	-	?	+	+	+	Medium
Szapocznik et al., 2004	+	?	+	?	+	+	+	High
Van Tam et al., 2012	?	?	-	?	?	+	+	Low
Vidrine et al., 2006	+	?	?	?	?	+	?	Low
Webel, 2010	?	?	+	?	?	+	?	Low
Weber et al., 2004	+	+	?	?	+	+	+	High
Williams et al., 2005	+	?	+	?	?	+	?	Medium
Williams et al., 2008	?	?	-	?	?	+	?	Low
Williams et al., 2013	?	?	-	?	?	+	?	Low

+ = low risk of bias; - = high risk of bias; ? = unclear risk of bias; NA = not applicable (e.g., when the intervention is a self-help program).

[a] = quality classification, this was calculated by adding up the low risk of bias ratings (see “Method” section).

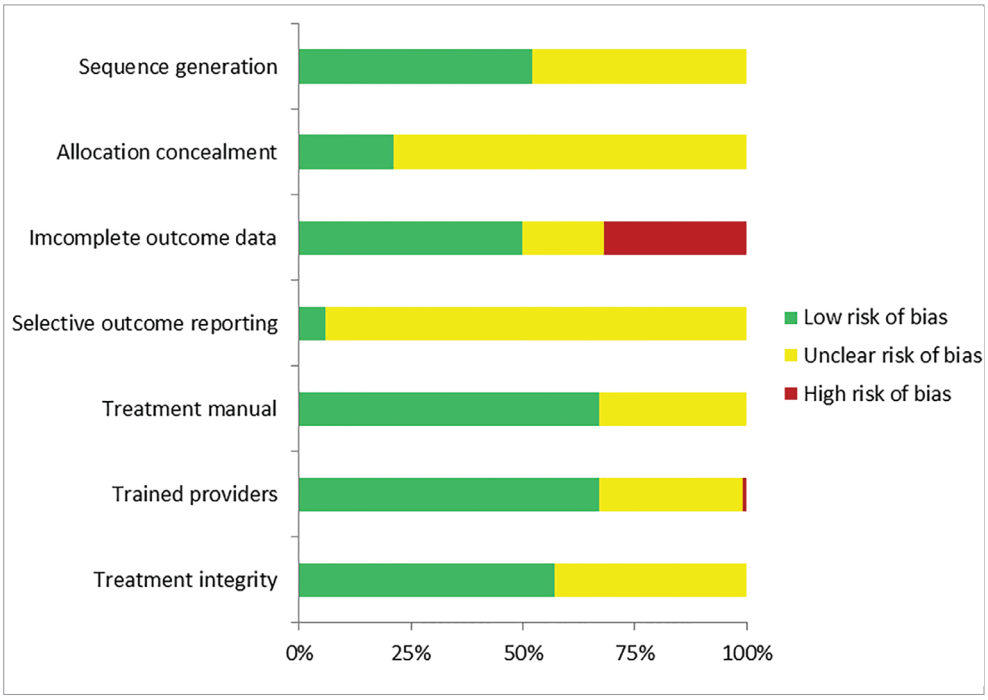


Figure 2. Risk of bias graph

Intervention effectiveness: analysis on last time point

The analysis on outcome type and intervention type described above was also conducted with the last available time point for each study, instead of the first time point. The analysis on the last time point was conducted, as we were also interested in the results on the long term, next to the results on the short term. Differences between those analyses were examined and will be depicted here. The overall effect of psychosocial interventions on mental health was comparable, $\hat{g}$ = 0.18, 95% CI [0.12, 0.25], p < 0.001; Q = 110.25, p < 0.001, I^2 = 45%. The pooled effect size on the outcome of anxiety was somewhat larger in this analysis, $\hat{g}$ = 0.14, 95% CI [0.02, 0.25], p < 0.05 and heterogeneity was significant, Q = 39.44, p < 0.01, I^2 = 47%. The pooled effect size on the outcome psychological well-being was comparable, but heterogeneity was smaller and not significant in this analysis, Q = 34.06, p = 0.08, I^2 = 30%. Furthermore, the effects of supportive interventions ($\hat{g}$ = 0.18, 95% CI [0.04, 0.33], p < 0.05) and meditation ($\hat{g}$ = 0.16, 95% CI [0.02, 0.31], p < 0.05) were somewhat smaller in this analysis and the effect of symptom-oriented interventions was larger ($\hat{g}$ = 0.21, 95% CI [0.14, 0.28], p < 0.001). Summarizing, the analysis on the first time point and the analysis on the last time point were comparable and only small differences were found.

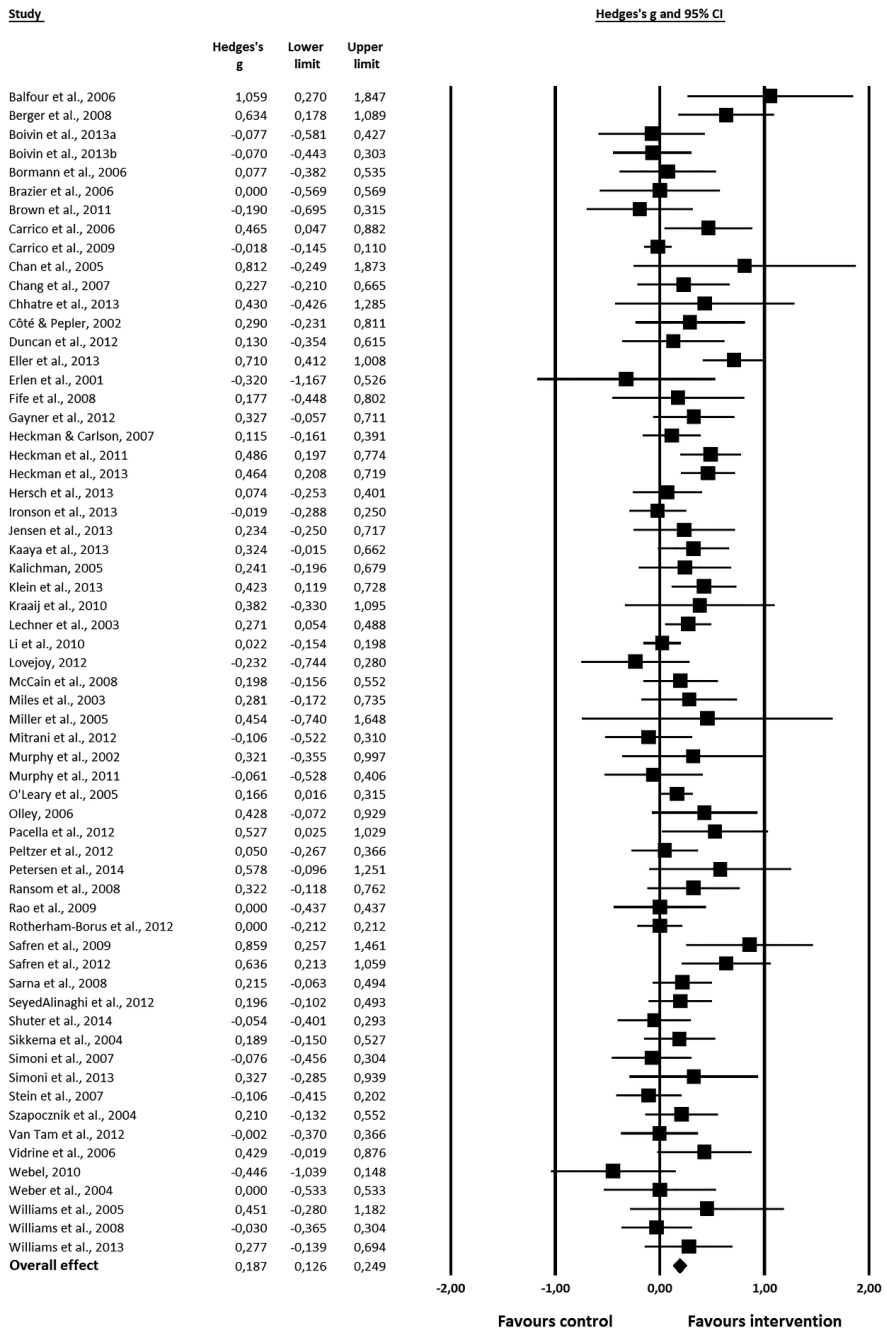


Figure 3. Forest plot showing the effect of psychosocial interventions on mental health outcomes

Table 4. Overall analysis and analysis separately for each outcome, intervention type and time point

Analysis	Subgroup	*k*[a]	Hedges' $\hat{g}$	95% CI	*Q*[b]	I^2 (%)[c]
Overall effect		62	0.19[d]	0.13, 0.25	99.35[d]	39
Outcome	Depression	47	0.21[d]	0.13, 0.29	87.32[d]	47
	Anxiety	22	0.09	-0.01, 0.19	31.29	33
	Quality of life	19	0.13[d]	0.04, 0.21	21.07	15
	Psychological well-being	25	0.20[d]	0.09, 0.31	44.63[d]	46
Intervention type	Symptom-oriented intervention	39	0.19[d]	0.11, 0.28	69.71[d]	46
	Supportive intervention	20	0.21[d]	0.09, 0.33	43.58[d]	56
	Meditation intervention	9	0.20[d]	0.06, 0.35	2.00	0
Time point	Posttest 0-3 months	59	0.18[d]	0.12, 0.25	85.79[e]	32
	Posttest 3-6 months	19	0.13[d]	0.05, 0.22	28.31	36
	Posttest 6-9 months	12	0.18[d]	0.05, 0.31	22.97[e]	52
	Posttest > 9 months	9	0.08	-0.05, 0.21	13.79	42

[a] k = number of studies, [b] Q = heterogeneity test, [c] I^2 = % of heterogeneity, [d] $p < 0.01$, [e] $p < 0.05$.

Publication bias

When the funnel plot was inspected (see Figure 4), it was clear that studies were missing on the left side of the plot. This may be an indication of publication bias. Egger's test of the intercept was significant, intercept 0.82, 95% CI [0.09, 1.54], $t(60) = 2.24$, $p < 0.05$. This also indicates that there may be publication bias. Lastly, Duval and Tweedie's trim and fill analysis demonstrated that 14 studies were missing on the left side of the plot (see black dots in Figure 4). After imputation of these 14 studies, the adjusted effect size was $\hat{g} = 0.11$, 95% CI [0.04, 0.17]. This effect size is substantially smaller than the unadjusted effect size of $\hat{g} = 0.19$. In sum, there seems to be evidence for publication bias in this meta-analysis, as studies with smaller effect sizes are missing.

Moderator analysis on the outcome depression

Table 5 shows the effects of the subgroup analysis on the outcome depression. It shows that the type of control group was a significant moderator. Contrary to expectations, studies that used a waiting list control group had smaller effect sizes in general, than studies that used an active or standard care control condition. However, there were only five studies in this analysis that used a waiting list control group. Also, the percentage of people with AIDS in a study was a significant moderator, i.e., when less than 40% of the participants in the studies had AIDS the effect sizes were on average larger than when 40% or more of the participants in the studies had AIDS. Furthermore, the moderator a priori screening on depression was significant, which means that studies that only included participants with depressive symptoms had larger effect sizes in general ($\hat{g} = 0.46$, 95% CI [0.25, 0.68]), than studies that did not had the presence of depressive symptoms as an inclusion criterion ($\hat{g} = 0.12$, 95% CI [0.05,

0.18]). Last, the moderator provider of the intervention was significant. Studies that had a psychologist or a psychotherapist as a provider of the intervention had the largest pooled effect sizes. Studies that used other providers (e.g., a counsellor or peer or a computer) had smaller pooled effect sizes. Concluding, the moderators that were found to be significant were: type of control group, percentage of people with AIDS, a priori screening on depression, and provider of the intervention.

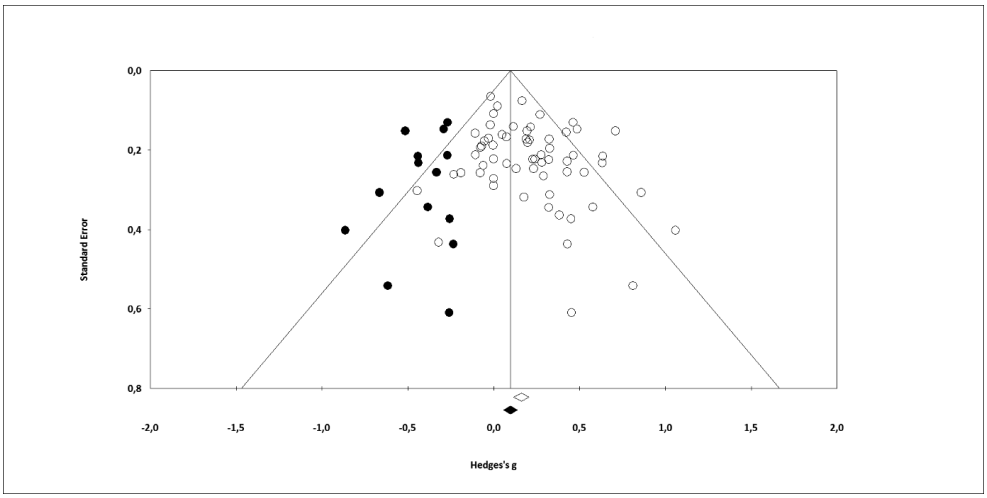


Figure 4. Funnel plot of standard error by Hedges' g with imputed studies from Duval and Tweedie's trim and fill analysis

Table 5. Moderators of intervention effect on depression (k = 47)

Moderator	**Subgroup**	***k***[a]	**Hedges' *ĝ***	**95% CI**	***Q* for difference**[b]
Control group	Active control group	24	0.22[c]	0.11, 0.33	6.74[d]
	Standard care	18	0.25[c]	0.14, 0.36	
	Waiting list	5	-0.04	-0.24, 0.16	
Location	Africa/Asia	8	0.19[c]	0.05, 0.33	0.01
	North America/Europe	38	0.19[c]	0.10, 0.27	
	Other[e]	1			
First year recruitment	1996-2001	16	0.13[d]	0.02, 0.24	4.37
	2002-2006	15	0.32[c]	0.16, 0.47	
	2007-2012	13	0.13	-0.01, 0.28	
	Missing	3			
% Attrition	0-10%	14	0.18[d]	0.01, 0.36	1.14
	10-20%	17	0.20[c]	0.08, 0.32	

Moderator	Subgroup	*k*[a]	Hedges' *ĝ*	95% CI	*Q* for difference[b]
	> 20%	14	0.28[c]	0.15, 0.41	
	Missing	2	0.03		
% Females	0-20%	14	0.27[c]	0.15, 0.40	4.54
	20-80%	22	0.21[c]	0.09, 0.33	
	80-100%	10	0.08	-0.06, 0.21	
	Missing	1			
Mean age	< 42.40 years	19	0.14[c]	0.04, 0.24	0.74
	≥ 42.40 years	22	0.21[c]	0.09, 0.32	
	Missing	6			
% MSM[f]	0%	10	0.10	-0.05, 0.24	0.50
	> 0%	10	0.17[d]	0.02, 0.31	
	Missing	27			
% Participants with AIDS	< 40%	5	0.54[c]	0.38, 0.71	7.24[c]
	≥ 40%	5	0.19	-0.01, 0.38	
	Missing	37			
Mean duration HIV	< 10.02 years	10	0.16	-0.05, 0.38	0.21
	≥ 10.02 years	13	0.22[c]	0.07, 0.38	
	Missing	24			
% on ART[g]	< 87%	10	0.34[c]	0.15, 0.52	0.00
	≥ 87%	12	0.34[c]	0.18, 0.49	
	Missing	25			
Screening on depression	No	37	0.12[c]	0.05, 0.18	9.13[c]
	Yes	10	0.46[c]	0.25, 0.68	
Mental health primary outcome	No	6	0.17	-0.02, 0.36	0.19
	Yes	41	0.22[c]	0.13, 0.30	
Provider intervention	Psychologist	13	0.42[c]	0.28, 0.56	12.92[d]
	Counsellor	21	0.15[c]	0.05, 0.25	
	Peer	2	0.10	-0.04, 0.25	
	None	5	0.18	-0.19, 0.54	
	Other (practitioner)	1	0.06	-0.22, 0.33	
	Missing	5			
Format intervention	Group	19	0.23[c]	0.14, 0.33	4.58
	Individual	20	0.25[c]	0.10, 0.40	
	Combination	4	0.09	-0.16, 0.33	
	Other	4	-0.01	-0.26, 0.23	
Analysis	ITT[h]	24	0.22[c]	0.11, 0.34	1.32
	No ITT[h]	15	0.13[d]	0.02, 0.24	
	Missing	8			
Study quality	Low	17	0.23[c]	0.08, 0.38	0.53

Moderator	Subgroup	k[a]	Hedges' $\hat{g}$	95% CI	Q for difference[b]
	Medium	24	0.19[c]	0.09, 0.29	
	High	6	0.28[d]	0.001, 0.57	

[a] k = number of studies, [b] Q = Q for difference between subgroups, [c] $p < 0.01$, [d] $p < 0.05$, [e] One study recruited participants in South Africa, Puerto Rico and the USA. This study could not be classified into one of the categories, so it was removed from the moderator analysis on location, [f] *MSM* = men that have sex with men, [g] *ART* = antiretroviral therapy, [h] *ITT* = intent to treat analysis.

Moderator analysis: effect of intervention characteristics on the outcome depression

Table 6 shows the effects of intervention characteristics on the outcome of depression. In this analysis, all interventions were investigated separately, so some studies are represented twice. When mental health (i.e., depression, anxiety, quality of life, or psychological well-being) was a primary focus of the intervention in a study, the effect sizes were in general larger than when mental health was not a primary focus of an intervention. Furthermore, treatment duration was a significant moderator. Studies with treatment durations of 12 to 18 hours had the largest effect sizes. Studies with shorter or longer treatment durations had smaller effect sizes in general. In sum, the following moderators were significant in this analysis: mental health primary focus of the intervention and treatment duration.

Moderator analysis on the outcome psychological well-being

The moderator analysis was also conducted on the outcome psychological well-being, next to the moderator analysis on the outcome depression. It was decided to do the moderator analysis on these two outcomes, because the largest pooled effect sizes were found for depression and psychological well-being and heterogeneity was highest and significant for these outcomes (see Table 4). Differences between the moderator analysis on the outcome depression and psychological well-being will be discussed here. The moderators percentage of people with AIDS, provider of the intervention, whether mental health was a primary focus of the intervention and treatment duration were not significant in the analysis on well-being, all p's > 0.06. The type of control group remained a significant moderator. The moderator screening on the presence of depressive symptoms was not included in this analysis, since the outcome was psychological well-being and therefore most studies did not screen on depressive symptoms in these studies. Furthermore, the percentage of people on ART ($Q = 4.10$, $p < 0.05$) and study quality ($Q = 8.71$, $p < 0.05$) were significant moderators in this analysis. Regarding the percentage of people on ART, the largest effect sizes were in general for studies with 87% or more of the participants on ART ($\hat{g} = 0.39$, 95% CI [0.14, 0.64], $p < 0.01$, $k = 8$), and studies with less than 87% of participants on ART had smaller effect sizes ($\hat{g} = 0.07$, 95% CI [-0.11, 0.25], $p = 0.45$, $k = 3$). Though, the last category contained only three studies. Regarding study quality, studies with a medium quality

had larger effect sizes on average ($\hat{g}$ = 0.30, 95% CI [0.14, 0.46], $p < 0.001$, k = 14), than studies with a low ($\hat{g}$ = 0.15, 95% CI [-0.05, 0.35], p = 0.15, k = 7) or high quality ($\hat{g}$ = -0.04, 95% CI [-0.21, 0.12], p = 0.61, k = 4). However, there were only four studies in the category high quality in this analysis. Summarizing, in the moderator analysis on the outcome psychological well-being the significant moderators were: type of control group, percentage of people on ART, and study quality.

Table 6. Effect of intervention characteristics on depression

Moderator	Subgroup	m[a]	Hedges' $\hat{g}$	95% CI	Q for difference[b]
Relaxation technique[c]	No	22	0.18[d]	0.06, 0.29	2.75
	Yes	9	0.38[d]	0.17, 0.59	
Cognitive behavioral technique[c]	No	9	0.15	-0.07, 0.38	0.53
	Yes	22	0.25[d]	0.13, 0.37	
Motivational interviewing technique[c]	No	25	0.23[d]	0.12, 0.34	0.07
	Yes	6	0.18	-0.16, 0.52	
Stress-management technique[c]	No	20	0.19[d]	0.06, 0.31	1.04
	Yes	11	0.29[d]	0.13, 0.45	
Mental health primary focus intervention	No	22	0.14[d]	0.06, 0.22	4.02[e]
	Yes	31	0.29[d]	0.02, 0.41	
Theory-driven intervention	No	19	0.22 [d]	0.09, 0.36	0.01
	Yes	34	0.21 [d]	0.12, 0.31	
Treatment duration	1-5 h	13	0.06	-0.09, 0.20	10.76[e]
	5-12 h	14	0.12	-0.01, 0.25	
	12-18 h	11	0.38[d]	0.23, 0.53	
	18-30 h	9	0.17	-0.003, 0.33	
	Missing	6			

[a] m = number of interventions, [b] Q = Q for difference between subgroups, [c] the effect of the use of specific intervention techniques was investigated in symptom-oriented interventions only (m = 31), [d] $p < 0.01$, [e] $p < 0.05$.

Discussion

The first aim of this systematic review and meta-analysis was to investigate the effectiveness for PLWH of various psychosocial interventions aimed at decreasing depression and anxiety, and improving quality of life and psychological well-being, and to investigate which interventions were the most effective on these outcomes. Sixty-two studies were included in the analysis, and it was found that psychosocial interventions had a positive effect on the mental health outcomes described, although the effect size was small. In addition, there was evidence of publication bias, so the corrected effect size was smaller. Most studies in the meta-analysis were categorized as low or medium quality studies, there was a lack of high quality studies. Furthermore, a range of psychosocial intervention types can

be effective for PLWH, from symptom-oriented interventions such as CBT, to supportive interventions and meditation. There were no differences in effectiveness between these different intervention types, so they all seem to be helpful in improving the mental health of PLWH.

The second aim of the current meta-analysis was to study moderators of intervention effect, to determine whether important characteristics of a study or a therapy may influence the effectiveness of the treatments in question. We found that six factors may influence the effectiveness of a treatment for depression. Of these six factors, three could be classified as intervention characteristics: who provided the intervention, whether mental health was a primary focus of the intervention, and what the duration of treatment was. The other three were study characteristics: whether there was a priori screening for depression, what percentage of the participants in a study had AIDS, and what type of control group was included. Other factors, such as intervention techniques, were shown not to moderate intervention effect.

We found that, overall, psychosocial interventions had a positive effect on depression, anxiety, quality of life, and psychological well-being of PLWH. However, the pooled effect size was small, $\hat{g}$ = 0.19. When the pooled effect sizes of the separate outcomes were examined, it was found that the pooled effect sizes on depression and psychological well-being were the largest; smaller pooled effect sizes were found on anxiety and quality of life. Previous meta-analyses (14-16) found mostly small to moderate effect sizes of psychosocial interventions for PLWH for the outcomes depression and anxiety. The effect size on the outcome quality of life was comparable with a previous meta-analysis, which also found a small effect (16). Furthermore, two previous meta-analyses investigated the effects of CBT and stress-management on stress (stress was included in the outcome psychological well-being in the present meta-analysis), and one of these found a moderate (14) and the other a small pooled effect size (16). These differences in effect sizes between the current study and previous ones may be explained by a difference in the focus of the interventions included. When the moderator analysis was conducted, it was found that when mental health was the primary focus of an intervention, the effects were larger than when this was not the primary focus of an intervention. Previous meta-analyses mainly included interventions whose primary aim was to improve mental health. This important difference between the current meta-analysis and previous meta-analyses may explain the smaller effects in this study. In addition, the current meta-analysis included 62 studies, while most previous meta-analyses included less than half this number of studies. The inclusion criteria of this meta-analysis were also broader: various psychosocial interventions and outcomes were included. For these reasons, this meta-analysis may have more power to detect a true effect.

Furthermore, the analysis was conducted at several time points, to study the effect of interventions in both the short and the long term. It was found that the effect size was much smaller at the last time point (nine months or more after the intervention had ended), than at the earlier time

points. Two previous meta-analyses (14, 18) about the effectiveness of CBT for PLWH with mental health problems also found that the effects were smaller on later follow-up assessments. This may indicate that the positive effects of interventions on the mental health of PLWH may wear off after a while. Booster sessions, follow-up sessions after termination of the therapy to prevent relapse, could be helpful to retain the effects. A similar finding emerged in a meta-analysis about the long-term effects of psychotherapy for depression (94). However, only nine studies in our meta-analysis had data available on the last time point, so the results should be interpreted with caution. For future studies into psychosocial interventions for PLWH with mental health problems, we advise including a longer follow-up period to further investigate the long-term effects. In addition, future research could study the effect of booster sessions.

In the analysis on intervention types, no differences were found between the various intervention types. This is in line with previous meta-analyses about psychological therapies for depression in the general population or in people with medical disorders, which also found no differences in effectiveness between interventions such as CBT, interpersonal therapy, supportive therapy, and problem-solving therapy (94-98). It seems that several types of interventions may be useful to improve the mental health of PLWH. It has previously been argued more generally that various forms of psychotherapy may have the same effect, because they share common factors, such as the relationship with the therapist (99, 100). The specific type of therapy does not seem to be that important. This corresponds with our findings. For a more thorough investigation of the differences in effect between psychosocial interventions for PLWH, it is important to design studies that compare different types of interventions. Furthermore, it would also be interesting to know more about how treatments work (mediating factors), and to compare this between different treatments. Future studies should focus on these topics.

In addition to the analysis on intervention types, we also investigated differences in effect between intervention techniques in the symptom-oriented interventions. No differences in effect were found between symptom-oriented interventions that included techniques of relaxation, CBT, stress-management, or motivational interviewing, on the one hand, and symptom-oriented interventions that did not include these techniques, on the other. This is related to the findings about intervention types and a previous meta-analysis that also did not find any differences between interventions that included or did not include stress management skills training (14).

The subgroup analyses indicated that there were several moderators that influenced the effects of interventions on depression. An important moderator was a priori screening for depressive symptoms: when studies included only participants with depressive symptoms the effect sizes were larger than when the presence of depressive symptoms did not serve as an inclusion criterion. This result seems evident: there is more to gain for PLWH with depressive symptoms than for PLWH without

depressive symptoms. A previous meta-analysis also found that in studies that included PLWH with more anxiety symptoms at baseline, the participants benefited more from stress-management interventions (16). On the other hand, another meta-analysis into the effectiveness of CBT for PLWH with depression and anxiety found no inclusion- related differences between studies: there was no difference between studies that restricted participation to those with depressive symptoms and studies that did not have the presence of depressive symptoms as an inclusion criterion (14). However, in this meta-analysis the number of studies in each category was low. All in all, when an intervention is aimed at reducing depression, it seems favorable to screen PLWH a priori and only offer them the treatment if they actually suffer from depressive symptoms.

Another significant moderator was whether mental health was the primary focus of an intervention. In studies where mental health was the primary focus of the intervention, the effects were larger than in studies where mental health was not the primary focus. Again, this result seems logical: if the aim of an intervention is to reduce depression, participants will work on reducing symptoms during treatment, and it is expected that this will be effective. If the aim of an intervention is to quit smoking, for example, this will be the focus of the therapy and it is not so likely that participants' psychological symptoms will also improve.

We found that studies that had a psychologist or psychotherapist as a provider of the intervention had the largest pooled effect sizes. Studies that had other providers, e.g., counsellors, peers, or computers, all had smaller effect sizes in general. This shows that it may not be so important which specific therapy or technique is used to treat mental health problems in PLWH; the key element may be the provider of the intervention. Psychologists have a broad training in treating mental health problems, so they may be more experienced and more competent to help PLWH in need. This is in contrast with most other providers; they may be trained to provide the intervention, but this may not be comparable to psychologists' education and experience in mental health care. However, a previous meta-analysis about CBT for depression and anxiety in PLWH found no differences in effects between studies in which interventions were provided by a psychologist or psychiatrist and studies in which interventions were delivered by trained research staff (e.g., graduate- and doctoral-level students) (14). Further, two meta-analyses on guided self-help (101) or guided computerized interventions (102) for depression or anxiety also did not find differences in effects between studies involving experienced providers (e.g., psychologists) and those involving less experienced providers (e.g., students). However, the moderator analysis in this meta-analysis comprised many more studies than those in the previous meta-analyses, so it has more power to detect differences. To conclude, psychologists and psychotherapists may be the most qualified providers of

psychosocial treatments for PLWH with mental health problems. More research is needed to confirm this.

The duration of treatment was another important moderator in this meta-analysis. We found that studies with a treatment duration of 12-18 hours had the largest effect sizes, compared to treatments of shorter or longer duration. So, it seems that therapies of average duration may be more effective than treatments of short or long duration. However, there is a trend toward designing concise treatments for mental health problems, which can be provided via the Internet and are thought to be more cost-effective. An RCT that compared the effectiveness of concise CBT with standard CBT for depression and anxiety found that they were equivalent (103). Most previous meta-analyses that have investigated the effectiveness of psychological interventions for depression or anxiety have also found no differences between treatments with a short or long duration (14, 95, 97, 101, 102). One meta-analysis about online CBT for patients with chronic somatic conditions and depression did find an effect of treatment duration, with a larger effect size for treatments with a longer duration (104). Some of the previous meta-analyses (14, 101, 102, 104) included a small number of studies in the moderator analysis, but other meta-analyses (95, 97) included more than 100 studies. Hence, it is not yet clear whether the effectiveness of a treatment is related to its duration. When comparing short and long treatments for mental health problems, it may be useful to take the severity of the symptoms into account. People with more severe symptoms may need more sessions than people with a mild or moderate symptom severity (105). Future studies may focus on this topic.

Contrary to expectations, the type of control group was a significant moderator in this meta-analysis. Studies that had a waiting list control group had smaller effect sizes than studies with a standard care or active control group. This is counterintuitive, since participants on a waiting list do not receive any treatment, which would lead us to expect large differences between the intervention and the control condition (106). However, there were only five studies in the moderator analysis that used a waiting list control condition, so firm conclusions cannot be drawn. Previous meta-analyses on the effectiveness of interventions for depression and anxiety found no differences between control group types (14, 94, 102), or found that the studies that used a waiting list control condition had larger effect sizes than other control group types (95, 101, 102).

The last significant moderator was the percentage of participants in the study who had AIDS. When fewer than 40% of the participants in a study had received a diagnosis of AIDS, the effect sizes were larger than when more than 40% of the participants had AIDS. People with AIDS are generally more physically ill – they suffer from more pain and lack of energy – than people without AIDS. This physical discomfort may have a great influence on their mental well-being: i.e., they may feel more sad, worry more, or have difficulties sleeping (1). Therefore, it may be more difficult to treat these psychological symptoms in people with AIDS. That is, the physical symptoms remain, and their

influence on the mental state may hamper a successful response to treatment. Therefore, it may be important to combine medical and psychosocial treatments in people with AIDS, to try to improve or stabilize both the physical and psychological symptoms. In this situation, effective collaboration between treatment providers is crucial. It should be noted that this moderator analysis was based on only ten studies, so the results should be interpreted cautiously and may not be generalizable to other study samples.

This meta-analysis had some limitations, which will be discussed here. First, there was evidence of publication bias. This may indicate that studies with negative effect sizes were missing in the analysis. When these possible missing studies were imputed and a corrected effect size was calculated, it was smaller than the uncorrected effect size. So, it has to be concluded that the overall effect of psychosocial interventions on the mental health of PLWH is small. Second, the quality of the studies included was mostly low or medium; only 16% of the studies included was of high quality. The quality criteria regarding the concealment of allocation to conditions and the availability of a published study protocol, especially, were often not clearly reported in the studies included. Therefore, it is possible that some studies were classified as low or medium quality studies now, while they may have been classified as high quality studies when there would be more information in the paper concerning these criteria. Besides this, it is evident that low quality studies often did not do an intent-to-treat analysis. It would be advisable for future studies to state whether they have complied with the criteria, and that incomplete outcome data will be adequately addressed. A limitation of the instruments used to assess study quality is that when many criteria are not clearly described in a paper, a study was classified as a low quality study. However, study quality was not a significant moderator in the analysis on depression, so studies of high quality did not have larger effect sizes than studies of lower quality. Third, in some of the moderator analyses, only a few studies could be included. This is related to the fact that some studies did not report on all moderator variables. Consequently, the results of the moderator analyses with few studies may not be representative for all of the studies included, and the power is lower in these analyses. Fourth, many moderator analyses were performed in this study, and no correction for multiple testing was applied. This increases the risk of finding spurious moderator effects. Fifth, the outcomes in this meta-analysis were restricted, so the effect of psychosocial interventions on other relevant outcomes (e.g., PTSD) was not investigated. Though, a recent review (107) found two CBT-based interventions that were effective in decreasing PTSD symptoms in PLWH. Therefore, it is possible that the findings of the current meta-analysis also apply to PTSD. However, only two studies were found in the review, so more research into interventions for PTSD in PLWH is necessary. Sixth, although we searched in three databases and in the references of previous meta-analyses and reviews, it is still possible that some relevant articles were not found with this search strategy. Seventh, the moderator concerning the theory content of the intervention had two

categories: theory driven or not theory-driven. For each study, it was determined to which of the categories it belonged by reading the paper. It could be argued that this is not a completely thorough approach, because an intervention may still be based on theory, despite the fact that it is not stated in the paper. Furthermore, interventions may be evidence-based, but not based on a specific theory. Or the other way around: it may be based on a theory, but it is not evidence-based. So, it is recommended for future studies to mention in the paper whether the investigated intervention was theory-driven and/or evidence-based. Last, in the moderator analysis on the effect of intervention characteristics, all interventions were investigated separately. This approach was chosen because in some studies two interventions were investigated, and the interventions did not always belong to the same category of a moderator (e.g., one intervention in a given study may have a treatment duration of four hours and another a treatment duration of eight hours). Therefore, six studies were represented twice in these analyses. It would be preferable to use each study just once in the analysis, but this was not possible here.

Some recommendations for future research may be derived from the results of this meta-analysis. First, future studies should focus on investigating differences between various interventions: how they work and for whom they work. Second, the long-term effects of psychosocial interventions and the effect of booster sessions should be investigated more thoroughly in the future. Third, most studies in the current meta-analysis were conducted in the USA and in Europe. Since the prevalence of HIV is high in low and middle income countries and mental health problems are common in this population, interventions to treat these problems are needed (108). However, there are significant barriers to providing mental health services in these countries, e.g., there is a lack of trained mental health workers (109). Therefore, it is important that these interventions are adapted to the local culture, are brief, can be provided by non-specialists, and are tailored for PLWH. It was found that interventions for PLWH in low and middle income countries were effective when they were focused on the family and integrated into community based health care (110). More research is recommended on mental health interventions for PLWH in low and middle income countries. Fourth, there were a lot of changes in the past twenty years in the mental health care for PLWH and in study methodologies. We investigated the effects of many moderators, but there will be issues that were not addressed. For future studies, it is important to be aware of the changes in mental health care and study design. Fifth, it is likely that moderator effects were relsated, e.g., when there was a screening for depression in a study, this may be related to the fact that the primary focus of the intervention in the study was on mental health. These relations between moderators were not examined in the current meta-analysis, but are interesting to investigate in future meta-analyses. The most optimal result of an intervention may be obtained when the most effective characteristics will be combined in an intervention. Sixth, the moderation analysis indicated that the effect sizes were larger for studies that solely included

PLWH with mental health problems and for interventions that were focused on mental health. Therefore, it is recommended in future intervention studies to restrict the inclusion to participants with mental health problems and to design interventions that are focused on improving mental health. Last, for new studies, it is important to measure and report on study and treatment characteristics, so that studies and interventions can be compared in meta-analyses.

To conclude, this systematic review and meta-analysis included 62 RCTs and therefore has high power. In addition, the effects of multiple intervention and study characteristics on treatment outcome were investigated. The meta-analysis found that, overall, psychosocial interventions may have a small positive effect on the mental health of PLWH. No differences in effect were found between the three intervention types, which means that symptom-oriented interventions, supportive interventions, and meditation may all be effective. A larger improvement in depression may be obtained when only participants with depressive symptoms are included in the study; when interventions are provided by psychologists; when treatment duration is 12-18 hours; and when the intervention is focused on improving mental health. Based on the results of this meta-analysis, it is important to incorporate psychosocial therapies into the care of PLWH with mental health problems.

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Appendix

Appendix 1. Search strategy

PubMed Search Term

(hiv [mesh] OR hiv infection [mesh] OR hiv [tiab] or aids [tiab]) AND (psychotherapy [mesh] OR mental health services [mesh] OR self-care [mesh] OR self-help groups [mesh] OR telemedicine [mesh] OR therapy, computer-assisted [mesh] OR psychotherap* [tiab] OR psychological therap* [tiab] OR psychological treatment* [tiab] OR psychological intervention* [tiab] OR counsel* [tiab] OR cbt [tiab] OR behavior therap* [tiab] OR behaviour therap* [tiab] OR interpersonal therap* [tiab] OR coping [tiab] OR peer support [tiab] OR social support [tiab] OR problem solving [tiab] OR stress manage* [tiab] OR self-help [tiab] OR internet therap* [tiab] OR online therap* [tiab] OR psychoed* [tiab] OR training [tiab] OR exposure [tiab] OR relaxation [tiab] OR mindfulness [tiab] OR reinforcement [tiab] OR risk reduction [tiab] OR commitment therap* [tiab] OR case manage* [tiab]) AND (depression [mesh] OR depress* [tiab] OR anxiety [mesh] OR anxi* [tiab] OR fear [tiab] OR quality of life [mesh] OR quality-of-life [tiab] OR well-being [tiab] OR stress, psychological [mesh] OR stress* [tiab] OR distress [tiab] OR mental health [tiab])

Filters used controlled clinical trial or randomized controlled trial, publication date from 1996/01/01, humans, English language.

PsycInfo Search Term

(DE (hiv OR aids) OR TX (hiv OR aids)) AND (DE (psychotherapy OR psychotherapeutic techniques OR mental health programs OR Counseling OR Stress management OR case management OR self management OR Telemedicine OR Computer Assisted Therapy OR Psychoeducation) OR TX (psychotherap* OR psychological-therap* OR psychological-treatment OR psychological-intervention OR counsel* OR cbt OR behavio#r-therap* OR interpersonal-therap* OR coping OR peer-support OR social-support OR problem-solving OR stress-manage* OR self-help OR internet-therap* OR online-therap* OR psychoed* OR training OR exposure OR relaxation OR mindfulness OR reinforcement OR risk-reduction OR commitment-therap* OR case-manage*)) AND (DE (major depression OR anxiety OR stress OR distress OR quality of life OR well being) OR TX(depress* OR anxi* OR fear OR quality-of-life OR well-being OR stress* OR distress OR mental-health))

Filters used publication year 1996-2015, adulthood (18 yrs & older), experimental replication or treatment outcome/clinical trial or follow-up study.

Embase Search Term

(exp "Human immunodeficiency virus"/ OR exp "Human immunodeficiency virus infection"/ OR exp "Acquired immune deficiency syndrome"/ OR hiv.tw. OR aids.tw.) AND (exp psychotherapy/ or exp "mental health services"/ or exp "self care"/ OR exp "self help"/ OR exp teletherapy/ OR exp "computer assisted therapy"/ OR psychotherap*.tw. OR psychological-therapy.tw. OR psychological-treatment.tw. OR psychological-intervention.tw. OR counsel*.tw. OR cbt.tw. OR behavio?r-therapy.tw. OR interpersonal-therapy.tw. OR coping.tw. OR peer-support.tw. OR social-support.tw. OR problem-solving.tw. OR stress-management.tw. OR self-help.tw. OR internet-therap*.tw. OR online-therap*.tw. OR psychoed*.tw. OR training.tw. OR exposure.tw. OR relaxation.tw. OR mindfulness.tw. OR reinforcement.tw. OR risk-reduction.tw. OR commitment-therap*.tw. OR case-manage*.tw.) AND (exp depression/ OR depress*.tw. OR exp anxiety/ OR anxi*.tw. OR exp fear/ OR fear.tw. OR "quality of life"/exp OR quality-of-life.tw. OR well-being.tw. OR exp stress/ OR "mental stress"/exp OR stress*.tw. OR distress.tw. OR mental-health.tw.)

Filters used human, English language, records from Embase, randomized controlled trial or controlled clinical trial, publication year 1996-2015, article and adult (18-64 years) or aged (65+ years).

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Chapter 3

Psychosocial interventions enhance HIV medication adherence: A systematic review and meta-analysis

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Abstract

About 40% of people living with HIV do not sufficiently adhere to their medication regimen, which adversely affects their health. The current meta-analysis investigated the effect of psychosocial interventions on medication adherence in people living with HIV. Databases were systematically searched, resulting in 43 included randomized controlled trials. Study and intervention characteristics were investigated as moderators. The overall effect size indicates a small to moderate positive effect (Hedges' g = 0.37) of psychosocial interventions on medication adherence in people living with HIV. No evidence for publication bias was found. This meta-analysis study concludes that various psychosocial interventions can improve medication adherence and thereby the health of people living with HIV.

Keywords: HIV, medication adherence, psychotherapy, meta-analysis.

Introduction

The WHO (2016) estimated that by the end of 2014, 37 million people worldwide were living with HIV, and two million became infected that year. If the virus is not treated with medication, it attacks the immune system, which may result in various health problems, AIDS, and eventually death (1). Medication adherence is important in tackling this pandemic and promoting health in people living with HIV (PLWH). Effective drug treatment has made HIV a chronic rather than a lethal condition. However, it also introduced new challenges. HIV drug treatment involves taking pills daily and adhering to treatment is difficult for many PLWH.

Antiretroviral therapy (ART) is a combination of at least two, but usually three, antiretroviral drug classes that suppresses viral replication (2). In addition, ART lowers the chances of transmission through sexual risk behaviour (3), birth and breastfeeding (4), and prevents spreading of the HIV pandemic. Its introduction in 1996 provided PLWH with the chance to stop disease progression and lethality (5). Initially, treatment involved taking several pills daily and had many adverse effects. Nowadays, ART has less side effects and simpler pill regimens. These developments have increased treatment adherence (6). Major remaining challenges are the daily dosing, lifelong treatment, and side effects. A meta-analysis that included 84 studies conducted worldwide from 1999 to 2009 found that only 62% of people on ART took their prescribed doses > 90% of the time (7). Increasing medication adherence should be a focus in the HIV care.

Non-adherence to ART is associated with mental health problems and psychological stressors such as depression (8), life events (9), substance abuse (10), and anxiety (11). A meta-analysis found that psychological factors are among the strongest correlates of non-adherence, stronger than other factors, for example, pill burden (12). Furthermore, mental health problems are highly prevalent in PLWH; the prevalence of depression is about 34%, and of anxiety 28% (13). The way in which mental health problems and non-adherence are related is complex. Some antiretroviral drugs can have side effects such as mood changes, depression, and anxiety. In turn, PLWH with mental health problems may have more difficulty adhering, because of cognitive or behavioural problems, for example, fatigue, hopelessness, lowered motivation and concentration (14).

Like physical and mental health, sexual health is related to ART. ART non-adherence has been linked to more sexual risk taking, for example, having unprotected sex, and greater risk of transmission. Depression, sexual risk behaviour, and adherence may be related: it was found that depression leads to less ART adherence and condom use (15). Non-adherence may also be related to lower socioeconomic status, such as lower income and education, and more unemployment. However, not all studies support this relationship (16). Psychosocial interventions may influence vulnerabilities in socioeconomic status physical, mental and sexual health.

It is important to treat medication non-adherence in PLWH, because optimal adherence should improve PLWH's health and well-being, and lower transmission risks. Treatments that do not address mental health problems as possible causes of non-adherence may be less effective than those that do. For instance, medication reminder devices focus on forgetfulness rather than mental health and have shown inconsistent effectiveness (17). In contrast, antidepressant treatments for PLWH consistently increase ART adherence (18). However, psychopharmacological treatment may cause side effects (e.g. reduced libido and inorgasmia), drug interaction, and increased pill burden, which predict lower adherence and worse virologic suppression (6). Therefore, psychosocial treatments may be preferred to treat non-adherence in PLWH.

Psychosocial interventions are primarily focussed on psychological or social factors, instead of purely focussing on medical factors such as pharmacological treatment or exercise (19). Systematic reviews and meta-analyses that investigated the effectiveness of psychosocial interventions on ART adherence, such as motivational interviewing, cognitive behavioural therapy (CBT), peer support, or counselling, have found promising but inconsistent results. Most reviews (20) and meta-analyses (21-23) found that psychosocial interventions may increase ART adherence. However, some reviews showed negative or mixed results (24-26). A limitation of these findings is that they are partly based on low quality studies. Furthermore, some results come from systematic reviews that do not recombine the raw data.

In addition to investigating the effectiveness of psychosocial interventions, it is important to examine factors (moderators) that may influence it. First, treatment characteristics are factors of the therapy, such as duration. Knowledge about which treatment characteristics influence effectiveness positively may be used when designing interventions. Furthermore, study characteristics, such as the geographical and temporal context of data collection, may partially explain differences between studies. Previous reviews and meta-analyses found larger effects on ART adherence when interventions involved CBT components (24), more therapist training (20), targeted adherence risk or difficulty groups (21) or people with more severe depression (23), longer duration (23, 26), individual setting (26), and adherence measures with recall periods > 7 days (22).

The current meta-analysis investigated the effectiveness of various types of psychosocial interventions on medication adherence in PLWH. To promote the methodological quality of the meta-analysis and strength of the conclusions, only randomized controlled trials (RCTs) were included. Furthermore, the effects of study characteristics and treatment characteristics were investigated.

Methods

Literature search and study selection

Published literature was searched on November 5, 2014 through the databases PsycInfo (EBSCOhost), Embase (Ovid), and Medline (PubMed). Search words were related to three categories; that is, words related to HIV, psychosocial interventions, and ART adherence. An overview of the used search terms is provided in Supplement A. Trials were also identified in published review articles and meta-analyses. Unpublished studies were not included.

Database searches yielded 687 unique articles; Figure 1 shows the search and selection process. Titles and abstracts were reviewed, and if the article appeared to meet inclusion criteria (described below), its full text was retrieved. Then, a final selection was made based on their accordance with the inclusion criteria. This process resulted in 51 unique articles. Consulting previous review articles and meta-analyses resulted in another three articles. Data from 19 articles were not sufficient to calculate an effect size. The study authors were requested by e-mail to provide such data; eight authors provided the data (42%), nine replied but could not provide data (47%), and two could not be reached (11%). The final analysis included 43 studies.

The selection of the first 50 titles and abstracts was executed independently by two researchers (first and second authors). The interrater reliability for this selection indicated substantial agreement (27), $\kappa = 0.63$, $p < 0.001$. The rest of the studies were selected by the first author. In cases of uncertainty, the co-authors were consulted and eligibility was discussed until consensus was reached.

Inclusion criteria

Studies were included in the meta-analysis if they (a) used a randomized controlled design, (b) provided a psychosocial intervention, (c) provided the intervention post 1996, after development of ART, (d) included PLWH age ≥ 18 years, (e) reported ART adherence as outcome, and (f) were published in English. For criterion (b), psychosocial interventions are defined as interventions primarily focussed on psychological or social factors, in contrast to treatments that focus purely on medical factors such as pharmacological treatment or exercise (19). Full-text articles' eligibility was inspected in the order: (f), (d), (a), (c), (b), and (e).

Using these criteria, selected studies could overlap in terms of sample or data. Rules for addressing multiplicity were set a priori. First, if multiple articles reported on the same trial, the article with the most relevant outcome data (e.g. on the complete sample) was used to determine the effect size. Second, if a study researched multiple interventions and a control group, the most intensive intervention was used in the analysis. Third, when studies had multiple control groups, the control group most similar to standard care was used in the analysis. Studies including only active interventions,

but no control group, were not included. If multiple outcome measures were used, the most precise or objective measure of adherence was selected (e.g. monitoring device).

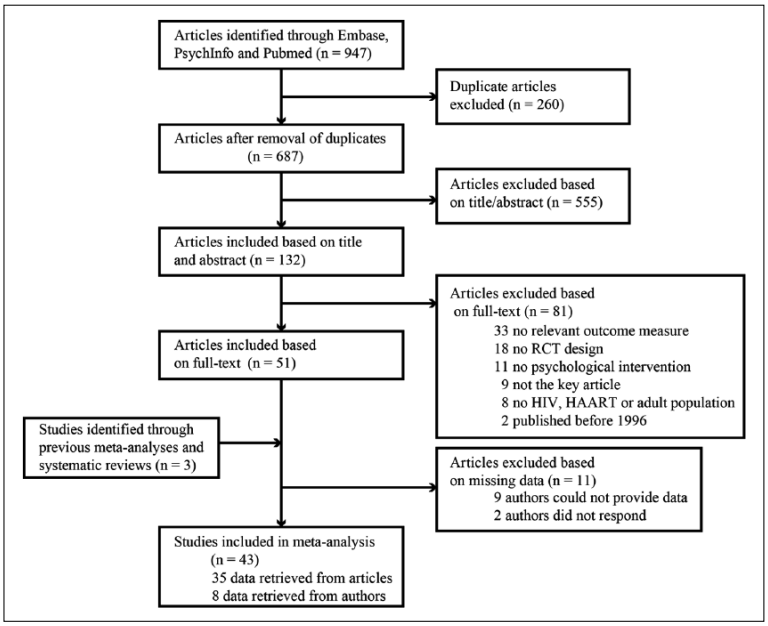


Figure 1. Flowchart illustrating study identification, inclusion and exclusion.

Data coding

Data coding was conducted with an a priori developed protocol. Coding included effect size data and sample, study and intervention characteristics data. Ten studies were coded by two independent researchers (first and second authors). The percentage of agreement over 37 variables was 86%, indicating acceptable agreement in most situations (28). In case of disagreement the article was consulted again. The first author coded the remaining studies.

Medication adherence was coded for the treatment and control group based on the average percentage of post-treatment ART adherence. When articles did not provide the statistics necessary to calculate the effect size (sample size, mean and standard deviation (*SD*) or mean difference, *t*-value or *p*-value), the authors were contacted by e-mail. When the data could be not obtained, studies were excluded.

Coding of study characteristics included study aim (increasing adherence or improving overall mental or physical health), location, type of control group (waiting list, standard care or active control group), measurement type (self-report, monitoring device or pill count), recall period of the measure

(≤ 14 days, > 14 days or no recall: monitoring devices or pill count), percentage retention (participants that were available at the post-treatment assessment), mean age of the sample, percentage of females, sexual orientation or identity (homosexual/gay, heterosexual/straight or bisexual), ethnicity (African American or Black, Caucasian or White and Hispanic or Latino), percentage of participants with AIDS, years since HIV diagnosis and type of risk group (general, risk group or difficulty group). The sample was considered an a priori risk group if known risk factors, for example, experiencing distress from side effects, were an inclusion criterion. The sample was considered an a priori difficulty group if problematic adherence was an inclusion criterion. Other samples were considered general PLWH groups. Standard care control groups usually consisted of consultations with a physician or nurse and short education on medication use and adherence (e.g. (29)). An active control group was an intensive control condition, for example, of similar duration (time-matched) or intensity (dose-matched) as the intervention.

The intervention characteristics included treatment type (CBT, peer/social support or counselling), provider (psychologist/psychiatrist, counsellor, nurse, peer, healthcare professional or other), setting (individual, group or both), treatment duration (1-5, 5-12, 12-30 hours), and use of cognitive and/or behavioural techniques, motivational interviewing and relaxation. An intervention was categorised as CBT if it involved treatment techniques aimed at behavioural and cognitive change. Peer or social support interventions included support through peers or others. Counselling interventions were non-directive or aimed at problem-solving or changing adherence motivation or behaviour. Treatment duration would originally be used in meta-regression to test a dose-response effect. However, meta-regression assumptions (normality and linearity) were not met. Therefore, it was transformed to a categorical variable.

Statistical analysis

The meta-analysis was conducted using Comprehensive Meta-Analysis Version 2 (CMA; (30)). Effect sizes were expressed as Hedges' *g*, computed with the standardized mean difference between the intervention and control group in average percentage of post-treatment medication adherence. Effect sizes of 0.2 were considered small, 0.5 medium and 0.8 large (31). Reported *p*-values are two-tailed. The effect sizes were checked for outliers with standardized residuals > 3. Outliers were transformed toward the mean (winsorized), so that they had a less disproportionate effect on the analyses. The effect sizes were winsorized to 3 *SDs* from the mean in the original direction (32). Two positive outliers were found and transformed (33, 34).

Effect sizes were analysed using the random effects model. This model assumes heterogeneity across studies (32). For moderator analyses, a mixed model was used. The random effects model combined the studies per subgroup. Because subgroups were assumed to be exhaustive, a fixed effects

model combined the subgroup effects. Between-study variance was assumed to be similar across subgroups and was pooled. To examine heterogeneity between studies, the *Q* and I^2 statistics were used. When *Q* is significant, this indicates important outcome differences across studies. I^2 represents the amount of heterogeneity, where values of 25%, 50% and 75% indicate low, moderate and high heterogeneity respectively (35). Unfortunately, CMA version 2 does not allow post hoc multiple comparisons. If a significant moderator analysis compares more than two subgroups, it is unclear which subgroups differ from each other. In these cases, confidence intervals (CIs) were inspected to interpret differences.

Trim-and-fill analysis and Egger's regression were conducted to test for publication bias. Duval and Tweedie's trim-and-fill analysis (36) estimates the amount of missing studies due to publication bias and the effect size when correcting for it. Egger's regression tests whether the intercept statistically differs from zero, indicating publication bias (37).

Results

Study characteristics

The 43 studies included 5095 participants recruited from 1997 to 2013. Key characteristics per study are presented in Supplement B. Almost two-thirds of the participants were male (65%). Study samples ranged from 33 to 249 participants. Most studies were conducted in the United States (35/43) and the rest in Brazil, China, India, Kenya, the Netherlands, Nigeria, Spain and Switzerland. Participant's average age was 42 years (*k* = 42, pooled *SD* = 8.9, *k* = 37; the discrepancy in the amount of studies is due to reporting differences). In studies that reported on the sexual orientation or identity of their sample, most participants described themselves as heterosexual or straight (38%, *k* = 17), homosexual or gay (35%, *k* = 13) and some as bisexual (8%, *k* = 13). Regarding ethnicity, the authors reported that 45% of participants self-identified as Black or African American (*k* = 35), 35% as White or Caucasian (*k* = 34) and 21% as Latino or Hispanic (*k* = 25). The average time of HIV infection at baseline was 10 years in the 18 studies that reported on it (pooled *SD* = 6.8, *k* =14) and 41% of participants had AIDS (*k* = 11). Forty percent of studies focussed on at-risk populations (17/43), 42% on adherence difficulties' populations (18/43) and 19% screened neither on risk factors nor difficulties (8/43).

Study aim was mostly increasing adherence (28/43) and sometimes improving (mental) health (15/43). Adherence was mostly measured with self-report (21/43) or a monitoring device (19/43), and rarely by pill count (3/43). Eleven self-report studies had recall periods ≤ 2 weeks; 10 had longer periods. Control groups frequently received standard care (28/43) and sometimes more active interventions (9/43). Alternatively, participants were put on a waiting list (6/43). The average percentage of retention was 83% in treatment groups and 84% in control groups (*k* = 41).

Intervention characteristics

In all, 22 studies investigated the effectiveness of counselling, 15 investigated CBT and 6 peer support. Cognitive and/or behavioural techniques were used in 58% of interventions (25/43), motivational interviewing in 40% (17/43) and relaxation in 19% (8/43). Most interventions were provided individually (32/43), some in group format (7/43) or a combination (4/43). All interventions except one were provided in an outpatient setting. Interventions were provided by psychiatrists or psychologists (10/43), counsellors (4/43), nurses (8/43), peers (7/43), healthcare professionals (case or social workers, 9/43) or other (including online interventions; 5/43).

Treatment duration could be estimated for 33 studies (77%). An outlier was removed from this analysis because the study was unique in terms of setting and an extreme, influential outlier (38). Its treatment duration was 104 hours and it was the only study with an inpatient setting. The average treatment duration in the rest of the studies was 8.15 hours (*SD* = 8.08, range: 1–30).

Main analysis

The random effects model meta-analysis of the overall sample (k = 43) resulted in a Hedges' g effect size of 0.37 (95% CI [0.23, 0.52], $p < 0.001$). This indicates that average post-treatment medication adherence was higher in treatment than control groups, and the overall effect size was statistically different from zero. It shows a small to moderate positive effect of psychosocial interventions on medication adherence in PLWH. Figure 2 shows the effect size and 95% CI per study in a forest plot.

The test of heterogeneity indicated significant between-study variance, $Q(42) = 240.05$, $p < 0.001$. The variance caused by effect differences between studies, rather than chance (I^2 = 83%), was considerable (35). This result supports the a priori choice of the random effects model and allows moderator analyses to explain heterogeneity.

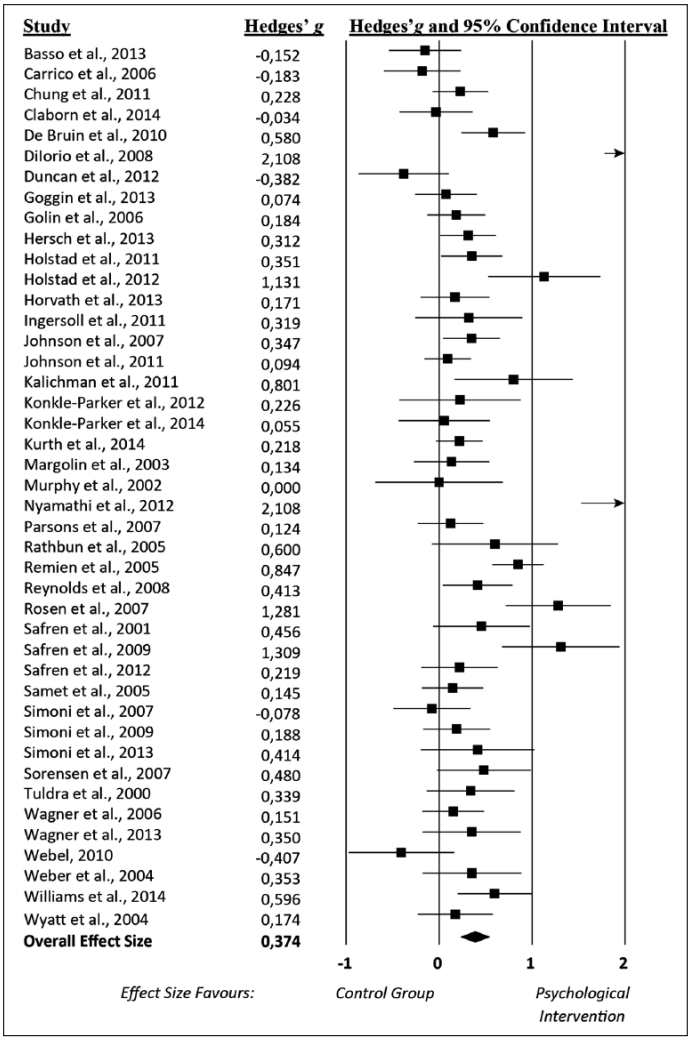


Figure 2. Forest plot showing the effect of psychosocial interventions on medication adherence.

Moderator analyses

Study characteristics explain some heterogeneity between studies, specifically the measurement type and recall period; see Table 1. Effect sizes were largest for studies measuring adherence by pill count; next were studies that used a monitoring device and the smallest effects were found for studies that used self-report measures. Unfortunately, the measurement type moderator analysis was unfit for further inferential interpretation; it included a subgroup based on three samples (pill count) and had incomparable CIs. Because the pill-count group was small, the results were influenced largely by a winsorized outlier, regardless of its transformation toward the mean (34). Therefore, the results in Table 2 regarding measure type should be interpreted with caution. The moderator analysis with recall

periods showed that studies with recall periods ≤ 14 days had smaller effect sizes than studies with no recall period. The studies with a recall period > 14 days did not differ significantly from those with shorter or no recall periods. Study aim, population, type of control group, and location did not moderate effect size, nor did intervention characteristics; see Table 2.

Table 1. Overview of subgroup effect sizes and heterogeneity for study characteristics.

Moderator	Subgroup	*k*[a]	Hedges' *g*	95% CI[b]	*Q*[c]	*P*
Study aim	Increasing adherence	28	0.44	0.25, 0.62	1.34	0.25
	Improving health	15	0.25	−0.001, 0.51		
Sample	General	8	0.43	0.08, 0.78	0.17	0.92
	Risk group	17	0.38	0.14, 0.63		
	Difficulties' group	18	0.34	0.11, 0.58		
Control group	Waiting list	6	0.13	−0.25, 0.52	5.52	0.06
	Standard care	28	0.33	0.14, 0.51		
	Active control group	9	0.71	0.37, 1.04		
Measure type	Self-report	21	0.19	−0.02, 0.39	8.65	0.01[d]
	Monitoring device	19	0.49	0.28, 0.71		
	Pill count	3	0.97	0.41, 1.53		
Recall period	<14 days	11	0.13	−0.16, 0.42	6.52	0.04[d]
	>14 days	10	0.25	−0.05, 0.54		
	No recall	22	0.55	0.35, 0.75		
Location	United States	35	0.32	0.16, 0.49	2.09	0.15
	Other	8	0.61	0.26, 0.95		

[a] *k* = number of studies, [b] *CI* = confidence interval, [c] *Q* = between-group *Q*, [d] $p < .05$.

Table 2. Overview of subgroup effect sizes and heterogeneity for intervention characteristics.

Moderator	Subgroup	*k*[a]	Hedges' *g*	95% CI[b]	*Q*[c]	*p*
Intervention	CBT[d]	15	0.29	0.03, 0.55	0.67	0.72
type	Peer or social support	6	0.45	0.05, 0.85		
	Counselling	22	0.41	0.20, 0.62		
CB[e]	No	18	0.49	0.27, 0.72	1.83	0.18
	Yes	25	0.29	0.09, 0.48		
MI[f]	No	26	0.31	0.12, 0.50	1.19	0.28
	Yes	17	0.48	0.24, 0.71		
Relaxation	No	35	0.42	0.26, 0.58	1.69	0.19
	Yes	8	0.16	−0.18, 0.51		
Setting	Group	7	0.11	−0.26, 0.48	2.47	0.29
	Individual	32	0.41	0.24, 0.59		
	Combination	4	0.52	0.02, 1.03		
Therapy	Psychologist/psychiatrist	10	0.39	0.07, 0.71	3.37	0.64
provider	Counsellor	4	0.35	−0.15, 0.84		
	Nurse	8	0.62	0.29, 0.95		
	Peer	7	0.37	0.00, 0.73		
	Healthcare professional	9	0.24	−0.08, 0.56		
	Other	5	0.21	−0.22, 0.63		
Treatment	Short	16	0.40	0.15, 0.64	1.13	0.57
duration	Medium	8	0.29	−0.06, 0.65		
	Long	8	0.17	−0.19, 0.52		
	Missing	10				

[a] *k* = number of studies, [b] *CI* = confidence interval, [c] *Q* = between-group *Q,* [d] *CBT* = cognitive behavioural therapy, [e] *CB* = cognitive and/or behavioural techniques, [f] *MI* = motivational interviewing.

Publication bias

Duval and Tweedie's trim-and-fill funnel plot showed that the studies in this meta-analysis are distributed symmetrically around the mean effect size. No studies were trimmed or filled, indicating no evidence of publication bias. Egger's test of the intercept was not significant, intercept 1.02, (95% CI [-1.74, 3.78], $t(41) = 0.75$, $p = 0.46$. This also indicates that there is no publication bias.

Discussion

The results of the current meta-analysis show that psychosocial interventions have a small to moderate positive effect on medication adherence in PLWH. This finding has important implications because better ART adherence is related to disease suppression and lowers transmission risk. This effect is likely due to psychosocial interventions treating important causes of ART non-adherence. Those may include the psychological correlates found in an earlier meta-analysis, such as depressive symptoms, stigma

and lack of social support. In addition to mental health, non-adherence is related to many factors including pill burden, side effects, physical health, sexual health and socioeconomic status. Psychosocial interventions may influence how PLWH cope with challenges in these fields. The findings of this study are in line with previous meta-analyses and reviews that have shown promising results for treatments involving behavioural components (22), counselling (21), motivational interviewing (20) and treatments aimed at depression (23). Contrastingly, some reviews found negative or mixed results of psychosocial interventions aimed at improving adherence (24-26). This may be explained by the method; this study uses meta-analysis on 43 studies, while previous reviews did not combine the individual study data to determine an overall effect. In addition, two reviews had fewer studies than the current meta-analysis (24, 26). In terms of geographical and temporal context, previous reviews and meta-analyses were similar to the current meta-analysis and featured studies conducted post 1996 and mainly in the United States. In short, the results of this meta-analysis are in line with a number of previous studies and indicate that offering psychosocial interventions to PLWH may improve medication adherence.

Intervention characteristics did not explain differences in treatment effectiveness in this study. Therefore, findings that interventions were more effective when they included at-risk or adherence difficulty groups (21), involved CBT components (24), had longer treatment duration (23, 26) or provided individual therapy (26) were not replicated. The current meta-analysis results indicate that many different forms of psychosocial treatment in many different settings may be effective. The results are in accordance with the dodo bird verdict and common factors theory. These claim that various psychosocial interventions lead to similar outcomes, due to common effective factors such as therapeutic alliance (39).

Differences in methodology and included studies may explain differences in results regarding the moderating effect of intervention characteristics between this study and previous studies. It may be that moderating factors that seem effective in a systematic review, based on the number of studies with positive findings, were not found to be effective in this meta-analysis, based on pooled and weighted results. It could also be that such findings were not present in this sample because it is based on RCTs only, or because the sample consists of a various psychosocial interventions rather than, for instance, motivational interviewing alone. Another explanation might be that moderating effects of these characteristics are small and more studies are necessary to find subgroup differences.

Two study characteristics showed a relationship with treatment effectiveness: the type of adherence measure and its recall period. However, the measure type analysis included a subgroup of three studies, including one influential outlier, hence findings should be interpreted with caution. With this in mind, the results indicate that studies that used pill-count measures may have larger effect sizes than studies that used self-report measures. This suggests that pill-count measures are more sensitive

to detect differences than self-report measures, which agrees with earlier findings (40). In addition, pill count and monitoring devices are more objective than self-report measures; they do not rely on the participant's memory. Second, studies that used measures without recall period had larger effect sizes than those with recall. This may be associated with the previous result that pill-count measures, which have no recall period, have larger effect sizes than self-report measures, which have a recall period. Combining previous and current study findings, it seems that objective measures that do not rely on recall may be more sensitive to changes in adherence than subjective measures that rely on self-report. For future studies, researchers should keep in mind these possible sensitivity differences when deciding on a measurement method.

Strengths and limitations

This study combined and analysed the data of 43 studies meta-analytically, which resulted in high statistical power. In addition, a wide range of psychosocial interventions were included in this meta-analysis. This study adds to previous research by analysing results from RCTs only, which are considered high-quality studies in experimental psychology. Another strength is that results indicated no influence of publication bias. However, some studies that were identified during the systematic search were excluded due to missing data.

The study also had limitations. First, the study investigated only short-term post-treatment effects. Therefore, the long-term effectiveness of psychosocial interventions remains unclear. Second, some moderators had categories with few studies, making it hard to generalize their results. Third, the mechanisms of change remain unclear, as psychosocial interventions may influence factors related to adherence, such as physical, mental and sexual health, and socioeconomic status.

The current meta-analysis was influenced by limitations of the included studies and identified some gaps in the literature. First, most studies were conducted in the United States, leaving other locations greatly influenced by HIV, such as Sub-Saharan Africa and Asia, underrepresented. The minority of women in the meta-analysis (35%) correspond with the ratio of women with HIV in the United States, (41) but not Sub-Saharan Africa (42), where HIV disproportionally impacts women. Furthermore, outcomes, study and sample characteristics, such as mean age and ethnicity, were not always reported, which hindered coding. ART pill burden and side effects were often not reported, and thus not analysed. Standardized reporting could be improved by following CONSORT guidelines (43).

Future research

It would be interesting to study common factors in psychosocial treatments, such as therapeutic alliance and empathy. Second, it would be interesting to investigate long-term effects of psychosocial treatments, to assess whether positive results can be retained. Since the intervention provider was not

a significant moderator, future research could study the effectiveness of online interventions, which may be more accessible and cost-effective. Fourth, future research might focus on investigating the effectiveness of psychosocial interventions in non-USA samples. Furthermore, studying factors that are related to high or consistent adherence, rather than non-adherence, might provide new insights for psychosocial interventions. Finally, since the effect size was small to moderate, research on supplemental strategies to increase adherence is recommended. The best result may be obtained by fine-tuning and combining medical and psychosocial treatments for PLWH.

Conclusion

This study adds to HIV care literature by establishing the positive effect of a wide range of psychosocial interventions on medication adherence in PLWH in the form of a meta-analysis of RCTs. Better medication adherence promotes the health of PLWH and impacts public health by lowering transmission risk. This study finds that various types of psychosocial interventions can be effective for various PLWH groups. It is important that healthcare professionals are made aware of this, so they can refer PLWH with adherence challenges. Increasing medication adherence in PLWH remains an important public health goal and can potentially help millions of people to suppress the virus and increase their well-being.

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Appendix

Appendix 1. Search Strategy

Embase Search Term

(exp "Human immunodeficiency virus"/ OR exp "Human immunodeficiency virus infection"/ OR exp "Acquired immune deficiency syndrome"/ OR hiv.tw. OR aids.tw.) AND (exp psychotherapy/ or exp "mental health services"/ or exp "self care"/ OR exp "self help"/ OR exp teletherapy/ OR exp "computer assisted therapy"/ OR psychotherap*.tw. OR psychological-therapy.tw. OR psychological-treatment.tw. OR psychological-intervention.tw. OR counsel*.tw. OR cbt.tw. OR behavio?r-therapy.tw. OR interpersonal-therapy.tw. OR coping.tw. OR peer-support.tw. OR social-support.tw. OR problem-solving.tw. OR stress-management.tw. OR self-help.tw. OR internet-therap*.tw. OR online-therap*.tw. OR psychoed*.tw. OR training.tw. OR exposure.tw. OR relaxation.tw. OR mindfulness.tw. OR reinforcement.tw. OR risk-reduction.tw. OR commitment-therap*.tw. OR case-manage*.tw.) AND (exp "patient compliance"/ OR adher*.tw. OR compliance.tw. OR exp "highly active antiretroviral therapy"/ OR exp "antiviral therapy"/ OR antiretroviral-therapy.tw.)

Filters used: Human subjects, Aged ≥ 18 (‘Adult’ and ‘Aged’ catagories), English Language, Article, Randomized Controlled Trial or Controlled Clinical Trial, Post 1996.

PsycInfo Search Term

(DE (hiv OR aids) OR TX (hiv OR aids)) AND (DE (psychotherapy OR psychotherapeutic techniques OR mental health programs OR Counseling OR Stress management OR case management OR self management OR Telemedicine OR Computer Assisted Therapy OR Psychoeducation) OR TX (psychotherap* OR psychological-therap* OR psychological-treatment OR psychological-intervention OR counsel* OR cbt OR behavio#r-therap* OR interpersonal-therap* OR coping OR peer-support OR social-support OR problem-solving OR stress-manage* OR self-help OR internet-therap* OR online-therap* OR psychoed* OR training OR exposure OR relaxation OR mindfulness OR reinforcement OR risk-reduction OR commitment-therap* OR case-manage*)) AND (DE (treatment compliance OR antiviral drugs OR drug therapy) OR TX (adher* OR compliance OR antiretroviral-therapy))

Filters used: Aged ≥ 18 (Adulthood), Article or Dissertation, Treatment Outcome/Clinical Trial or Follow-up study or Experimental Replication, Post 1996.

Medline Search Term

(hiv [mesh] OR hiv infection [mesh] OR hiv [tiab] or aids [tiab]) AND (psychotherapy [mesh] OR mental health services [mesh] OR self-care [mesh] OR self-help groups [mesh] OR telemedicine [mesh] OR therapy, computer-assisted [mesh] OR psychotherap* [tiab] OR psychological therap* [tiab] OR psychological treatment* [tiab] OR psychological intervention* [tiab] OR counsel* [tiab] OR cbt [tiab] OR behavior therap* [tiab] OR behaviour therap* [tiab] OR interpersonal therap* [tiab] OR coping [tiab] OR peer support [tiab] OR social support [tiab] OR problem solving [tiab] OR stress manage* [tiab] OR self-help [tiab] OR internet therap* [tiab] OR online therap* [tiab] OR psychoed* [tiab] OR training [tiab] OR exposure [tiab] OR relaxation [tiab] OR mindfulness [tiab] OR reinforcement [tiab] OR risk reduction [tiab] OR commitment therap* [tiab] OR case manage* [tiab]) AND (patient compliance [mesh] OR adher* [tiab] OR compliance [tiab] OR HAART [mesh] OR antiretroviral therapy [tiab])

Filters used: Human Subjects, English language, Controlled Clinical Trial or Randomized Controlled Trial, Post 1996.

Appendix 2. Summary of RCT studies on the Effect of Psychosocial Interventions on Medication Adherence in PLWH.

Study	**Population**[a]	**Intervention**[b]	**Study Design**[c]	**Outcome**[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when	**Type and techniques used**	**Analysed sample (when**	
	applicable)	**Duration and setting**	**applicable)**	
Basso, 2013 (29)	*N* = 121 PLWH	*Human Right- Based Intervention*	Aim: increasing adherence.	MEMS
Brazil	Mean age: 43 years; 37% female	Provider: healthcare professional	CG: SC	
	Screened on detectable viral load (DG).	Categorized as: counselling		
		Length: 4 hrs; Setting: individual		
Carrico, 2006 (44)	*N* = 130, male PLWH	*Cognitive Behavioural Stress Management*	Aim: improving health.	ACTG, self-report, 4 days recall.
USA	Mean age: 42 years; 0% female	Provider: psychologist/psychiatrist	CG: SC	
		Categorized as: CBT (CB, REL)		
		Length: 22.5 hrs; Setting: group		
Chung, 2011 (45)	*N* = 200 PLWH	*Adherence Counselling*	Aim: increasing adherence.	Pill-Count
Kenya	Mean age: 36 years; 66% female	Provider: counsellor	CG: SC	
	Screened on initiating ART (RG)	Categorized as: counselling (CB)		
		Length: 1.9 hrs; Setting: individual		
Claborn, 2014 (46)	*N* = 97 PLWH	*eLifeSteps*	Aim: increasing adherence.	ACTG, self-report, 4 days recall.
USA	Mean age: 44 years; 16% female	Provider: computer	CG: SC	
	Screened on adherence ≤ 95% (DG)	Categorized as: CBT (CB)		
		Length: 1 hour; Setting: individual		
De Bruin, 2010 (47)	*N* = 133 PLWH	*Adherence Improving Self-Management*	Aim: increasing adherence.	MEMS
The Netherlands	Mean age: 48 years; 10% female	*Strategy*	CG: SC	
		Provider: HIV-nurse		
		Categorized as: counselling (MI)		

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when applicable)	**Type and techniques used**	**Analysed sample (when applicable)**	
		Duration and setting		
		Length: 1 hour; Setting: individual		
Dilorio, 2008 (33)	*N* = 247 PLWH	*Motivational Interviewing*	Aim: increasing adherence.	MEMS
USA	Mean age: 42 years; 28% female	Provider: HIV-nurse	CG: SC	
	Screened on initiating or changing ART (RG)	Categorized as: counselling (MI)		
		Length: 2.8 hrs; Setting: individual		
Duncan, 2012 (48)	*N* = 76 PLWH	*"FOCUS" MBSR*	Aim: improving health	VAS, self-report, 30 days recall
USA	Mean age: 48 years; 16% female	Provider: MBSR (healthcare) professional	CG: SC	
	Screened on experiencing distress from side effects (RG)	Categorized as: CBT (CB, REL)		
		Length: 30 hrs; Setting: group		
Goggin, 2013 (49)	*N* = 135 PLWH	*Motivational Interviewing - CBT*	Aim: increasing adherence	MEMS
USA	Mean age: 40.6 years; 26% female	Provider: psychologist	CG: SC	
	Screened on adherence problems, initiating or changing ART (DG)	Categorized as: counselling (CB, MI)		
		Length: 4.2 hrs; Setting: individual		
Golin, 2006 (50)	*N* = 155 PLWH	*Motivational Interviewing*	Aim: increasing adherence	MEMS
USA	Mean age: 40 years; 34% female	Provider: healthcare professional	CG: Active control group: PE	
	Screened on detectable or increased viral load or initiating ART (DG)	Categorized as: counselling (MI)		
		Length: 2.3 hrs; Setting: individual		
Hersch, 2013 (51)	*N* = 168 PLWH	*eLifeSteps*	Aim: increasing adherence	MEMS
USA	Mean age:46 years; 24% female	Provider: computer	CG: WLC[p]	
	Screened on detectable viral load(DG)	Categorized as: CBT (CB, REL)		
		Length: 1 hour; Setting: individual		

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when applicable)	**Type and techniques used**	**Analysed sample (when applicable)**	
		Duration and setting		
Holstad, 2011 (52)	*N* = 207, female PLWH	*KHARMA – Motivational Interviewing*	Aim: improving health	MEMS
USA	Mean age: 44 years; 100% female	Provider: nurse	CG: Active control group: PE	
		Categorized as: counselling (MI)	Analysed if ≥ 7 of 8 sessions	
		Length: 14 hrs; Setting: group	were followed	
Holstad, 2012 (53)	*N* = 60, female PLWH	*KHARMA – Motivational Interviewing*	Aim: improving health	AGAS, self-report, 30 days recall
Nigeria	Mean age: 31 years; 100% female	Provider: healthcare professional	CG: Active control group: PE	
		Categorized as: counselling (MI)	Analysed if ≥ 7 of 8 sessions	
		Length: 14 hrs; Setting: group	were followed	
Horvath, 2013 (54)	*N* = 145, gay or bisexual PLWH	*Thrive With Me - online social support*	Aim: increasing adherence	Self-report item, 30 days recall
USA	Mean age: 43 years; 0% female	Provider: peer	CG: WLC	
	Screened on adherence problems (DG)	Categorized as: peer support		
		Length: NR[e]; Setting: individual		
Ingersoll, 2011 (55)	*N* = 56, crack cocaine using PLWH	*Motivational Interviewing*	Aim: improving health	TLB, self-report, 14 days recall
USA	Mean age: 45 years; 52% female	Provider: psychologist	CG: Active control group: PE	
	Screened on adherence problems (DG)	Categorized as: counselling (CB, MI)		
		Length: 6 hrs; Setting: individual		
Johnson, 2007 (56)	*N* = 204 PLWH	*The Healthy Living Project*	Aim: improving health	ACTG, self-report, 3 days recall
USA	Mean age: 40 years; 22% female	Provider: healthcare professional.	CG: WLC	
	(DG; see analysed sample)	Categorized as: counselling (CB)	Analysed if ≤ 85% adherence	
		Length: 22.5 hrs; Setting: individual		
Johnson, 2011 (57)	*N* = 249 PLWH	*The Balance Project*	Aim: increasing adherence	VAS, self-report, 30 days recall
USA	Mean age: 46 years; 9% female	Provider: healthcare professional.	CG: WLC	

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when applicable)	**Type and techniques used**	**Analysed sample (when applicable)**	
		Duration and setting		
	Screened on side effect distress (RG)	Categorized as: counselling (CB)		
		Length: 5 hrs; Setting: individual		
Kalichman, 2011 (58)	*N* = 41 PLWH	*Cell Phone Adherence Counselling*	Aim: increasing adherence	Pill-count
USA	Mean age: 51 years; 35% female	Provider: counsellor	CG: Active control group: pill-count calls	
	Screened on ≤ 95% adherence (DG)	Categorized as: counselling (CB)		
		Length: 3.75 hrs; Setting: individual		
Konkle-Parker, 2012 (59)	*N* = 56 PLWH	*Motivational Interviewing*	Aim: increasing adherence	VAS, self-report, 21-28 days recall
USA	Mean age: 35 years; 38% female	Provider: nurse	CG: SC	
	Screened on initiating or changing ART (RG)	Categorized as: counselling (MI)		
		Length: 2.5 hrs; Setting: individual		
Konkle-Parker, 2014 (60)	*N* = 100 PLWH	*Motivational Interviewing*	Aim: increasing adherence	VAS, self-report, 21-28 days recall
USA	Mean age: 37 years; 51% female	Provider: other (research coordinator)	CG: SC	
	Screened on adherence problems (DG)	Categorized as: counselling (MI)		
		Length: 2.5 hrs; Setting: individual		
Kurth 2014 (61)	*N* = 240 PLWH	*CARE+: online counselling*	Aim: increasing adherence	VAS, self-report, 30 days recall
USA	Mean age: 45 years; 9% female	Provider: computer	CG: SC	
		Categorized as: counselling (MI)		
		Length: NR; Setting: individual		
Margolin, 2003 (38)	*N* = 90 PLWH in a methadone maintenance program	*HIV+ Harm Reduction Program*	Aim: improving health	TLB, self-report, 7 days recall
USA	Mean age: 41 years; 30% female	Provider: counsellor	CG: SC	
	Screened on injection drug use (RG)	Categorized as: CBT (CB)		
		Length: 104 hrs; Setting: group (inpatient)		

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when applicable)	**Type and techniques used**	**Analysed sample (when applicable)**	
		Duration and setting		
Murphy, 2002 (62)	*N* = 52 PLWH	*CBT*	Aim: increasing adherence	ACTG, self-report, 3 days recall
USA	Mean age: 39 years; 12% female	Provider: psychologist	CG: SC	
	Screened on missing ≥ 1 dose per week (DG)	Categorized as: CBT (CB)		
		Length: NR; Setting: group & individual		
Nyamathi, 2012 (34)	*N* = 68, female PLWH, aged 18-45	*ASHA-life*	Aim: increasing adherence	Pill-Count
India	Mean age: 31 years; 100% female	Provider: peer	CG: Active control group: PE	
	Screened on CD4 count ≥ 100	Categorized as: peer support		
		Length: NR; Setting: group & individual		
Parsons, 2007 (63)	*N* = 143 PLWH	*Project PLUS – CBT and MI*	Aim: improving health	Self-report item, 14 days recall
USA	Mean age: 44 years; 21% female	Provider: healthcare professional	CG: Active control group: PE	
	Screened on hazardous drinking (RG)	Categorized as: CBT (CB, MI)		
		Length: 8 hrs; Setting: individual		
Rathbun, 2005 (64)	*N* = 33 PLWH	*Psycho-educative counselling*	Aim: increasing adherence	MEMS
USA	Mean age: 38 years; 15% female	Provider: healthcare professional	CG: SC	
	Screened on initiating ART (RG)	Categorized as: counselling		
		Length: NR; Setting: individual		
Remien, 2005 (65)	*N* = 215 PLWH in relationship with	*SMART Couples Support Study*	Aim: increasing adherence	MEMS
USA	seronegative partner (≥ 6 months)	Provider: nurse	CG: SC	
	Mean age: 42 years; 46% female	Categorized as: social support (CB)		
	Screened on ≤ 80% adherence (DG)	Length: 3.3 hrs; Setting: individual		
Reynolds, 2008 (66)	*N* = 109 PLWH	*Telephone Adherence Counselling*	Aim: increasing adherence	ACTG, self-report, 4 days recall
USA	Mean age: 37 years; 15% female	Provider: nurse	CG: SC	

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when applicable)	**Type and techniques used**	**Analysed sample (when applicable)**	
	Screened on initiating ART (RG)	Categorized as: counselling		
		Length: 1.5 hrs; Setting: individual		
Rosen, 2007 (67)	*N* = 56 PLWH	*Contingency Management and counselling*	Aim: increasing adherence	MEMS
USA	Mean age: 44 years; 41% female	Provider: psychologist	CG: Active control group:	
	Screened on ≤ 80% adherence (DG)	Categorized as: CBT (CB)	counselling	
		Length: NR; Setting: individual		
Safren, 2001 (68)	*N* = 56 PLWH	*Life-Steps: CBT for Adherence*	Aim: increasing adherence	ACTG, self-report, 14 days recall
USA	Mean age: 41 years; 13% female	Provider: healthcare professional	CG: SC	
	Screened on adherence problems (DG)	Categorized as: counselling (CB, MI)		
		Length: NR; Setting: individual		
Safren, 2009 (69)	*N* = 45 PLWH	*Life-Steps: CBT for Adherence*	Aim: improving health.	MEMS
USA	Mean age: NR; 16% female	Provider: psychologist	CG: Enhanced SC	
	Screened on mood disorder (RG)	Categorized as: CBT (CB, MI, REL)		
		Length: 9.2 hrs; Setting: individual		
Safren, 2012 (70)	*N* = 89 PLWH	*Life-Steps: CBT for Adherence*	Aim: improving health	MEMS
USA	Mean age: 47 years; 39% female	Provider: psychologist	CG: Enhanced SC	
	Screened on opioid dependence & mood disorder (RG)	Categorized as: CBT (CB, MI, REL)		
		Length: 7.5 hrs; Setting: individual		
Samet, 2005 (71)	*N* = 151 PLWH	*ADHERE – Motivational Interviewing*	Aim: increasing adherence	ACTG, self-report, 30 days recall
USA	Mean age: 43 years; 46% female	Provider: nurse	CG: SC	
	Screened on alcohol problems (RG)	Categorized as: counselling (MI)		
		Length: 2.4 hrs; Setting: individual		

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when applicable)	**Type and techniques used**	**Analysed sample (when applicable)**	
		Duration and setting		
Simoni, 2007 (72)	*N* = 136 PLWH	*Peer Support*	Aim: increasing adherence	MEMS
USA	Mean age: 43 years; 45% female	Provider: peer	CG: SC	
		Categorized as: peer support		
		Length: 6 hrs; Setting: group & individual		
Simoni, 2009 (73)	*N* = 114 PLWH	*Peer Support*	Aim: improving health	MEMS
USA	Mean age: 40 years; 24% female	Provider: peer	CG: SC	
	Screened on initiating or changing ART (RG)	Categorized as: peer support		
		Length: 6 hrs; Setting: group & individual		
Simoni, 2013 (74)	*N* = 40 PLWH of Mexican descent	*CBT for Depression & Life-Steps*	Aim: improving health	MEMS
USA	Mean age: 46 years; 28% female	Provider: psychologist	CG: SC	
	Screened on depressive complaints & non-adherence or detectable viral load (DG)	Categorized as: CBT (CB, MI, REL)		
		Length: 9.17 hrs; Setting: individual		
Sorensen, 2007 (75)	*N* = 66 PLWH	*Contingency Management and Counselling*	Aim: increasing adherence	MEMS
USA	Mean age: 43 years; 41% female	Provider: other (not specified)	CG: Active control group: counselling and reward	
	Screened on receiving methadone treatment and ≤ 80% adherence (DG)	Categorized as: CBT (CB)		
		Length: NR; Setting: individual		
Tuldra, 2000 (76)	*N* = 116 PLWH	*Psycho-educative Counselling*	Aim: increasing adherence	Self-report item, 30 days recall
Spain	Mean age: 39 years; 24% female	Provider: psychologist	CG: SC	
	Screened on initiating ART (RG)	Categorized as: counselling		
		Length: NR; Setting: individual		

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when applicable)	**Type and techniques used**	**Analysed sample (when applicable)**	
Wagner, 2006 (77)	*N* = 230 PLWH	*CBT or CBT plus Adherence Practice Trial*	Aim: improving health	MEMS
USA	Mean age: 39 years; 20% female	Provider: nurse	CG: SC	
	Screened on adherence problems & initiating or changing ART (DG)	Categorized as: CBT (CB)		
		Length: 3.1 hrs; Setting: individual		
Wagner, 2013 (78)	*N* = 60 PLWH	*Adherence Readiness Program*	Aim: increasing adherence	MEMS
USA	Mean age: 39 years; 6% female	Provider: counsellor	CG: SC	
	Screened on initiating or changing ART (RG)	Categorized as: counselling (CB, MI)		
		Length: 3.5 hrs; Setting: individual		
Webel, 2010 (79)	*N* = 89, female and transgender (identifying female), PLWH	*Peer-Supported Self-management*	Aim: improving health	ACTG, self-report, 7 days recall
USA	Mean age: 47 years; 100% female	Provider: peer	CG: WLC	
		Categorized as: peer support (CB, REL)		
		Length: 14 hrs; Setting: group		
Weber, 2004 (80)	*N* = 60 PLWH	*CBT*	Aim: improving health	MEMS
Switzerland	Mean age: 41 years; 17% female	Provider: psychologist	CG: SC	
	Screened on detectable viral load (RG)	Categorized as: CBT (CB)		
		Length: 18.8 hrs; Setting: individual		
Williams, 2014 (81)	*N* = 110 PLWH	*Ai Sheng Nuo (Love, Life, Hope)*	Aim: increasing adherence	VAS, self-report, 30 days recall
China	Mean age: 38 years; 29% female	Provider: peer	CG: SC	
	Screened on ≤ 90% adherence and detectable viral load (DG)	Categorized as: counselling		
		Length: NR; Setting: individual		
Wyatt, 2004 (82)	*N* = 147, female, PLWH	*ESHI: Enhanced Sexual Health Intervention*	Aim: increasing adherence	Self-report item, 14 days recall
USA	Mean age: 41 years; 100% female	Provider: peer	CG: WLC	

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when	**Type and techniques used**	**Analysed sample (when**	
	applicable)	**Duration and setting**	**applicable)**	
	Screened on childhood sexual abuse	Categorized as: counselling (CB, REL)		
	history (RG)	Length: 27.5 hrs; Setting: group		

[a] Population. With *ART* = antiretroviral therapy, *CD4* = cluster of differentiation 4 (immune parameter), *DG* = difficulties group, *PLWH* = people living with HIV, *RG* = risk group.

[b] Intervention. With *CB* = cognitive and/or behavioural techniques, *CBT* = cognitive behavioural therapy, *MBSR* = mindfulness based stress reduction, *MI* = motivational interviewing techniques, *PE* = psychoeducation, *REL* = relaxation techniques.

[c] Study design. With *CG* = control group, *SC* = standard care, *WLC* = waiting-list condition.

[d] Outcome. With *ACTG* = AIDS Clinical Trials Group adherence questionnaire, *AGAS* = Antiretroviral General Adherence Scale, *MEMS* = Medication Event Monitoring System, *TLB* = Time-Line Back, *VAS* = Visual Analogue Scale.

[e] *NR* = not reported.

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Chapter 4

An Internet-based self-help intervention for people with HIV and depressive symptoms: Study protocol for a randomized controlled trial

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Abstract

Background: Many people living with HIV suffer from depressive symptoms. In a previous pilot study, self-help cognitive behavioral therapy (in booklet format) was found to be effective in treating depressive symptoms in people with HIV. We developed an online self-help program in Dutch and English (based on the booklet) for people with HIV and depressive symptoms. Besides the main question regarding the effectiveness of the program aimed at lowering depressive symptoms, sub-questions will focus on the moderators of treatment success (for which patients is the program especially beneficial?) and the mechanisms of change underlying the treatment outcome (which mediators affect the outcome of treatment?). In this paper, the protocol of the study will be described.

Methods/design: The effectiveness of the program will be investigated by comparing the intervention group with a waiting list-control group in a randomized controlled design, by including a pretest and three post-tests. The self-help program contains four main components: activation, relaxation, changing maladaptive cognitions, and goal attainment. Participants with mild to moderate depressive symptoms will work on the program for six to ten weeks, during which a coach will provide motivational support by telephone once a week. Participants in the control condition will receive weekly minimal support from a coach for eight weeks, and after the second post-test, they can gain access to the self-help program. Depressive symptoms and possible mediators (e.g., activation, cognitive coping, self-efficacy, and goal adjustment) will be assessed by self-report three times during the intervention/waiting period and at the pretest and first post-test.

Discussion: The proposed study aims to evaluate the effectiveness of an online self-help intervention for people with HIV and depressive symptoms. If the intervention is shown to be effective, the program will be implemented.

Consequently, many patients with HIV could be reached, and their psychological care may be improved.

Trial registration: Netherlands Trial Register: NTR5407

Keywords: HIV, Depression, Internet, Self-help, Cognitive behavioral therapy, Coaching, Randomized controlled trial

Introduction

Currently, HIV is a chronic disease that requires the use of medication. Along with the physical problems that people living with HIV (PLWH) may experience (e.g., linked to the side effects of medication or comorbidities), psychological symptoms are also prevalent (1, 2). Specifically, depressive symptoms are often reported by PLWH. Many PLWH struggle, for example, with the daily use of medication and thinking about whom to tell about their HIV (3). This and more general life stressors may lead to depressive symptoms in PLWH. In turn, PLWH with depressive symptoms have a higher chance of non- adherence to their medication (4). This can result in more physical symptoms and illness. Therefore, the treatment of depressive symptoms in PLWH is important.

Various treatments are available for PLWH with depressive symptoms. Group and individual therapies exist, and many of these contain cognitive behavioral components (see review studies (5-9). These treatments are effective in decreasing depressive symptoms and improving the quality of life in PLWH (2, 5, 7-9). Furthermore, beneficial effects were also found for medication adherence (6).

These group and individual therapies have some disadvantages. First, patients and therapists should meet in person during office hours for the treatment. Second, the costs of these treatments are high. Third, for HIV- specific programs, the stigma is a significant barrier to service delivery and utilization (10). A self-help program could be a way to overcome these disadvantages and barriers. The evidence base for low-intensity interventions has been growing in recent years, with high-quality trials supporting the effectiveness of self-help cognitive behavioral therapy (CBT) for depression (11-13).

A low-cost CBT self-help booklet for PLWH was developed based on prior research and a needs assessment (14-17). The self-help booklet contains three main components: relaxation, changing maladaptive cognitions, and goal attainment. The effectiveness of this booklet was tested in a pilot randomized controlled trial (RCT) (18). The results indicated that this intervention was effective in reducing the depressive symptoms in PLWH, compared to waiting list controls. However, in this RCT, 25% of the participants dropped out during the intervention phase. Elements should therefore be added to retain more PLWH in the program and to increase the effectiveness. In addition, several participants indicated they were worried that having the booklet in their home would disclose their HIV-positive status. They would have valued a less stigmatizing mode.

Therefore, the self-help booklet was converted into an Internet version. The online program contains eight lessons, which can be completed in six to ten weeks. An online program has a lower stigma, is easily accessible, can reach more people, and has lower long-term costs. Previous studies showed that online self-help therapy for depression in people with chronic illness was effective (19). In addition to being converted from a booklet into an Internet version, the program was expanded in three ways in the proposed study:

1. An activation component was added, in which participants will be stimulated to perform (small) activities (e.g., wake up on time). Activation is often used in CBT for depression as a first step (20).
2. Minimal coaching with motivational interviewing will be offered. A meta-analysis (12) showed a greater effectiveness of the Internet therapy when coaching was included, also when given in a minimal format. In addition, our recent studies including minimal coaching showed attrition rates between 10 and 15% (21).
3. Finally, in the current study, the online intervention will be available in Dutch and English to reach more PLWH in the Netherlands (and possibly in other countries in the future).

In 2014, the development of the online program was finalized, and we asked a focus group (four volunteers from the Dutch HIV Association) to evaluate the program. Thereafter, we adapted the program, and we conducted a pilot study with 20 PLWH with depressive symptoms (14 males; mean age = 48.65 years, *SD* = 10.86) to test the feasibility of the program. Participants were approached via advertisements on the website and in the magazine of the Dutch HIV Association and were representative of the Dutch HIV population. The results of the pilot study showed that the program was effective in this small group; depressive symptoms decreased from pre-test to post-test. Furthermore, participants thought the program was easy to use and helpful to them. These results encouraged us to execute a large study on the effectiveness of the online self-help program.

The aim of the present paper is to describe the study protocol. The proposed study is a randomized controlled trial; the online self-help program will be compared with a waiting list control condition. The study will include a pretest and three post-tests for the intervention condition (directly after the intervention and three and six months afterward) and a pretest and two post-tests (directly after the eight week waiting period and three months afterward) for the control condition. After the second post-test (five months after the pretest), the participants in the control group can also begin the program. Concluding, we will investigate the effectiveness of the online self-help program in decreasing depressive symptoms in the short and long term. In addition, the moderators (for which patients is the program especially beneficial?) and mediators (which mechanisms affect the outcome of treatment?) will be assessed.

Methods

Design

The study is a randomized controlled trial; participants will be randomly allocated to the intervention or the control group. Stratified randomization by treatment center and sex will be conducted.

Stratification by sex is conducted, as there will be more male participants in the study, and the allocation of approximately the same number of females to the intervention group as to the control group is preferred. In addition, stratification by treatment center is being conducted because the number of (included) patients will differ among the treatment centers. Approximately equal allocation to each of the groups also in the small treatment centers, is important. This will be realized by creating random number tables for each treatment center, divided by sex. Randomization will take place in blocks of 12 participants for each treatment center. Males and females will represent separate blocks, with six males and six females for each treatment center, of which half will be randomly allocated to the intervention group, and half will be allocated to the control group. Participants, coaches, and researchers cannot be blind for allocation to conditions. Participants will be allocated to one of the conditions after the pretest. The random number tables will be created by an independent researcher, and the allocation sequence will be concealed from the main researcher, who enrolls and informs participants.

The design consists of multiple measurements, one pretest, three post-tests (two in the control group), and three assessments during the intervention/waiting period. Figure 1 shows a flow chart of the study design, and the SPIRIT Checklist is presented in Additional file 1. The study is approved by the medical ethics committee of the Leiden University Medical Center (LUMC; nr. P14.091). Online informed consent will be obtained from all participants.

Participants

At least 200 participants who are PLWH with mild to moderate depressive symptoms will be included. Participants will be approached in 23 of the 27 HIV treatment centers throughout the Netherlands during their regular visits to the HIV nursing consultants and doctors. To be eligible to participate in the study, a participant must meet all of the following criteria: being HIV positive, exhibiting mild to moderate depressive symptoms (defined as Patient Health Questionnaire 9 (PHQ-9) (22) score > 4 and < 20), age 18 and older, having sufficient knowledge of the Dutch or English language, able to access the Internet, having an e-mail address, and available for the next eight weeks to work on the intervention.

An eligible participant who meets any of the following criteria will be excluded from participation in the study: being in the first half year following HIV diagnosis, having severe cognitive impairments (e.g., forgetfulness), exhibiting severe depressive symptoms (defined as PHQ- 9 score of 20 or higher), experiencing suicidal ideation (indicated by a score > 1 on the suicide item of the PHQ-9), showing an absence of depressive symptoms (indicated by a PHQ-9 score of four or lower), undergoing treatment presently by a psychologist or psychiatrist, or on antidepressants for less than three months or has experienced a change of type or dose of antidepressants in the past three months.

In case of severe depressive symptoms (using the set criterion) and/or suicide ideation, patients will be referred to their general practitioner or the HIV treatment center.

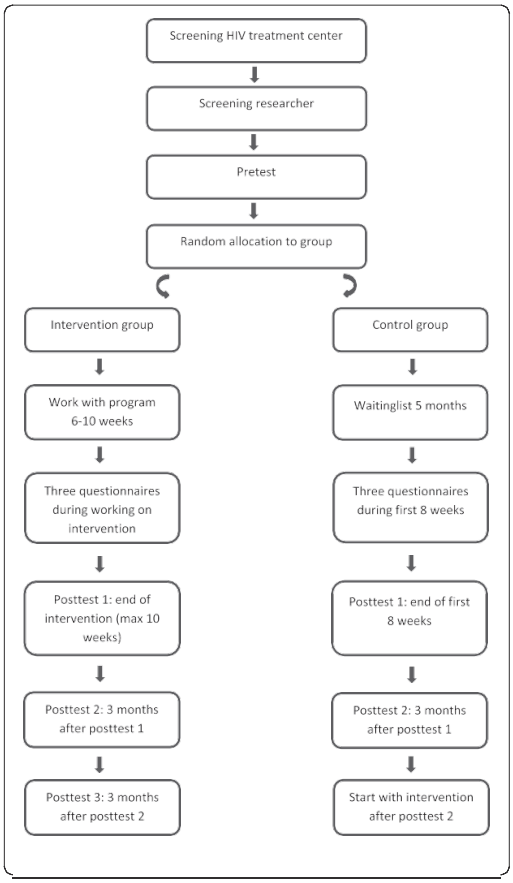


Figure 1. Flow chart of study design

Sample size

A power analysis was performed (with the program Power Analysis and Sample Size Software: PASS; (23)) to determine the sample size needed to assess the long- term effect of the intervention on the primary outcome depressive symptoms. Based on a medium effect size of 0.50, which proved to be realistic according to the previous pilot RCT, and assuming an alpha of 0.05 and a power of 0.80, both groups should consist of 64 participants who complete the four measurements. This sample size is also large enough to detect moderate pre-defined two-way cross-product interactions, such as the interactions of group by sex. Taking into account a drop- out rate of 15% during working on the self-help program (based on our recent studies, which included coaching (21)), at least 150 patients should

be allocated to the two groups at baseline (n = 75 in each group). We will aim for at least 200 participants because dropout will also occur during the follow-up.

Procedure

HIV nursing consultants and doctors in the treatment centers will screen as many PLWH as possible for the level of depression at regular check-ups by means of the PHQ-2 (24). In some of the treatment centers, the Hospital Anxiety and Depression Scale (HADS (25)) will be used instead of the PHQ-2 because this scale was already in use in these centers. HIV treatment centers will receive information about the study and a guideline for the screening. A form will be used for the screening, and the forms will be sent to the researchers. Patients will be screened over approximately six months; most patients visit the HIV treatment center once every six months. If the PHQ-2 score is > 0, patients may be referred to the researchers. Patients will receive written information about the study and permission will be asked to provide the researchers with their e-mail addresses and telephone numbers, so the researchers may contact the patients. The researchers will provide additional information to the patients and screen them more extensively with the PHQ-9. If the depression score is mild (PHQ-9 > 4) to moderate (PHQ-9 < 20), patients are eligible for the study and will be invited to participate. After giving online informed consent, participants will be asked for permission to inform their general practitioner and the HIV treatment center about participation in the study. Thereafter, all participants will complete the pretest via online questionnaires (T0). Next, participants will be randomly allocated to either the intervention or the control condition. At the start of the intervention, the personal coach will contact the participant by telephone in order to check and improve motivation by using the technique of motivational interviewing.

Subsequently, participants in the intervention group will follow the self-help program for six to ten weeks and receive support from a coach (see study conditions). They will be asked to fill out online questionnaires three times during the intervention, after they complete the program (T1, a maximum of ten weeks after T0), three months later (T2), and again three months later (T3). Participants who are allocated to the control condition will receive minimal support for eight weeks (for details see study conditions). They will also be asked to fill out the questionnaires, including the T2. After the T2 (which is completed approximately five months after T0), the participants will also receive the online intervention. Coaches will monitor the well-being of participants in both groups (see ethical precautions). We will raffle off gift cards and iPods among the participants who completed all questionnaires during the study.

Study conditions

Online self-help intervention

The self-help intervention is grounded in the theories of self-regulation and stress-coping, incorporating techniques of CBT and stress-management. The content of the program reflects four main components covered in eight lessons: activation, relaxation, changing maladaptive cognitions, and goal attainment. The program contains a combination of psycho-education, exercises, and assignments, all strengthened by motivation and support to increase the effectiveness and to minimize the attrition over time.

The intervention is offered through a secured website that contains the complete work program. Participants work on the intervention one to two hours a week for a period of six to ten weeks. The program starts with an introduction, and participants are asked to think of a small activity to perform (e.g., taking a short walk; lesson 1). They are stimulated to perform this activity in the following weeks and to expand this to other activities. Furthermore, participants will be instructed to do relaxation exercises and to continue these exercises in the coming weeks (lesson 2). Thereafter, participants learn to identify and change irrational cognitions (by challenging negative thoughts) and to evoke a strong and positive feeling when they experience negative feelings (lessons 3-5). Furthermore, participants are guided to formulate a new, realistic, concrete goal (such as quit smoking) and work on the stepwise attainment of this goal (lessons 6-7). Finally, the participant will work on a concluding and summarizing lesson (lesson 8). All participants will receive support from a coach during the intervention (see below).

Waiting list control condition

Participants randomized to the control group will be placed on a waiting list and will receive the intervention after T2. They will receive an initial phone call to explain the procedures (to minimize attrition). Participants will receive minimal support from a coach (see below).

Support from a coach

Participants in the intervention group will be allocated to a coach, who will provide motivation and support throughout the program. During the first telephone contact, the coach will introduce the program, motivate the participant, and address technical aspects. Once a week, a prescheduled telephone call of approximately 15 minutes will be arranged between the participant and the allocated coach. Coaching will be provided through queries about the participant's progress, motivational remarks, support in case problems are encountered, and encouragement to continue the program. Coaching will not include formal psychotherapy and will be provided until the participant completes

the program or for a maximum of ten weeks. If the participant is not finished with the program after ten weeks, the coaching will end, but the participant can continue the program.

Participants in the control group will also be allocated to a coach, who will provide minimal support over eight weeks. Participants will have a pre-scheduled weekly telephone call of approximately five minutes with the coach. The coach will address the well-being of the participant. Coaches will try to prevent participant dropout and monitor their depressive symptoms. When depressive symptoms or suicidal thoughts increase, the coach will act appropriately (see ethical precautions).

A protocol for coaching will be used, with guidelines available for the provision of support. Coaches will receive a short training to inform them about the study and the coaching procedures. After each telephone call, coaches will note the elements that were used during the call (e.g., motivation, support) to monitor treatment integrity. Coaches will be Master students in clinical psychology or individuals with a Master's degree in the field of psychology. The coaches will have completed clinical courses during their Master's degree program in which they learned communication skills, interview techniques, and treatment strategies. In addition, coaches will be selected in a personal interview on the basis of adequate communication skills for the support and motivation of participants. Coaches will be supervised by the researchers and a psychotherapist. Once every two weeks (every week during the first month of the study), the coaches and the main researcher will hold an intervision meeting. Coaches can discuss difficulties and questions with each other and the researcher. If a problem arises between intervision sessions, the coach may contact the researcher. The researcher and the coach can consult a psychotherapist if necessary.

Ethical precautions

Coaches will monitor the well-being of participants in both the intervention and control groups. Each week, they will ask how the participant is doing. When depressive symptoms worsen or when suicidal thoughts increase, the coach will discuss this with the participant. The coach can refer the participant to the general practitioner or the HIV treatment center, if necessary. The coach can discuss this with the researcher and the psychotherapist. When a participant is referred for more intensive treatment from a psychologist or psychiatrist, the participant may continue with the study. As this may influence the outcomes, the referral will be added as a covariate in the analysis.

Participants will complete questionnaires to assess depressive symptoms during the course of the study. When depressive symptoms of a participant increase, the researcher will notify the coach about this. The coach will discuss this increase of symptoms with the participant and will act appropriately. These guidelines are also described in the protocol for coaches.

Assessments

All assessments are self-reports and will be conducted online (except for the PHQ-2, which will be on paper for screening by the HIV nursing consultants and doctors and the PHQ-9, which will be used by the researchers for screening by telephone). Table 1 depicts all the assessment instruments that will be used in each stage of the study. The primary outcome is depression severity, as measured by the PHQ-9 (22) and the Center for Epidemiologic Studies Depression Scale (CES-D (26)). Secondary outcomes are physical tension, activation (Behavioral Activation for Depression Scale (BADS) (27)), cognitive reappraisal (Emotion Regulation Questionnaire (ERQ) (28)), cognitive coping (Cognitive Emotion Regulation Questionnaire (CERQ) (29)), depressive thoughts (Crandell Cognitions Inventory (CCI) (30)), behavioral coping (Behavioral Emotion Regulation Questionnaire (BERQ) Kraaij & Garnefski, unpublished questionnaire), coping self-efficacy (Kraaij & Garnefski, unpublished questionnaire), goal adjustment (Goal Disengagement and Reengagement Scale (31)), personal growth (Garnefski & Kraaij, unpublished questionnaire), symptoms of anxiety (Generalized Anxiety Disorder 7 (GAD-7) (32)), negative life events (Life Events Scale, (33)), motivation to start with the intervention, compliance, dropout and reasons for dropout, medical data, and user satisfaction.

As potential moderators of treatment outcome demographic variables (sex, age, education, and nationality), clinical and psychological characteristics (severity of depressive symptoms at baseline, anxiety symptoms at baseline, coping self-efficacy, physical health, HIV status, motivation, and alcohol and drug use) will be tested at first. Previous research indicated that some of these moderators (e.g., sex and baseline depression severity) might be important in online CBT for depression (34, 35). In addition, other possible moderators will be investigated exploratory.

The mediator variables and the dependent variable will be measured three times during the intervention/waiting period, at the pretest, and at the first post-test. The following mediator variables will be assessed in the study: activation (two items of the BADS), physical tension (two items), cognitive reappraisal (two items of the ERQ), cognitive coping (12 items of the CERQ), goal adjustment (two items of the Goal Disengagement and Reengagement Scale), symptoms of anxiety (PHQ-4 (36)), and coping self-efficacy (two items). The dependent variable in the mediational analysis is the depressive symptoms (PHQ-4). The questions (regarding, for example, symptoms and cognitions) that will be asked during the intervention/waiting period will refer to the last week. The assessments will be administered three times during the intervention/waiting period because, at these moments, we expect change in the mediating variables. The assessments are linked to the lessons of the self-help program for participants in the intervention group. At the first measurement, we expect a change in the behavioral activation; at the second measurement, we expect a change in the physical tension; at the third measurement, we expect a change in the cognitive reappraisal and cognitive coping; and at

the post-test, we expect a change in the goal adjustment. Coping self-efficacy and anxiety are expected to change over the entire course of the treatment.

Patient Health Questionnaire 9 (PHQ-9)

Depressive symptoms will be measured with the PHQ-9 at the pre- and post-tests (22). The questionnaire consists of nine items and includes the DSM-V criteria for a major depressive disorder. The items are rated on a four-point scale ranging from zero "not at all" to three "nearly every day," e.g., "Over the last two weeks, how often have you been bothered by: little interest or pleasure in doing things?" Scores range from 0 to 27, and cutpoints of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe levels of depressive symptoms. The PHQ-9 is sensitive to change, has good sensitivity and specificity for detecting depressive disorders, and has adequate psychometric properties (37). Furthermore, the questionnaire is often used with PLWH (38). This questionnaire will be used to screen participants on depressive symptoms and to measure change in depressive symptoms from baseline to the post-tests.

Center of Epidemiologic Studies Depression Scale (CES-D)

The CES-D (26) will be used to measure depressive symptoms during the past week. The questionnaire consists of 20 items, such as "During the past week: I felt sad." Items are rated on a four-point scale ranging from zero "rarely or none of the time (less than 1 day)" to three "most or all of the time (5-7 days)." Total scores can range from 0 to 60, and the cut-off score for clinical depression is 16. The internal consistency, reliability, and convergent validity of the CES-D are adequate (26, 39), and sensitivity and specificity are high (40). Furthermore, the questionnaire is often used with PLWH (41). We will use this questionnaire to measure the change in depressive symptoms from the pretest to the post-tests.

Table 1. Overview of assessments during the study

Assessment	**Screening HIV treatment centers** ***(+/- 5 minutes)***	**Screening researchers** ***(+/- 10 minutes)***	**T0: Pretest** ***(+/- 25 minutes)***	**Three times during intervention / waiting period** ***(+/- 10 minutes)***	**T1: post intervention / waiting period: 6-10 weeks after T0** ***(+/- 20 minutes)***	**T2: 3-month follow-up** ***(+/- 20 minutes)***	**T3: 6-month follow-up[a]** ***(+/- 20 minutes)***
PHQ-2[b] or HADS[c]	X	-	-	-	-	-	-
PHQ-9[d]	-	X	X	-	X	X	X
CES-D[e]	-	-	X	-	X	X	X
Demographics and other information	-	-	X	-	X	X	X
Physical tension questionnaire	-	-	X	X	X	X	X
BADS[f]	-	-	X	X	X	X	X
ERQ[g]	-	-	X	X	X	X	X
CERQ[h]	-	-	X	X	X	X	X
CCI[i]	-	-	X	-	X	X	X
Self-efficacy questionnaire	-	-	X	X	X	X	X
Goal disengagement and reengagement scale	-	-	X	X	X	X	X
BERQ[j]	-	-	X	-	X	X	X
Personal growth questionnaire	-	-	X	-	X	X	X
GAD-7[k]	-	-	X	-	X	X	X
PHQ-4[l]	-	-	-	X	-	-	-
Life Events Scale	-	-	X	-	X	X	X
Motivation	-	-	X	-	-	-	-
Compliance	-	-	-	X	X	X[a]	X
Dropout	-	-	-	X	X	X	X
Medical data	-	-	X	-	-	-	X

User satisfaction questionnaire	-	-	-	-	X	-	-

[a] Not send to participants in the control group, [b] *PHQ-2* = Patient Health Questionnaire 2, [c] *HADS* = Hospital Anxiety and Depression Scale, [d] *PHQ-9* = Patient Health Questionnaire-9, [e] *CES-D* = Center of Epidemiologic Studies Depression Scale, [f] *BADS* = Behavioral Activation for Depression Scale, [g] *ERQ* = Emotion Regulation Questionnaire, [h] *CERQ* = Cognitive Emotion Regulation Questionnaire, [i] *CCI* = Crandell Cognitions Inventory, [j] *BERQ* = Behavioral Emotion Regulation Questionnaire, [k] *GAD-7* = Generalized Anxiety Disorder 7, [l] *PHQ-4* = Patient Health Questionnaire 4.

Demographic variables and other information

A self-designed questionnaire will be used to ask participants about sex, age, educational level, nationality, marital status, sexual orientation, social support, disclosure of HIV positive status, alcohol and drug use, previous depressive and anxiety episodes, treatment of psychological symptoms, and physical health. This information will be used to describe the demographic and clinical characteristics of the sample. In the follow-up assessments, questions will be asked about the use of medication for psychological problems and treatment received from a psychologist or a psychiatrist since the start of the study. The use of medication and treatment received will be added as covariates in the analysis.

Furthermore, participants will complete a self-designed questionnaire about information regarding the HIV infection. Questions include time since the HIV diagnosis, how the infection occurred, symptoms of the infection, cluster of differentiation 4 (CD4) cell count, viral load, use of antiretroviral therapy (ART), medication adherence, and side effects of the medication. This information will be used to describe the HIV status and use of ART by the sample.

Physical tension questionnaire

Physical tension will be measured with a self-designed ten item questionnaire. Questions include difficulty to relax, ways to relax, and symptoms of physical tension (e.g., trembling hands, tense neck and shoulder muscles, and increased heart rate). Items can be answered on a three-point scale (no, sometimes, and yes). Higher scores reflect less physical tension.

Behavioral Activation for Depression Scale (BADS)

The subscale activation of the BADS (27) will be used to measure activation during the past week. The subscale consists of seven items that will be measured on a seven-point scale ranging from zero “not at all” to six “completely,” e.g., “I am content with the amount and types of things I did.” Higher scores reflect greater levels of activation. The psychometric properties of the Dutch BADS are adequate (42).

Emotion Regulation Questionnaire (ERQ)

The reappraisal subscale of the ERQ (28) will be used to measure the cognitive reappraisal. The six items are rated on a scale ranging from one “strongly disagree” to seven “strongly agree,” e.g., “When I want to feel less negative emotion, I change the way I’m thinking about the situation.” Higher scores indicate that cognitive reappraisal is often used to regulate emotions. The convergent and discriminant validity of the ERQ are adequate (28).

Cognitive Emotion Regulation Questionnaire (CERQ)

The subscales rumination, catastrophizing, positive refocusing, refocus on planning, positive reappraisal, and putting into perspective of the CERQ (29) will be used to measure the use of these cognitive coping strategies when thinking about having HIV. The subscales consist of four items each, which will be rated on a five-point scale ranging from one "(almost) never," to five "(almost) always." Higher scores on a subscale indicate that this cognitive coping strategy is often used when thinking about having HIV. Examples of items include "I keep thinking about how terrible it is that I have HIV" (catastrophizing) and "I think about pleasant experiences" (positive refocusing). The psychometric properties of the CERQ are adequate (43).

Crandell Cognitions Inventory (CCI)

The hopelessness subscale of the CCI (30) will be used to measure black and white depressive thoughts. The subscale consists of seven items that are rated on a five-point scale ranging from one "(almost) never" to five "(almost) always," e.g., "I'll never feel good again." Higher scores indicate a higher frequency of black and white depressive thinking. The reliability and validity of the CCI are good (30, 44).

Coping self-efficacy questionnaire

Self-efficacy to cope with having HIV will be measured with a self-designed eight-item questionnaire (Kraaij & Garnefski, unpublished questionnaire). The questionnaire is based on the Generalized Self-Efficacy Scale, which has a good reliability and validity (45). Items will be measured on a five-point scale ranging from one "totally disagree" to five "totally agree," e.g., "I have the necessary skills to deal with having HIV." High scores reflect more self-efficacy to cope with having HIV.

Goal Disengagement and Reengagement Scale

Goal adjustment will be measured with the Goal Disengagement and Reengagement Scale (31). We slightly adapted the scale so that questions will be asked regarding the disengagement and reengagement of goals that one has to stop pursuing because of having HIV. The scale consists of four items that measure goal disengagement (e.g., "If I have to stop pursuing an important goal in my life because I have HIV, it's easy for me to reduce my effort toward the goal") and six items that measure goal reengagement (e.g., "If I have to stop pursuing an important goal in my life because I have HIV, I start working on other new goals"). Items are measured on a five-point scale ranging from one "totally disagree" to five "totally agree." Higher scores indicate more goal disengagement and reengagement. A question about new goals that have already been found will be added: "I have already found new

goals." This last question will be handled separately, with higher scores indicating that more new goals were found.

Behavioral Emotion Regulation Questionnaire (BERQ)

The subscales seeking distraction, actively approaching, seeking social support, and withdrawal from the BERQ (Kraaij & Garnefski, unpublished questionnaire) will be used to measure the use of these behavioral strategies to cope with having HIV. Each subscale consists of four items that will be measured on a five-point scale ranging from one "never/hardly ever" to five "(nearly) always," e.g., "I do other things to distract myself." Higher scores on a subscale indicate that the strategy is often used to cope with having HIV. A previous study (Kraaij & Garnefski, in preparation) has shown a good reliability of this questionnaire.

Personal growth questionnaire

Personal growth due to having HIV will be measured with a self-designed five-item questionnaire (Garnefski & Kraaij, unpublished questionnaire). Items will be rated on a five-point scale ranging from one "not at all" to five "certainly," e.g., "Because of having HIV I appreciate life more." High scores indicate personal growth due to having HIV. In a previous study, the reliability of this questionnaire was adequate (15).

Generalized Anxiety Disorder 7 (GAD-7)

The severity of symptoms of anxiety will be investigated with the GAD-7 (32). The questionnaire consists of seven items that are rated on a four-point scale ranging from zero "not at all" to three "nearly every day," e.g., "Over the last two weeks, how often have you been bothered by: feeling nervous, anxious or on edge." Higher scores indicate more anxiety symptoms. The psychometric properties of the GAD-7 are adequate, and the scale also may be used as a screener for panic, social anxiety, and post-traumatic stress disorder (37).

Patient Health Questionnaire 2 and Patient Health Questionnaire 4 (PHQ-2 and PHQ-4)

The PHQ-4 (36) will be used to assess depressive and anxiety symptoms during the intervention or waiting period (for the mediational analysis). It consists of the first two questions of the PHQ-9 and the first two questions of the GAD-7. Items are rated on a four-point scale ranging from zero "not at all" to three "nearly every day." Higher scores indicate more pathology. The internal reliability, construct validity, and factorial validity are adequate (36). The PHQ-2 (24) consists of the first two questions of the PHQ-9 and will be used by the HIV treatment centers to screen for depressive symptoms.

Hospital Anxiety and Depression Scale (HADS)

The HADS (25) will be used by some of the HIV treatment centers to screen for depressive symptoms. The HADS consists of an anxiety and a depression subscale, and each subscale consists of seven questions, e.g., "I still enjoy the things I used to enjoy." Items are rated on a four-point scale, and the response categories are different for each question. Higher scores indicate more anxiety and depressive symptoms. The HADS is widely used and is a reliable and valid questionnaire to screen for anxiety and depressive symptoms (25, 46).

Life Events Scale

Life events will be assessed with the Life Events Scale (33). The scale consists of 17 negative life events (e.g., divorce of parents), and participants indicate if they have not experienced the life event, experienced it longer than one year ago, or experienced it last year. For each of the two periods, a total score of negative life events will be calculated.

Motivation to start with the intervention

Three questions will be used to measure the motivation to start the intervention. Two questions will be asked regarding the expected usefulness of the intervention, and one question about the motivation to start with the intervention. Questions will be answered on a five-point scale, and the scores on the items will be summed.

Compliance

Two measures of program adherence will be used in this study. During the intervention, program adherence will be measured three times by asking participants whether they read the information on the website and performed the exercises. Furthermore, we will monitor whether the participant calls with the coach. These two measures will be handled separately.

Dropout and reasons for dropout

Two types of dropout will be investigated three times during the intervention and at T1, T2, and T3. We will register the participants who stopped using the intervention and the participants who did not complete the questionnaires. We will remind participants to fill in the questionnaires. When they drop out, we will ask them why they do not wish to participate anymore to investigate the reasons for dropout. We will examine the difference in dropout between groups and differences between participants who completed and stopped using the intervention.

Medical data

Medical data will be obtained from the Athena/SHM Cohort Study after consent from the participant. The ATHENA Cohort Study is maintained by Stichting HIV Monitoring, which is supported by the Dutch Ministry of Health via the National Institute for Public Health and Environment (RIVM). The data that will be used include the time since HIV diagnosis, medication use, CD4 cell count, and viral load.

User satisfaction questionnaire

At T1, we will ask participants about their satisfaction with the self-help program and the coach with a self-designed questionnaire. The questionnaire consists of 31 items to evaluate the intervention, for example, the components of the self-help program and the support from the coach. Open-ended and closed-ended questions will be used in the questionnaire. The questions for participants in the control group will concern the support from the coach (13 questions). The answers to these questions will be used to adjust the self-help program before implementing it.

Statistical analyses

A two-tailed alpha of 0.05 will be used for significance testing. All analyses will be based on an intention-to-treat (ITT) analysis, which includes all participants who were randomized to one of the groups at the beginning of the study (47). Baseline differences between conditions will be investigated with chi-square tests for categorical variables and ANOVAs for continuous variables.

To examine the effect of condition on the depressive symptoms at the post-tests, longitudinal multilevel regression analysis (LMRA) will be conducted (48). A two- level model will be studied: time at level 1 and participants at level 2. The variable time will have four categories indicating the four time points (T0–T3). The baseline (T0) will be used as reference category. The independent variable is condition, the dependent variable is the score on the PHQ-9 or the CES-D, and several covariates will be included in the model (e.g., sex and age). Multiple imputation for missing data is not necessary in LMRA because it can include participants with missing data on one or more time points (48). The existence of an effect of HIV treatment center will be investigated exploratory.

Furthermore, Cohen's d will be calculated to indicate within- and between-group effect sizes (49). In addition, clinically important differences for individual change in depressive symptoms will be examined. Change scores of five or more from the pretest to the post-tests will be considered as clinical important differences for the PHQ-9 (50).

With regard to all secondary outcomes, we will study the pre-treatment versus post-treatment changes by using the analyses described above for the PHQ-9 and the CES-D. To examine moderators of the treatment outcome, LMRA will be conducted. Potential moderators will be entered individually. Interaction effects will be investigated (e.g., time x condition x moderator). A limited number of cross-

product interactions will be examined, and we will correct for multiple testing. Furthermore, the QUINT (Qualitative Interaction Trees (51) method will be used to identify subgroups for which the intervention is most effective, by exploratory investigation of the multiple moderators.

Mediation will be tested by examining the indirect effect of the independent variable (condition) on the dependent variable (depressive symptoms) through the proposed mediators. Mediation analysis will be conducted by using latent difference score models, which are recommended with repeated measurements and multiple mediators (52). These models focus on intra-individual change and individual differences in that change.

Discussion

In the proposed study, we will investigate the effectiveness of an online self-help intervention for PLWH with depressive symptoms in a randomized controlled trial. Additionally, moderators and mediators of the treatment outcome will be assessed. This study has some strengths and limitations that will be discussed in the following section. First, a strength of this study is that the self-help program is online, so many people can be reached. Only PLWH without Internet or an e-mail address cannot participate, but most people in The Netherlands have access to the Internet. Second, participants can work on the program when and where they want and at their own pace. Third, the content of the program is based on prior research and a needs assessment among PLWH (14-18); that is, the program is designed especially for PLWH. Fourth, moderators of the treatment outcome will be studied; we will investigate for whom the program is especially beneficial. Investigations of the effect of personal characteristics on the treatment outcome are useful, so patients could receive the treatment that is most likely to decrease their depressive symptoms. Fifth, mediators of the treatment outcome will be assessed; the mechanisms of change of the intervention will be studied. Knowing more about exactly how the invention works is important. Knowing what is effective would allow the adaptation of the treatment to make it more efficient (53). Sixth, the support participants receive from the coach is also a strength in this study. The coach will motivate participants to continue with the program, and this will probably decrease the dropout. Lastly, most HIV treatment centers in the Netherlands agreed to screen patients for the study. This means that we will have PLWH from across the country participating in the study.

Furthermore, some limitations are present in the study. Patients with severe depressive symptoms and/or suicidal ideation will be excluded from the study. We argue that these patients should be closely monitored by a therapist. We expect that these patients would benefit from the self-help program, as has also been found in previous research (54), but more intense treatment is desirable for these patients. In addition, the follow-up period of participants in the control group is

only three months (they may start with the intervention after the three month follow-up), while this period is six months for the participants in the intervention group. However, we argue that it is not ethical to let people in the control group wait for approximately eight months before providing the intervention (eight weeks plus six months of follow-up). Therefore, the intervention will be offered to the control group after the second post-test. The last limitation concerns the screening of participants for depressive symptoms. We will use a questionnaire with nine items to measure depressive symptoms in PLWH. One could argue that a diagnostic interview will screen depressive symptoms more extensively and allow the identification of a possible depressive disorder. However, this approach would be time consuming, and the PHQ-9 is a reliable and valid measure of severity of depressive symptoms (37). Furthermore, the program is designed for people with mild to moderate depressive symptoms, so a diagnosis of depression is not an inclusion criterion for participation in the study.

To conclude, in the proposed study, we will evaluate an online self-help program for PLWH with depressive symptoms. Since depressive symptoms exist frequently in PLWH, low-cost and low-stigmatizing interventions are needed for these individuals. The proposed study offers an online self-help program that complies with this request. If the self-help program proves to be effective in the proposed study, implementation of the website will be done in cooperation with the Dutch patient organization (HIV Vereniging Nederland) and HIV treatment centers. Furthermore, the program may be implemented in other countries as well.

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Appendix

Appendix 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents[a]

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	25-27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,25
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	10-12

Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9, 12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11, 12, 20
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-21
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6, 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, 7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-21
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	20, 21

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	-
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	-
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

[a] It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Chapter 5

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

Published as:

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Abstract

Background Many people living with HIV have depressive symptoms, but some individuals do not receive adequate treatment. We developed an online self-help intervention for people with HIV with depressive symptoms on the basis of previous research. The aim of this study was to investigate the effectiveness of the intervention on depressive symptoms in individuals with HIV.

Methods In this randomized controlled trial, participants recruited from 23 HIV treatment centers in the Netherlands were eligible if they were aged 18 years and older, had been diagnosed with HIV at least 6 months before the study, and had mild to moderate depressive symptoms (Patient Health Questionnaire-9 [PHQ-9] score > 4 and < 20). Individuals also had to speak English or Dutch and have internet access and an email address. Participants were randomly assigned (1:1) to an internet-based intervention (Living positive with HIV) or an attention-only waiting-list control condition. Randomization was done using random number tables, with permuted blocks of 12, stratified by treatment center and sex. Participants, researchers, and coaches were not masked to group allocation. The primary outcome was depressive symptoms assessed with the PHQ-9 and the Center for Epidemiologic Studies Depression Scale (CES-D) at pretest, eight weeks after baseline, and three months after completion of the intervention or control condition (post-test 2). The primary analysis was done by intention to treat. Between group effect size was assessed with Cohen's *d*. This trial is registered with the Netherlands Trial Registry, number NTR5407.

Findings Between Feb 1, and Dec 31, 2015, we randomly assigned 188 participants to the intervention group (n = 97) or the control group (n = 91). Mean pretest PHQ-9 score was 11.74 (SD 2.49) in the intervention group and 11.11 (2.37) in the control group; at the post-test visits it was 6.73 (3.00) and 6.62 (3.03) in the intervention group and 8.60 (3.12) and 8.06 (3.17) in the control group. Mean pretest CES-D score was 24.91 (5.93) in the intervention group and 22.94 (6.48) in the control group; at the post-test visits it was 13.94 (6.39) and 15.71 (6.39) in the intervention group and 19.09 (7.05) and 18.43 (7.05) in the control group. The reduction in depressive symptoms was significantly larger in the intervention group than in the control group (*d* = –0.56 95% CI [–0.85, –0.27] for PHQ-9 and –0.72 [–1.02, –0.42] for CES-D at post-test 1; –0.46 [–0.75, –0.17] for PHQ-9 and –0.47 [–0.76, –0.18] for CES-D at post-test 2). No adverse events were reported.

Interpretation This guided internet-based intervention might be effective for the treatment of depressive symptoms. Future research should focus on the effectiveness of online psychological interventions for people with HIV who have mental health problems in low-income and middle-income countries.

Funding Aidsfonds.

Introduction

Depressive symptoms occur in around 33% of people with HIV (1). A possible consequence of depression in people with HIV is reduced adherence to antiretroviral therapy (2). Although several psychological interventions have been found to effectively reduce depressive symptoms (3, 4) and improve antiretroviral therapy adherence (5) and quality of life (4), many individuals with HIV do not seek treatment when they feel depressed because of factors such as perceived stigma (6). Internet-based interventions might increase the accessibility of treatment for people with HIV who have depression. Additionally, these interventions have the potential to reach a large number of people, can be followed anonymously at preferred times and places, and might be more cost-effective than face-to-face interventions. Previous studies found that internet-based treatments are effective for the treatment of 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 studies (10-13) have assessed the effectiveness of computerised or internet treatments for depressive symptoms in people with HIV. Three of these interventions did not improve mood (10-12). An online support group intervention for individuals with HIV reduced depressive symptoms, but this study did not include a control condition (13). The other studies investigated a metacognitive therapy and positive psychology intervention (11), a cognitive behavioural intervention (12), and stress-management training (10). These interventions might have been ineffective because they did not meet the needs of people with HIV who have depressive symptoms (10, 12). For example, one of the interventions focused more on adherence than on depression (12). Therefore, the development of online interventions for people with HIV that effectively reduce depressive symptoms is needed.

We designed an internet-based treatment termed Living positive with HIV (14). The intervention is based on a booklet self-help programme for people with HIV who have depression (15). The booklet was designed specifically for individuals with HIV, to meet their needs and preferences (16). A randomized controlled trial (15) showed that the booklet was effective in decreasing depressive symptoms, compared with a waiting-list control condition. On the basis of these findings, we adapted the self-help booklet and converted it into the current internet-based self-help intervention. Thereafter, a focus group evaluated the intervention and we adjusted it accordingly. In a pilot study (14) in 2014, 20 individuals with HIV completed the intervention with telephone coaching. Depressive symptoms decreased after the intervention and user satisfaction was high (14).

The aim of this study was to investigate the effectiveness of the guided internet-based self-help intervention in decreasing depressive symptoms in people with HIV compared with an attention-

only waiting-list control condition. We also investigated the effect of the intervention on anxiety and user satisfaction with the intervention.

Research in context

Evidence before this study

In a previous study, we did a meta-analysis of 62 randomized controlled trials published up to Sept 29, 2014, to investigate the effectiveness of psychosocial interventions for people with HIV in improving mental health. The meta-analysis included one internet-based intervention for people with HIV that investigated effects on mood. On Augustus 30, 2017, our search was updated; we searched PubMed, PsycINFO, and Embase using terms related to "HIV", "Internet-based therapy", and "depression". One additional study was found. To date, only two studies have investigated the use of internet-based interventions for people with HIV who have depressive symptoms and both found that the interventions did not improve mood.

Added value of this study

Our results show that the guided internet-based intervention, Living positive with HIV, might be effective in improving depressive symptoms in people with HIV compared with an attention-only waiting-list control condition.

This improvement was sustained over time, and anxiety was significantly reduced in patients who followed the intervention compared with the control. Online interventions have advantages, such as large potential reach and accessibility. Additionally, this intervention is available in Dutch and English and could be adapted for use in other countries.

Implications of all the available evidence

People with HIV who have depressive symptoms should be referred to effective psychological treatments. eHealth interventions are emerging and have been shown to be as effective as face-to-face interventions. Therefore, treatment providers might refer people with HIV who have depressive symptoms to an online intervention, such as the intervention used in this study. More research on moderators, mediators, and the cost-effectiveness of internet-based interventions is needed.

Methods

Study design and participants

In this randomized controlled trial, participants were recruited from 23 HIV treatment centers in the Netherlands. Patients at these centers underwent a two-step screening for depressive symptoms.

Nursing consultants and doctors in HIV treatment centers initially screened patients with HIV for depressive symptoms during regular check-ups using the Patient Health Questionnaire-2 (PHQ-2) (17). Patients with PHQ-2 scores higher than zero who were interested in participating in the study were referred to the researchers for a second screening with the Patient Health Questionnaire-9 (PHQ-9), using established cutoff scores (18). One HIV treatment center screened patients with the Hospital Anxiety and Depression Scale (19), because this questionnaire was already in use. Patients with total scores higher than 2 and less than 16 on the Hospital Anxiety and Depression Scale were deemed eligible for referral to the researchers. The study was also advertised by the Dutch HIV Association. Researchers contacted all interested patients to provide more information and to screen for eligibility.

Eligible individuals were aged 18 years and older, had been diagnosed with HIV at least six months before the study, and had mild to moderate depressive symptoms (PHQ-9 score of > 4 and < 20). Eligible patients were also required to speak Dutch or English, have internet access and an email address, and to be available for eight weeks to work on the intervention. We excluded individuals with severe cognitive impairments, severe depressive symptoms (PHQ-9 score ≥ 20), or severe suicidal ideation (score > 1 on the suicide item of the PHQ-9), and those who were receiving treatment from a psychologist or psychiatrist, had been on antidepressants for less than three months, or had changed type or dose of antidepressants in the past three months. The study was approved by the medical ethics committee of Leiden University Medical Center. The study protocol has been published elsewhere (14). All participants provided online informed consent.

Randomization and masking

Participants were randomly assigned (1:1) to the internet-based intervention or the attention-only waiting-list control condition. Randomization was done using random number tables to generate the randomization sequence with block sizes of 12, stratified by treatment center and sex, and concealed from the main researcher. The main researcher allocated participants to conditions, but the characters in the randomization file were white until assignment of a participant was carried out (then the letters on one line in the file were made visible). Participants, researchers, and coaches were not masked to the participant's assigned treatment condition.

Procedures

Medical data (e.g., viral load) were obtained from the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort study after obtaining consent from the participant. The ATHENA cohort study is maintained by Stichting HIV Monitoring, which is supported by the Dutch Ministry of Health via the National Institute for Public Health and Environment. A self-designed questionnaire, included in the pretest, was used to obtain information about patient demographics.

All participants completed the pretest and were randomly assigned to one of two conditions. Participants in the intervention group did the first post-test after they had completed the intervention (duration six to ten weeks), followed by two further post-tests three and six months after completion of the intervention. Participants in the control group received two post-tests: the first post-test was sent eight weeks after the pretest and the second post-test was sent three months after the first post-test was completed (Appendix 1). Participants who completed all questionnaires received €25. The last post-test was completed on October 14, 2016. All assessments were completed online via a secured website, with the exception of screening with the PHQ-9, which was completed via telephone conversations.

The internet-based self-help intervention consisted of cognitive behavioural therapy. Psychoeducation was alternated with exercises and assignments. The intervention was based on a self-help booklet for people with HIV with depressive symptoms (15), which was extended to include an activation component and minimal coaching with motivational interviewing, and the programme was translated into English to reach more people with HIV. The intervention included four main components covered in eight lessons. The first component was activation, in which participants were encouraged to do pleasant activities. The second component contained relaxation exercises. The third component included assignments to identify and change negative thoughts. The fourth component included goal setting and increasing confidence to attain goals. Participants received login details for the secured website of the intervention. Participants did the intervention for one to two hours per week for a period of around eight weeks, and received telephone coaching.

Participants in the control condition were put on a waiting list and received attention only via telephone calls from a coach. After the second post-test, participants in the control condition were invited to start the intervention. Participants in the control group who started the intervention received one post-test, the results of which are not reported in this paper and will not be reported elsewhere.

All participants received minimal telephone coaching. Participants in the intervention group were called weekly for approximately 15 minutes by a personal coach, who asked the participants how they were doing and how they were progressing 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 (maximum duration ten weeks). After ten weeks, participants could complete the intervention independently and ask questions via email. Participants in the control group were called weekly for around five minutes by a personal coach, for a period of eight weeks. The coach asked participants how they were doing and motivated individuals to stay in the study. Coaches monitored depressive symptoms and suicidal thoughts in both the intervention and control groups and

patients with severe depressive symptoms or suicidal ideation were referred to their general practitioner or HIV treatment center.

All coaches were clinical psychology Masters students or graduates with an MSc in Psychology who had attended several clinical courses during their Masters, in which they learned communication skills and therapeutic strategies. Coaches were trained by the main researcher. During training, coaching procedures and motivational interviewing were explained and practiced. Coaches received a coaching manual with additional information about motivational interviewing, the study, the procedures, and content of coaching (e.g., what to do when depressive symptoms of a participant increase). At the beginning of the study, 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, but coaches and researchers could contact each other directly via telephone or email when needed.

Outcomes

The primary outcome was depressive symptoms, assessed with the PHQ-9 (18) and the Center for Epidemiologic Studies Depression Scale (CES-D; (20)) at pretest (baseline), immediately after the intervention (or eight weeks after baseline in the control group; post-test 1), and at three months after the first post-test. As a secondary outcome, in the intervention group only, we also assessed the PHQ-9 and CES-D scores six months after completion of the intervention. Total scores ranged between 0 and 27 for the PHQ-9 and 0 and 60 for the CES-D, with higher scores indicating increasing symptom severity. The secondary outcomes were anxiety symptoms, assessed with the Generalized Anxiety Disorder-7 (GAD-7) scale (21) (total score 0–21) at all assessment time points, with higher scores indicating increasing symptom severity, and user satisfaction, measured with a self-designed questionnaire at the first post-test. In the intervention group, participants were asked to grade the intervention (0–10; a higher score indicated higher user satisfaction) and whether they would recommend the intervention (yes, maybe, or no). In both groups, participants were also asked to grade the coach (0–10; a higher score indicated higher satisfaction with the coach).

Other secondary outcomes not reported in this paper were physical tension, activation (Behavioral Activation for Depression Scale; (22)), cognitive reappraisal (Emotion Regulation Questionnaire; (23)), cognitive coping (Cognitive Emotion Regulation Questionnaire; (24)), depressive thoughts (Crandell Cognitions Inventory; (25)), behavioral coping (Kraaij & Garnefski, Behavioral Emotion Regulation Questionnaire, unpublished questionnaire), coping self-efficacy (Kraaij & Garnefski, unpublished questionnaire), goal adjustment (Goal Disengagement and Reengagement Scale; (26)), personal growth (Garnefski & Kraaij, unpublished questionnaire), negative life events (Life Events Scale), motivation to start with the intervention, compliance, and dropout and reasons for

dropout. These outcomes were used in moderator and mediator analyses. The results of these outcomes will be reported elsewhere.

There was no data safety monitoring board. Participants were assessed multiple times during the intervention and the study, and the results regarding their symptoms were monitored by the researcher. Additionally, coaches monitored the participants.

Statistical analysis

A power analysis with the program Power Analysis and Sample Size Software (PASS) was performed. On the basis of the randomized controlled trial on the effectiveness of the self-help booklet (15), and an expected dropout of 15% at the first post-test, a sample size of 150 participants was required to detect an effect size of 0.50 with 0.80 power at the 5% significance level. We aimed to include 200 participants because attrition was expected during follow-up (14).

Statistical analysis was done with SPSS software (version 23.0), and a p value of less than 0.05 was considered to indicate statistical significance. Primary and secondary analyses were done by intention to treat.

χ^2 tests and ANOVA were used to investigate differences between participants who dropped out and those who completed the intervention. We did longitudinal multilevel regression analyses (27) using the maximum likelihood estimation method to investigate differences between the groups in changes in depressive and anxiety symptoms from the pretest to the post-tests. Time and group were included as fixed effects and slopes for time and the intercept as random effects. Pretest, post-test 1, and post-test 2 scores were included in the between-group analyses. Pretest and the three post-test scores for the intervention group were included in the within-group analyses to assess the long- term effects of the intervention. The variance components variance–covariance matrix was used for between-group analyses and the heterogeneous autoregressive matrix was used for within-group analyses. Additionally, all outcomes were analysed in the per-protocol sample, which included all randomly assigned participants who completed at least five lessons of the intervention (indicated by self-report); using this minimum ensured that at least three of the four main intervention components were completed. The effect of HIV treatment center on the random intercept was investigated in an exploratory analysis, by adding treatment center as an extra level in the analysis.

Cohen's *d* was calculated to assess effect size. For the between-group effect sizes, the mean difference scores for the control group were subtracted from the mean difference scores for the intervention group and divided by the pooled SD of the raw scores at pretest (28). For the effect size of time (i.e., long-term effect of the intervention), we used the formula unstandardized coefficient (b)/SD (28), using the SD of the raw scores of the intervention group at pretest. Effect sizes were calculated using the estimated values from the longitudinal multilevel regression analyses. The formula

used by de Zeeuw and colleagues (29) was used to calculate the SE of the between-group effect size and 95% CIs.

Clinically significant differences, deterioration, and number needed to treat from pretest to the first post-test were assessed for the PHQ-9 and the CES-D. A reliable change index was calculated for each individual to determine improvement and their pretest score was subtracted from their first post-test score and divided by the SE of difference between the two scores (30). To calculate the SE of difference, test–retest reliability (rxx) was used, where rxx was equal to 0.84 for both the PHQ-9 (18) and the CES-D. Reliable change index scores of less than –1.96 indicated symptom improvement. Recovery was calculated by examining whether a cutoff for depression (score 10 on the PHQ-9 (31) and 22 on the CES-D (32)) was reached at the first post-test. Recovery was only assessed in participants who scored above this cutoff at pretest (clinical cases), because participants who scored below this cutoff at pretest had already reached the criterion (30). For participants who scored above the cutoff at pretest, we assessed both improvement and recovery; in cases of both, the criteria for clinically significant change according to Jacobson and Truax (30) were met. Deterioration was also assessed, whereby a reliable change index score higher than 1.96 indicated deterioration. The number needed to treat was calculated using the percentage of participants who met the criteria for clinically significant change. Clinically significant change, deterioration, and number needed to treat were calculated in the per-protocol analysis sample that also completed the first post-test; the raw data were used.

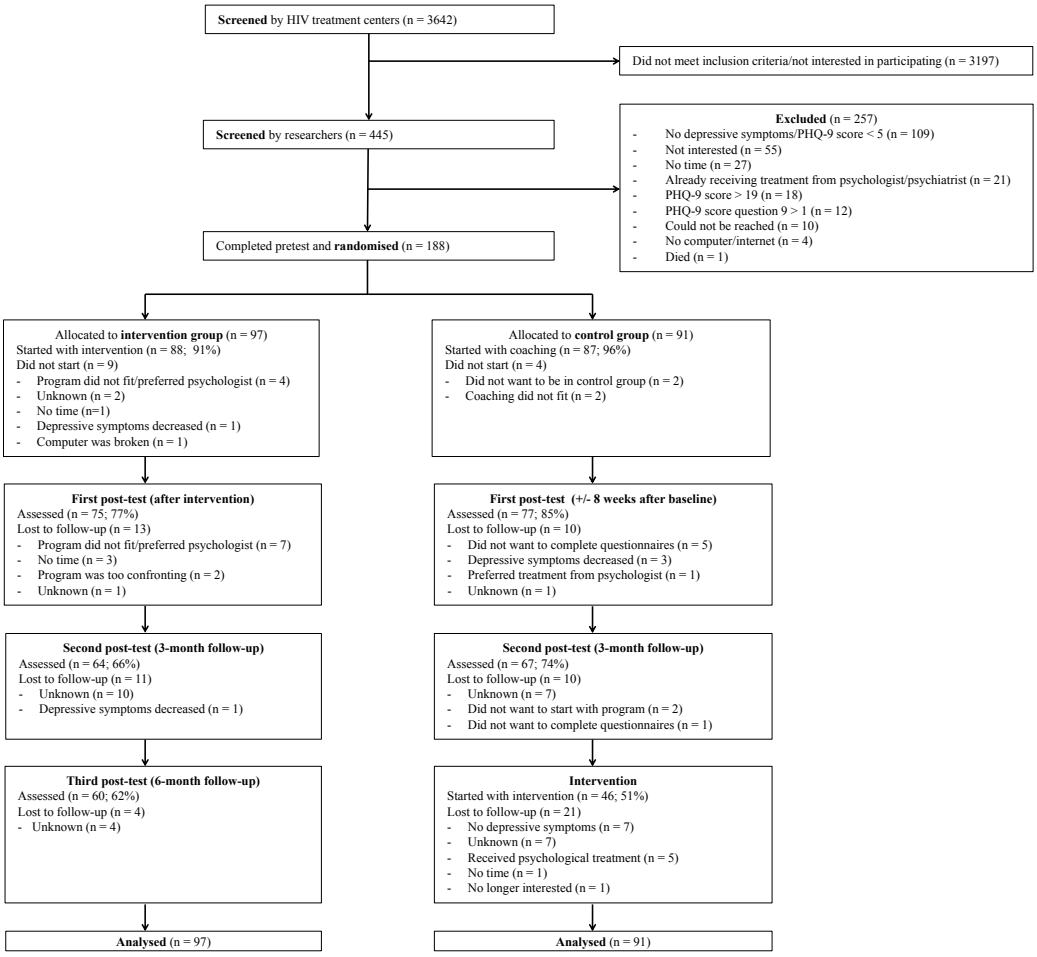


Figure 1. Trial profile

Results

Between February 1, and December 31, 2015, 3642 people with HIV were screened for depressive symptoms in HIV treatment centers, of whom 445 were screened for eligibility. One hundred eighty-eight participants were randomly assigned to the intervention group (n = 97) or the control group (n = 91; Figure 1). Of the 91 participants in the control group, 77 (85%) completed the first post-test and 67 (74%) completed the second post- test. Forty-six (51%) of 91 participants started the intervention after the second post-test. Of the 97 participants in the intervention group, 88 (91%) started the intervention, 75 (77%) completed the first post-test, 64 (66%) completed the second post-test, and 60 (62%) completed the third post-test. All participants in the intervention group who dropped out (i.e., did not complete the first post-test) stopped the intervention before completion of the fifth lesson.

Fourteen participants did not finish the intervention in ten weeks. We identified no significant differences in the proportion of participants who did not complete the first post-test between the two groups. Additionally, no significant differences in the baseline characteristics were identified between participants who completed the first post-test and those who did not.

Most participants were men, homosexual, and educated to a medium or high level, with a mean age of about 46 years (Table 1). Mean time since HIV diagnosis was about 10 years and most participants were on antiretroviral therapy. Participants in the intervention group received a mean of 6.38 telephone calls from the coach compared with a mean of 6.23 telephone calls in the control group, with no significant differences identified between groups ($p = 0.67$). The mean duration of phone calls per participant was significantly higher in the intervention group than the control group (90.74 minutes ($SD = 60.32$) vs 60.52 minutes ($SD = 42.30$); $p < 0.0001$).

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)	45.53 (10.32)	47.12 (10.94)	46.30 (10.63)
Sex			
Male	85 (88%)	81 (89%)	166 (88%)
Female	12 (12%)	10 (11%)	22 (12%)
Nationality			
Dutch	80 (83%)	78 (86%)	158 (84%)
Other	10 (10%)	8 (9%)	18 (10%)
Dutch and other	7 (7%)	5 (5%)	12 (6%)
Education			
Low	20 (21%)	22 (24%)	42 (22%)
Medium	44 (45%)	33 (36%)	77 (41%)
High	33 (34%)	36 (40%)	69 (37%)
Marital status			
Married or cohabiting	41 (42%)	44 (48%)	85 (45%)
Single or living without partner	56 (58%)	47 (52%)	103 (55%)
Sexual orientation			
Heterosexual	19 (20%)	13 (14%)	32 (17%)
Homosexual	73 (75%)	71 (78%)	144 (77%)
Bisexual	5 (5%)	7 (8%)	12 (6%)
Psychotropic medication			
No	85 (88%)	81 (89%)	166 (88%)
Yes	12 (12%)	10 (11%)	22 (12%)
Time since HIV diagnosis (years)[a]	9.35 (6.46)	10.41 (6.70)	9.87 (6.58)
Diagnosis of AIDS			

Characteristic	Intervention group (n = 97)	Control group (n = 91)	Total sample (n = 188)
No	88 (91%)	77 (85%)	165 (88%)
Yes	9 (9%)	14 (15%)	23 (12%)
CD4 count (cells per µl)[b]	726 (290)	647 (280)	690 (287)
Viral load[c]			
Undetectable (< 50 copies per mL)	59 (88%)	59 (86%)	118 (87%)
Detectable (≥ 50 copies per mL)	8 (12%)	10 (14%)	18 (13%)
Antiretroviral therapy			
Yes	94 (97%)	90 (99%)	184 (98%)
No	3 (3%)	1 (1%)	4 (2%)

Data are mean (SD), n (%), or n/N (%). Some percentages do not sum to 100% because of rounding.

[a] available for 187 participants, [b] available for 86 participants, [c] available for 136 participants.

Mean pretest PHQ-9 score was 11.74 (*SD* = 2.49) in the intervention group and 11.11 (2.37) in the control group; at the post-test visits it was 6.73 (3.00) and 6.62 (3.03) in the intervention group and 8.60 (3.12) and 8.06 (3.17) in the control group. Mean pretest CES-D score was 24.91 (5.93) in the intervention group and 22.94 (6.48) in the control group; at the post-test visits it was 13.94 (6.39) and 15.71 (6.39) in the intervention group and 19.09 (7.05) and 18.43 (7.05) in the control group (Appendix 2). A group-by-time interaction effect was identified for the PHQ-9 and CES-D: the reduction in depressive symptoms between pretest and post-test 1 was significantly larger in the intervention group than in the control group (Table 2 and Figure 2). The effect sizes for the differences in scores 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, time had a significant effect on the PHQ-9 and CES-D: depressive symptoms decreased significantly between pretest and post-test 1 in both groups (Table 2). For the GAD-7, the time effect was not significant, but a significant group-by-time interaction effect was identified: the reduction in anxiety symptoms between pretest and post-test 1 was significantly larger in the intervention group than in the control group (*d* = –0.75, 95% CI [–1.05, –0.45]). No time effect or group-by-time interaction effect was identified between post-test 1 and post-test 2 for PHQ-9, CES-D, or GAD-7 (Table 2). The effect sizes for the differences in scores at post-test 2 (corrected for baseline) were smaller than those for the differences in scores at post-test 1 for the PHQ-9 (*d* = –0.46, 95% CI [–0.75, –0.17]), CES-D (–0.47, [–0.76, –0.18]) and the GAD-7 (–0.56, [–0.85, –0.27]).

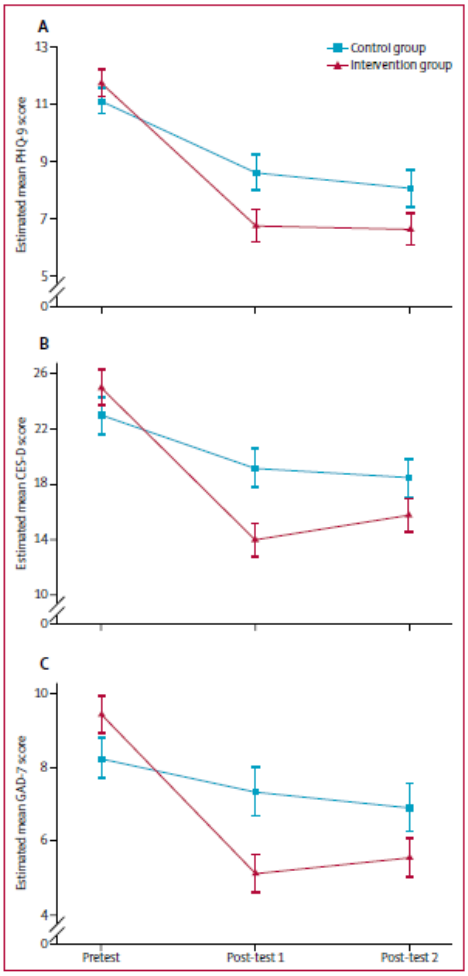


Figure 2. Estimated mean PHQ-9, CES-D, and GAD-7 scores over time in both groups. Error bars show 95% CI.

In the intervention group, time had a significant effect on all outcomes. Depressive and anxiety symptoms decreased from pretest to post-test 1 and remained low at post-tests 2 and 3 (Table 3). No significant time effect was identified from post-test 1 to post-test 2 or from post-test 2 to post-test 3 for PHQ-9, CES-D, and GAD-7. Within- group effect sizes were moderate between the pretest and post-test 1 and around zero between post-test 1 and post-test 2; and between post-test 2 and post-test 3.

In an exploratory analysis, we assessed the effect of HIV treatment center by use of an unconditional means model with three levels. The intraclass correlation was estimated to be

approximately zero in all models, indicating that treatment center had no effect; therefore we did not include it in the analyses. Furthermore, per-protocol analyses confirmed the findings of the intention-to-treat analyses (data not shown).

Table 2. Mixed model analyses comparing the differences in depressive and anxiety symptom scores over time in the intervention and control groups

	Time effect			**Time-by-group effect**		
	b[a] (SE)	**t[b]**	***P***	**b[a] (SE)**	**t[b]**	***p***
Primary outcome measures						
PHQ-9[c]						
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[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
Secondary outcome measure						
GAD-7[e]						
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

[a] *b* = unstandardized coefficient [b] t-test statistic, [c] *PHQ-9* = Patient Health Questionnaire 9, [d] *CES-D* = Center for Epidemiologic Studies Depression Scale, [e] *GAD-7* = Generalized Anxiety Disorder 7.

In the intervention group, significantly more participants improved (reliable change index score less than –1.96) than in the control group ($p = 0.003$ for PHQ-9; $p = 0.001$ for the CES-D; Appendix 3). Sixty-two percent of participants scored above the cutoff on the PHQ-9 at pretest and were considered to be clinically depressed and 55% of participants scored above the cutoff on the CES-D. The proportion of participants who scored above the cutoff at pretest and recovered was significantly higher in the intervention group than in the control group ($p = 0.005$ for PHQ-9; $p = 0.001$ for the CES-D). A higher proportion of participants reached the criteria for clinically significant change (both recovery and improvement) in the intervention group than in the control group on PHQ-9 ($p = 0.005$) and CES-D ($p < 0.0001$; Appendix 3). Deterioration was rare and no significant differences were identified between the groups for the PHQ-9 (χ^2 1.35, $p = 0.25$) or CES-D (χ^2 3.42, $p = 0.06$). The number needed to treat was 3.30 for the PHQ-9 and 2.20 for the CES-D (Appendix 3).

Most participants were satisfied with the intervention (mean overall score 7.34 (*SD* = 1.62); n = 74). Of the 74 patients who graded the intervention at post-test 1, 55 participants (74%) would definitely recommend the intervention to others, 18 (24%) would maybe recommend it, and one (2%)

would not recommend the intervention. The mean score for the coach was 7.62 (*SD* = 1.52; n = 146): 7.92 (*SD* = 1.31) in the intervention group compared with 7.32 (1.66) in the control group (*p* = 0.02). No adverse events were reported.

Table 3. Mixed model analyses investigating the effects of the intervention on short-term and long-term depressive and anxiety symptoms in the intervention group

	b[a] (SE)	t[b]	*P*	Cohen's d (95%CI)
Primary outcome measures				
PHQ-9[c]				
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[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)
Secondary outcome measure				
GAD-7[e]				
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)

[a] *b* = unstandardized coefficient [b] t-test statistic, [c] *PHQ-9* = Patient Health Questionnaire 9, [d] *CES-D* = Center for Epidemiologic Studies Depression Scale, [e] *GAD-7* = Generalized Anxiety Disorder 7.

Discussion

We found that a guided internet-based self-help intervention was effective for decreasing depressive symptoms in people with HIV compared with an attention-only control condition. Significantly more participants in the intervention group than in the control group had a clinically significant reduction in depressive symptoms. Additionally, anxiety symptoms decreased in the intervention group compared with the control group and user satisfaction was high. The results of this study are important, since only four previous studies have investigated the effectiveness of computerised or internet-based interventions for people with HIV, and three (10-12) of those studies found that the intervention had no effect on mood. This is the first randomized controlled trial to show that an internet-based intervention for people with HIV can significantly reduce depressive symptoms. Our results add to previous findings that online interventions for depression could be effective for the general population (7) and for people with a chronic somatic disease (8). In this study, the between-group effect sizes for depressive symptoms on the first post-test were larger than reported in previous research (7, 8).

Furthermore, the long term effect of the intervention on mental health was found to be enduring. The follow-up period in the present study was six months in the intervention group and three months in the control group; thus longer follow-up measurements are necessary.

Depressive symptoms were also reduced in the control group, and participants appreciated the coaching and graded the coaches highly. The weekly telephone contact with coaches might lead to a decrease in depressive symptoms, as reported previously (33). Furthermore, the coach also seemed important in the intervention group. Participants were satisfied with the coaching and this component of the intervention was made feasible because the coaches were Masters students and graduates in clinical psychology. Thus, this method of coaching could be used when implementing the intervention. Additionally, nurses in HIV treatment centers could also be trained to provide the coaching to increase scalability of the intervention.

The current study has important strengths and limitations. This randomized controlled trial was well designed and included a large sample of people with HIV treated at 23 of 26 HIV treatment centers in the Netherlands. Additionally, the intervention was designed specifically for individuals with HIV and was done online, which has advantages compared with face-to-face treatment, such as more people can be reached and stigma might be lessened. Furthermore, the intervention is available in Dutch and English and could be translated into other languages for use in other countries. Both the PHQ-9 and CES-D questionnaires were used to increase the strength of the findings and because they were recommended for people with HIV (34). The results of the PHQ-9 and CES-D questionnaires were comparable, which increases confidence in our results. The primary outcome was analysed in the intention-to-treat population. The number of patients who had not started or had dropped out at the first post-test was high (22 individuals in the intervention group and 14 individuals in the control group), which is a limitation of the study. However, internet-based interventions often have high dropout rates (7, 8). In the current study, no differences in baseline characteristics were identified between participants who dropped out and those who completed the intervention, which indicates that none of the characteristics assessed in this study were associated with dropout and that the results might be generalised. 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. Additionally, participants in the intervention group might have met participants in the control group and shared their experiences. However, since participants lived in various locations across the Netherlands we expect that this would be unlikely. Waiting-list control conditions might inflate the effects of interventions in studies and it is possible that this occurred in the current study. We used an attention-only waiting-list control condition, which is more active than a waiting-list only control and might have reduced the inflation. An additional limitation is that the intervention was developed by the

researchers. Every effort was made to avoid contact with participants after allocation to conditions. We recommend independent replication of this study. Our findings might not be generalizable to all people with HIV in the Netherlands. However, given that almost all HIV treatment centers in the Netherlands participated and there were no baseline differences between patients who dropped out and those who completed the study, the HIV population in our study is representative of the HIV population in the Netherlands (regarding characteristics such as sex, sexual orientation, and education). Study generalizability to non-western, low-income countries deserves further study.

For future research, it is important to investigate moderators and mediators of treatment effect to identify the subgroups for whom this intervention is the most optimal and the mechanisms that make this intervention effective. It would be valuable to investigate the cost-effectiveness of the intervention. Furthermore, the intervention could be implemented and the long-term effectiveness should be studied. HIV is highly prevalent in other parts of the world, such as Africa, and the intervention could be adapted to the local culture of these countries and its effectiveness could be investigated there.

In conclusion, this randomized controlled trial found that the guided internet-based intervention Living positive with HIV might be effective in decreasing depressive symptoms in the short-term and the long-term up to six months. Anxiety was reduced after the intervention, and the intervention and the coach were mostly positively evaluated. This new, online intervention might represent a clinically meaningful enhancement to psychological care for individuals with HIV who have depressive symptoms. Our findings suggest that implementation of the intervention including coaching might be justified in the Netherlands.

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Appendix

Appendix 1. Overview of assessments during the study

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

[a] Not sent to participants in the control group, [b] *PHQ-2* = Patient Health Questionnaire-2, [c] *HADS* = Hospital Anxiety and Depression Scale, [d] *PHQ-9* = Patient Health questionnaire-9, [e] *CES-D* = Center of Epidemiologic Studies Depression Scale, [f] *GAD-7* = Generalized Anxiety Disorder-7.

Appendix 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[a]					
	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[b]	7.18	3.45		
CES-D[c]					
	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[b]	16.26	7.22		
GAD-7[d]					
	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[b]	5.69	3.18		

[a] = *PHQ-9* = Patient Health Questionnaire 9, [b] Intervention group only, [c] *CES-D* = Center for Epidemiologic Studies Depression Scale, [d] *GAD-7* = Generalized Anxiety Disorder 7.

Appendix 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[a]	
	PHQ-9[b]	CES-D[c]	PHQ-9	CES-D	PHQ-9	CES-D	PHQ-9	CES-D	PHQ-9	CES-D	PHQ-9	CES-D
Intervention	33/64 (52%)	30/64 (47%)	40/65 (62%)	37/65 (57%)	29/39 (74%)	27/36 (75%)	25/39 (64%)	24/36 (67%)	1/64 (2%)	0/64 (0%)	3.30	2.20
Control	21/77 (27%)	15/77 (19%)	56/91 (62%)	49/91 (54%)	21/47 (45%)	15/41 (37%)	16/47 (34%)	9/41 (22%)	4/77 (5%)	4/77 (5%)		

Clinically significant change, deterioration, and number needed to treat were calculated in the per-protocol analysis sample that also completed the first post-test.

[a] *NNT* = number needed to treat, [b] *PHQ-9* = Patient Health Questionnaire-9, [c] *CES-D* = Center for Epidemiologic Studies Depression Scale.

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Chapter 6

For whom does online self-help work? Moderators of change in guided online self-help for people with HIV and depressive symptoms

Manuscript in revision for publication in AIDS care:

Van Luenen, S., Kraaij, V., Spinhoven, P., Dusseldorp, E. & Garnefski, N. For whom does online self-help work? Moderators of change in guided online self-help for people with HIV and depressive symptoms.

Abstract

Objective: The goal of the study was to investigate moderators of intervention effect of a guided Internet-based self-help intervention for people with HIV and depressive symptoms. This study was part of a randomized controlled trial where the intervention was found to be effective in reducing depressive symptoms compared to an attention-only control group.

Methods: The intervention consisted of guided online cognitive behavioral therapy. Demographic characteristics (e.g. age), HIV characteristics (e.g. duration of HIV), and psychological characteristics (e.g. coping self-efficacy) were investigated as potential moderators of intervention effect.

Results: In 2015, 188 people with HIV and depressive symptoms were included in the study: 97 were randomized to the intervention group and 91 to the control group. One moderator of intervention effect was found: coping self-efficacy. Participants with low coping self-efficacy improved more in the intervention group than in the control group, and participants with high coping self-efficacy improved in both groups.

Conclusions: The results indicate that the intervention may be provided to all people with HIV and depressive symptoms. It may be especially important for people with HIV and low coping self-efficacy to start with the intervention, since they do not improve in the control group with only minimal attention.

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

Keywords: HIV; depression; Internet; cognitive behavioral therapy; moderator; randomized controlled trial.

Introduction

Cognitive behavioral therapy (CBT) is frequently used to treat depressive symptoms in people living with HIV (PLWH). Numerous studies have found that it is an effective therapy for PLWH (1-5). Online treatments may be an alternative to face-to-face CBT, and may be more easily accessible, more cost-effective, and reach more people. A large body of research has found that Internet-based CBT was effective to treat depressive symptoms (6-9). In the last years, we have developed an Internet-based intervention for PLWH with depressive symptoms: Living positive with HIV (10). This CBT intervention was found to be effective in decreasing depressive symptoms in PLWH, compared to a control condition that received attention only (11).

However, we did not examine yet for whom the online intervention is especially effective. It is important to investigate this, as it may inform us which PLWH may benefit most from the treatment and for which PLWH it may be more beneficial to refer them to another treatment (12). Consequently, PLWH may be referred to a treatment that is more likely to decrease their symptoms and this may lead to lower costs, reduced therapy duration, and personalised care. For whom the intervention is most effective can be investigated by examining moderators: factors that influence the effectiveness of treatment (13). For example, it is possible that the intervention works better for men than for women, while in the control condition both men and women do not improve. In this case, sex is the moderator that affects outcome of treatment. Moderators have to be distinguished from general predictors: factors that have an effect on the outcome irrespective of treatment condition (12). A factor can be both moderator and general predictor.

As far as we know, no studies have been conducted in PLWH with depressive symptoms regarding moderators of effects of (online) CBT. Though, moderators of change in face-to-face CBT have been investigated in other patient groups with depression. Marriage, unemployment, and experience of more recent life events predicted superior response to cognitive therapy, compared to antidepressants (14). In a recent meta-analysis, gender was not found to be a moderator of CBT versus pharmacotherapy (15), just as baseline depression severity (16).

There are few studies into moderators of treatment outcome in online CBT for depressive symptoms. One study has found that baseline depression severity was a moderator: for participants with severe depressive symptoms online CBT resulted in a larger improvement than the waiting list control group and for participants with less severe depressive symptoms the differences in improvement between both groups were smaller (17). The same result was found for marital status, where widowed/divorced participants that received online CBT showed the largest improvement (17). Age was also found to be a moderator: for older participants online CBT was more effective, while online interpersonal psychotherapy was more effective for younger participants (18).

The current exploratory study investigated moderators of outcome of the online intervention Living positive with HIV. The first research question of the study was: which factors moderate the effectiveness of the intervention? Since moderators were not previously explored in CBT interventions for PLWH and depressive symptoms, a large selection of moderators was investigated: demographic characteristics (e.g. age), HIV characteristics (e.g. duration of HIV), and psychological characteristics (e.g. coping self-efficacy). The second research question of the study was: which subgroups of participants benefit most from the intervention? To answer this question, interactions between multiple moderators and the treatment variable were examined.

Methods

Participants and procedure

This study is based on a randomized controlled trial (RCT) on the effectiveness of the CBT-based online self-help intervention 'Living positive with HIV'. The methods of the RCT are explained in more detail elsewhere (10). In 2015, nursing consultants and doctors in 23 of 26 HIV treatment centers in the Netherlands screened PLWH during regular consultations on depressive symptoms with the Patient Health Questionnaire-2 (PHQ-2; (19)). When the PHQ-2 score was > zero, patients interested in the study were informed and their contact information was transferred to the researchers. The researchers called the patients and screened them on the inclusion criteria: being HIV positive for > six months, age > 17 years, mastery of Dutch or English language, available for eight weeks, having Internet and an e-mail address, no use of antidepressants or use for > three months and no change of type or dose in the past three months, absence of severe cognitive impairments, not currently treated by psychologist or psychiatrist, mild to moderate depressive symptoms (Patient Health Questionnaire-9 (PHQ-9 (20) score > 4 and < 20), and no severe suicide ideation (score < 2 on question 9 of PHQ-9).

When patients were eligible for the study and agreed to participate, online informed consent was signed. Thereafter, the pretest was completed and participants were randomly allocated to the intervention or control condition. Stratified randomization by treatment center and sex was conducted. Random number tables were used and the randomization sequence was generated by an independent researcher and concealed from the main researcher. There were multiple measurement moments; the pretest, first post-test (approximately eight weeks after pretest), and second post-test (approximately five months after pretest) were used in the current analyses. Participants received €25 when they completed all questionnaires. The study was approved by the medical ethics committee of Leiden University Medical Center (LUMC; nr. P14.091).

Study conditions

Guided online self-help intervention

The online self-help intervention was based on CBT. Four main components were included in the intervention: activation, relaxation, changing negative cognitions, and goal attainment. Participants worked approximately eight weeks on the intervention, one to two hours a week. In addition, they were supported by a personal coach, who called them each week for about 15 minutes until they had finished the intervention (maximum ten weeks). The coach motivated participants to continue with the intervention by using motivational interviewing. Well-being of participants was checked by the coach, as well as progress with the intervention. Coaches were Master students in clinical psychology or graduates with an MSc in psychology. They received a training concerning coaching procedures and they followed a coaching manual. Supervision sessions were arranged with coaches and the researcher in the beginning of the study (later via e-mail and phone).

Control condition

Participants in the control condition were put on a waiting list and received attention only. They were called by a personal coach for about five minutes per week during the first eight weeks of the waiting period. The coach asked how the participant was doing, enhanced motivation to stay in the study, and monitored depressive symptoms. Part of the protocol was to refer the participant to the HIV treatment center or general practitioner when symptoms deteriorated and became severe. Participants gained access to the intervention after post-test 2.

Assessments

All assessments were completed online. Potential moderating variables were measured at pretest and the outcome variable was measured at pretest, post-test 1 and post-test 2. For more information on the assessments, see (10).

Outcome variable

Depressive symptoms in the last two weeks, measured by the PHQ-9 (20), was the outcome variable. Higher scores indicate more depressive symptoms and total scores range from 0 to 27.

Potential moderators

Demographic characteristics

The following questions were asked regarding demographic characteristics: sex, age, education, marital status, and employment status.

HIV characteristics

Regarding HIV characteristics the following questions were asked: physical symptoms in last two weeks, diagnosis of AIDS, use of antiretroviral therapy (ART) known to have depression as side effect based on the *Farmacotherapeutisch Kompas* (Farmacotherapeutic Compass (21)). Data on the duration of HIV of participants was obtained from the Athena/SHM Cohort Study (22) 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).

Psychological characteristics

Treatment for psychological symptoms. Two questions were asked about treatment for psychological symptoms: use of psychotropic medication and treatment for psychological symptoms in last five years.

Depressive symptoms at pretest. The PHQ-9 score at pretest was included as potential moderating variable.

Anxiety symptoms. The Generalized Anxiety Disorder-7 (GAD-7) (23) was used to measure symptoms of anxiety in the last two weeks. Total scores range from 0 to 21 and higher scores represent more anxiety symptoms.

Coping self-efficacy. Self-efficacy to cope with having HIV was measured with an adapted version of the Generalized Self-Efficacy scale, which has good reliability and validity (24). The scale was adjusted for PLWH, Cronbach's α at pretest for the adjusted scale was 0.92. Total scores range from 8 to 40 and higher scores indicate more self-efficacy to cope with having HIV.

Use of alcohol, soft drugs, hard drugs, and sedatives. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (25) was used to measure psychoactive substance use (alcohol, soft drugs, hard drugs, and sedatives/sleeping pills) and related problems. Total scores for each substance range from 0 to 39. For alcohol, a total score of zero to ten indicates that no intervention is needed (i.e. no problematic alcohol use), and a score > ten indicates that an intervention is needed (i.e. problematic alcohol use). For soft drugs, hard drugs, and sedatives, a total score of zero to three indicates that no intervention is needed (i.e. no problematic drug use), and a score higher than three indicates that an intervention is needed (i.e. problematic drug use). The categorical variables with two categories (no intervention needed; intervention needed) were used in the moderator analyses.

Depressive thoughts. The hopelessness subscale of the Crandell Cognitions Inventory (CCI) (26) was used to measure depressive thoughts. Total scores range from 7 to 35 and higher scores reflect more black and white depressive thinking.

Physical tension. Physical tension was measured with a self-designed 10 item questionnaire. Questions were asked regarding difficulty to relax, ways to relax, and symptoms of physical tension. Total scores range from 10 to 30 and higher scores indicate less physical tension.

Behavioral activation. The subscale activation of the Behavioral Activation for Depression Scale (BADS) (27) was used to measure behavioral activation during the past week. Total scores range from 0 to 42 and higher scores reflect higher levels of activation.

Life events. The number of life events that a participant had ever experienced was measured with the Life Events Scale (28). The scale consists of 17 negative life events and it was counted how many life events (e.g. divorce, dead of a loved one) a participant experienced during life.

Statistical analysis

Analyses were conducted in SPSS version 23 and R version 3.2.2. SPSS was used to answer the first research question regarding moderators[1] of intervention effect. In SPSS, longitudinal multilevel moderated regression analyses (LMRA) (31) were conducted. Time, Group, moderators, and interactions were included as fixed effects and slopes for Time and the intercept were included as random effects. Two time contrasts were created: short term (pretest to post-test 1) and long term (pretest to post-test 2). Continuous moderator variables were grand mean centered and moderators were individually included in the model. All two-way and three-way interactions were included in the model. When the interaction Time x Group x Moderator was significant, this indicated a moderator effect. The moderator depressive symptoms at pretest was not included in the SPSS analysis, because it was part of the dependent variable. Maximum likelihood estimation was used to estimate the effects in the model. The variance components covariance structure provided the best fit and was chosen for the analyses. The analysis was intention-to-treat (ITT) and $\alpha = 0.05$ was used for significance testing.

The second research question regarding subgroups of participants that benefit most from the intervention was answered with an analysis in R. It was conducted with the method Qualitative Interaction Trees (QUINT), using the corresponding R-package QUINT (32, 33). The aim of QUINT is to

[1] Moderators are called predictive factors in medicine and general predictors are called prognostic factors (29, 30).

identify three subgroups of participants, based on different combinations of certain participant characteristics at baseline (i.e. moderators). For the first subgroup the intervention is more effective than the control condition, for the second subgroup the control condition is more effective than the intervention, and for the optional third subgroup both conditions are equally effective. The subgroups are to be found by splitting on values of moderators. QUINT has some advantages; multiple moderators can be included in the analysis at the same time, without a priori specifying which moderators interact and which type of interaction (as opposed to linear regression, where interactions are pre-specified and usually only first order interactions, also called two-way interactions, are included). In this way, higher order interactions can be detected, and QUINT may identify subgroups for which the direction of the intervention effect is different. The created subgroups are graphically represented in a binary tree with nodes and leaves that is easy to interpret. The QUINT algorithm starts with all participants in the root node. Then a moderator is searched that has the largest intervention-subgroup interaction. All moderators, possible split points on moderators, and possible assignments of leaves to the subgroups are considered. Then, the node splits into two child nodes (leaves) based on the best combination of moderator, split point, and assignment. Thereafter, the child nodes split again, etc. QUINT uses some criteria to stop the tree building process, e.g. the number of participants in a leaf should be large enough (for more information see (32)). The whole procedure may result in a large and complex tree which also models noise in the data, and may not fit future data. QUINT reduces this overfitting by pruning the tree back to an optimal subtree, using bias-corrected bootstrapping.

In QUINT analyses, type of partitioning criterion was set at effect size criterion, and the minimum absolute value of *d* (effect size) in each of two leaves after the first split (d_{min}) was set at 0.40 (as suggested by (32)). Minimal sample size of a group in a leaf was 10, and number of bootstrap samples was 1000. Two analyses were conducted. First, PHQ-9 pretest minus PHQ-9 post-test 1 was used as outcome variable, and Group and all moderators were included in the formula. Second, PHQ-9 pretest minus PHQ-9 post-test 2 was used as outcome variable, and Group and all moderators were included. The analysis in QUINT was based on participants that completed questionnaires at post-test 1 or post-test 2.

Results

Participants

In HIV treatment centers 3642 PLWH were screened on depressive symptoms, of which 445 were referred to and screened by the researchers. One hundred and eighty eight PLWH participated in the study: 97 in the intervention group and 91 in the control group. The first post-test was completed by 75 participants (77%) in the intervention group and 77 (85%) in the control group and the second post-

test was completed by 64 participants (66%) in the intervention group and 67 (74%) in the control group. A flow chart of participants through the study including reasons for drop-out is available elsewhere (11).

The majority of participants was male, around 46 years, and had HIV for about ten years, see Table 1. The mean PHQ-9 score was 11.44 at pretest, which indicates moderate depressive symptoms.

Table 1. Baseline characteristics of the intervention and control group. Data are provided as M (SD) or n (%).

Characteristic	Intervention group (n = 97)	Control group (n = 91)	Total sample (n = 188)
Sex			
Male	85 (88%)	81 (89%)	166 (88%)
Female	12 (12%)	10 (11%)	22 (12%)
Education			
Low	20 (21%)	22 (24%)	42 (22%)
Medium	44 (45%)	33 (36%)	77 (41%)
High	33 (34%)	36 (40%)	69 (37%)
Marital status			
Married or cohabiting	41 (42%)	44 (48%)	85 (45%)
Single or living without partner	56 (58%)	47 (52%)	103 (55%)
Employment status			
Employed	52 (54%)	43 (47%)	95 (51%)
Not employed	45 (46%)	48 (53%)	93 (49%)
Diagnosis of AIDS			
No	88 (91%)	77 (85%)	165 (88%)
Yes	9 (9%)	14 (15%)	23 (12%)
Use of ART[a] with side effect depression[b]			
Often	45 (48%)	40 (45%)	85 (46%)
Rarely	27 (29%)	29 (32%)	56 (30%)
Never	22 (23%)	21 (23%)	43 (24%)
Use of psychotropic medication			
No	85 (88%)	81 (89%)	166 (88%)
Yes	12 (12%)	10 (11%)	22 (12%)
Treatment of psychological symptoms last 5 years			
No	47 (48%)	41 (45%)	88 (47%)
Yes	50 (52%)	50 (55%)	100 (53%)
Age (years)	45.53 (10.32)	47.12 (10.94)	46.30 (10.63)

Characteristic	Intervention group (n = 97)	Control group (n = 91)	Total sample (n = 188)
Number of physical symptoms last 2 weeks	9.09 (3.57)	9.44 (3.66)	9.26 (3.61)
Time since HIV diagnosis (years) [c]	9.35 (6.46)	10.41 (6.70)	9.87 (6.58)
Depressive symptoms (PHQ-9[d])	11.74 (4.74)	11.11 (4.22)	11.44 (4.50)
Anxiety symptoms (GAD-7[e])	9.44 (4.72)	8.24 (4.41)	8.86 (4.60)
Coping self-efficacy	28.63 (6.38)	28.75 (6.02)	28.69 (6.20)
Alcohol use (ASSIST[f]) [g]	10.29 (8.83)	7.11 (6.74)	8.75 (8.02)
Soft drugs use (ASSIST[f]) [h]	7.73 (9.19)	6.27 (6.80)	7.00 (8.09)
Hard drugs use (ASSIST[f]) [i]	8.06 (8.70)	7.96 (9.16)	8.01 (8.87)
Sedatives use (ASSIST[f]) [j]	6.20 (6.75)	8.64 (9.21)	7.38 (8.09)
Depressive thoughts (CCI[k])	15.27 (6.44)	15.09 (6.46)	15.18 (6.43)
Physical tension	21.14 (3.64)	21.58 (3.77)	21.36 (3.70)
Behavioral activation (BADS[l])	18.88 (8.93)	17.90 (8.15)	18.40 (8.55)
Number of life events	5.66 (3.32)	5.18 (3.42)	5.43 (3.37)

[a] ART = antiretroviral therapy, [b] = based on 184 participants that use ART, [c] = available for 187 participants, [d] PHQ-9 = Patient Health Questionnaire-9, [e] GAD-7 = Generalized Anxiety Disorder-7, [f] ASSIST = Alcohol, Smoking and Substance Involvement Screening Test, [g] = based on 169 participants that ever used alcohol, [h] = based on 120 participants that ever used soft drugs; [i] = based on 98 participants that ever used hard drugs; [j] = based on 97 participants that ever used sedatives, [k] CCI = Crandell Cognitions Inventory, [l] BADS = Behavioral Activation for Depression Scale.

Moderators of intervention effect: results of multilevel moderated regression analyses

Coping self-efficacy was found to be a significant moderator on the short term. Figure 1 displays the moderator effect, with coping self-efficacy based on a median split (i.e. value of 29) for illustrative purposes. The graph shows that participants in the intervention group improved, regardless of level of coping self-efficacy. However, in the control group, participants improved less when they have low coping self-efficacy, compared to high coping self-efficacy. In other words, participants with low coping self-efficacy seem to benefit more in the intervention group than in the control group. No other significant moderators were found, see Table 2.

In addition, to obtain more insight in the influence of coping self-efficacy on the development of depressive symptoms over time, we also inspected whether coping self-efficacy was a general predictor (Time x coping self-efficacy effect). It was not found to be a general predictor on the short term (b = -0.07, t = -1.15, p = 0.25) and on the long term (b = -0.07, t = -1.00, p = 0.32).

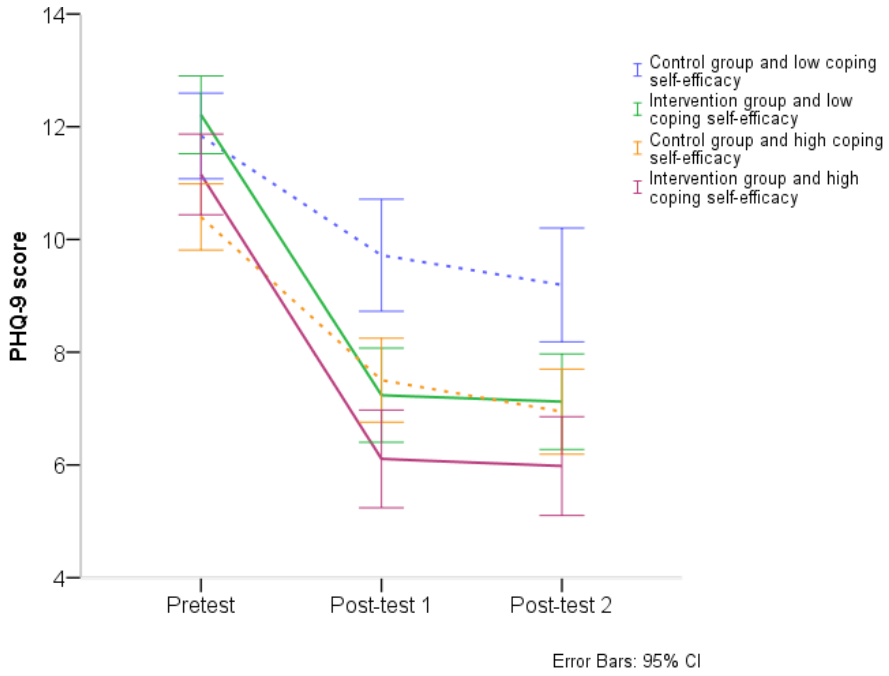


Figure 1. Coping self-efficacy as moderator of intervention effect.

Interactions between moderators: results of QUINT analyses

The results of the QUINT analyses show that no higher order interactions (e.g. three-way or four-way) between moderators and the treatment variable were present. The final pruned tree had two leaves and was split on the variable coping self-efficacy. The results indicate that participants with low/average coping self-efficacy (≤ 33.5) showed larger reductions in PHQ-9 score from pretest to post-test 1 in the intervention group than in the control group (d = 0.68, 95% CI [0.31, 1.05]). Furthermore, for participants with high coping self-efficacy (> 33.5), there were no differences between groups (d = -0.40, 95% CI [-1.28, 0.48]). The analysis with the change score from pretest to post-test 2 as outcome variable yielded the same results.

Table 2.

Results of LMRA[a] investigating Time x Group x Moderator effects of an Internet-based intervention for PLWH[b] to improve depressive symptoms

Moderator	Short term effect				Long term effect			
	b	*t*	*p*	95% CI	b	*t*	*p*	95% CI
Sex	-2.43	-1.07	0.29	-6.90, 2.04	1.38	0.56	0.57	-3.44, 6.20
Education[c]	-2.67	-1.31	0.19	-6.68, 1.34	0.08	0.04	0.97	-4.29, 4.45
Marital status	-2.33	-1.52	0.13	-5.35, 0.68	-1.60	-0.98	0.33	-4.84, 1.63
Employment status	-0.17	-0.11	0.91	-3.18, 2.85	2.11	1.30	0.20	-1.09, 5.31
Diagnosis of AIDS	-0.95	-0.40	0.69	-5.64, 3.74	-1.63	-0.65	0.52	-6.61, 3.36
Use of ART[d] with side effect depression[e]	-1.21	-0.62	0.54	-5.07, 2.66	-3.10	-1.50	0.14	-7.18, 0.98
Use of psychotropic medication	-1.35	-0.57	0.57	-6.03, 3.33	-2.08	-0.81	0.42	-7.13, 2.98
Treatment psychological symptoms last 5 years	-2.41	-1.58	0.12	-5.41, 0.59	-2.35	-1.43	0.16	-5.59, 0.90
Age	-0.04	-0.54	0.59	-0.19, 0.11	-0.003	-0.04	0.97	-0.16, 0.16
Number of physical symptoms last 2 weeks	0.29	1.38	0.17	-0.13, 0.71	0.21	0.90	0.37	-0.25, 0.68
Time since HIV diagnosis	0.01	0.09	0.93	-0.23, 0.25	-0.23	-1.83	0.07	-0.47, 0.02
Anxiety symptoms (GAD-7[f])	-0.19	-1.14	0.26	-0.52, 0.14	-0.27	-1.48	0.14	-0.63, 0.09
Coping self-efficacy	0.28	2.26	0.03[g]	0.04, 0.53	0.26	1.95	0.05	-0.004, 0.53
Alcohol use (ASSIST[h])	-2.33	-1.30	0.20	-5.86, 1.20	-0.54	-0.28	0.78	-4.35, 3.27
Soft drugs use (ASSIST[h])	0.08	0.05	0.96	-3.16, 3.32	0.68	0.38	0.70	-2.86, 4.23
Hard drugs use (ASSIST[h])	-0.16	-0.09	0.93	-3.66, 3.34	0.08	0.04	0.97	-3.75, 3.92
Sedatives use (ASSSIT[h])	-1.84	-1.11	0.27	-5.12, 1.44	-0.75	-0.41	0.68	-4.33, 2.83
Depressive thoughts (CCI[i])	-0.11	-0.93	0.35	-0.34, 0.12	-0.08	-0.64	0.52	-0.34, 0.17

Moderator	Short term effect				Long term effect			
	b	*t*	*p*	95% CI	b	*t*	*p*	95% CI
Physical tension	0.11	0.55	0.59	-0.29, 0.51	-0.07	-0.34	0.73	-0.49, 0.34
Behavioral activation (BADS[i])	0.09	0.97	0.33	-0.09, 0.28	-0.10	-1.02	0.31	-0.30, 0.09
Number of life events	0.002	0.01	0.99	-0.45, 0.45	-0.10	-0.43	0.67	-0.58, 0.37

[a] LMRA = longitudinal multilevel regression analyses, [b] PLWH = people living with HIV, [c] Comparison between low and high education; comparison with medium education provided the same results, [d] ART = antiretroviral therapy, [e] comparison between often and never depression as a side effect of the ART that was used; comparison with sometimes depression as a side effect provided the same results, [f] GAD-7 = Generalized Anxiety Disorder-7, [g] $p < 0.05$, [h] ASSIST = Alcohol, Smoking and Substance Involvement Screening Test, [i] CCI = Crandell Cognitions Inventory, [j] BADS = Behavioral Activation for Depression Scale.

Discussion

The first aim of this study was to investigate moderators of intervention effect of an online CBT intervention for PLWH with depressive symptoms. It has been found previously that this intervention may be effective in decreasing depressive symptoms among PLWH, compared to a control condition that received minimal attention (11). One moderator of intervention effect was found in the current study: coping self-efficacy. Participants with high coping self-efficacy improved on average in both groups, and participants with low coping self-efficacy improved more in the intervention group than in the control group. These results indicate that especially for PLWH with low coping self-efficacy it is important to start with this intervention to decrease their depressive symptoms. The second aim of this study was to investigate which subgroups of participants benefit most from the intervention by examining higher order interactions between moderators and treatment group, and none were found. As coping self-efficacy was found to be a moderator in this analysis, the two analyses yielded similar results.

This study shows that no moderators of intervention effect other than coping self-efficacy were found. The study was conducted to find factors that influence the effect of the intervention, to find out who benefits the most (12). Subgroups of participants that would not benefit from the intervention or would be harmed by the intervention, could be referred to other treatments in the future. Since we only found one moderator of intervention effect and based on the value of this moderator the treatment effect only differed in strength and not in sign, it can be concluded that the intervention could be beneficial for all participants, irrespective of certain demographic characteristics, HIV characteristics, or psychological characteristics. This knowledge is relevant for implementation; the intervention can be offered to all PLWH with mild to moderate depressive symptoms.

Previous studies did not investigate (coping) self-efficacy as moderator, but it has been investigated as general predictor of outcome of CBT for people with depression in three uncontrolled studies (34-36). Two studies have found that self-efficacy is not a general predictor of outcome (34, 35). However, another study has found that coping self-efficacy is a general predictor of outcome of face-to-face and telephone CBT for depression: participants with moderate or high coping self-efficacy were more likely to improve than participants with low coping self-efficacy (36). The current study investigated coping self-efficacy as moderator and general predictor and found that it was a moderator, but not a general predictor.

Some limitations of the study have to be mentioned. This was an exploratory post hoc analysis, so findings need to be interpreted with caution and replicated in future studies. Many possible moderators were investigated in SPSS, which is a strength, but the disadvantage is that some moderators may be found which may not all be ‘real’ moderators (type I error). However, the analysis

was exploratory and an additional analysis was conducted in QUINT where all moderators were included in one model. Furthermore, the analysis in SPSS was ITT, but the analysis in QUINT was with participants that completed questionnaires at the post-tests and there was some drop-out. Yet the results of both analyses support each other. In addition, there was no follow-up more than three months in the current study. It is possible that moderator effects will be evident on the long term, this needs to be investigated in future research.

To conclude, this study found one factor that influenced the effectiveness of the intervention: coping self-efficacy. PLWH with high coping self-efficacy improved in both groups, and PLWH with low coping self-efficacy improved more in the intervention group than in the control group. This indicates that it may be particularly important to provide the intervention to PLWH with low coping self-efficacy, as they do not improve with minimal attention only. When these findings are confirmed in future studies, it may be recommended to screen PLWH with depressive symptoms on coping self-efficacy before referral to an intervention. The results suggest that the intervention may be provided to all PLWH with mild to moderate 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.

Manuscript in revision for publication in Journal of Medical Internet Research Mental Health:
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.

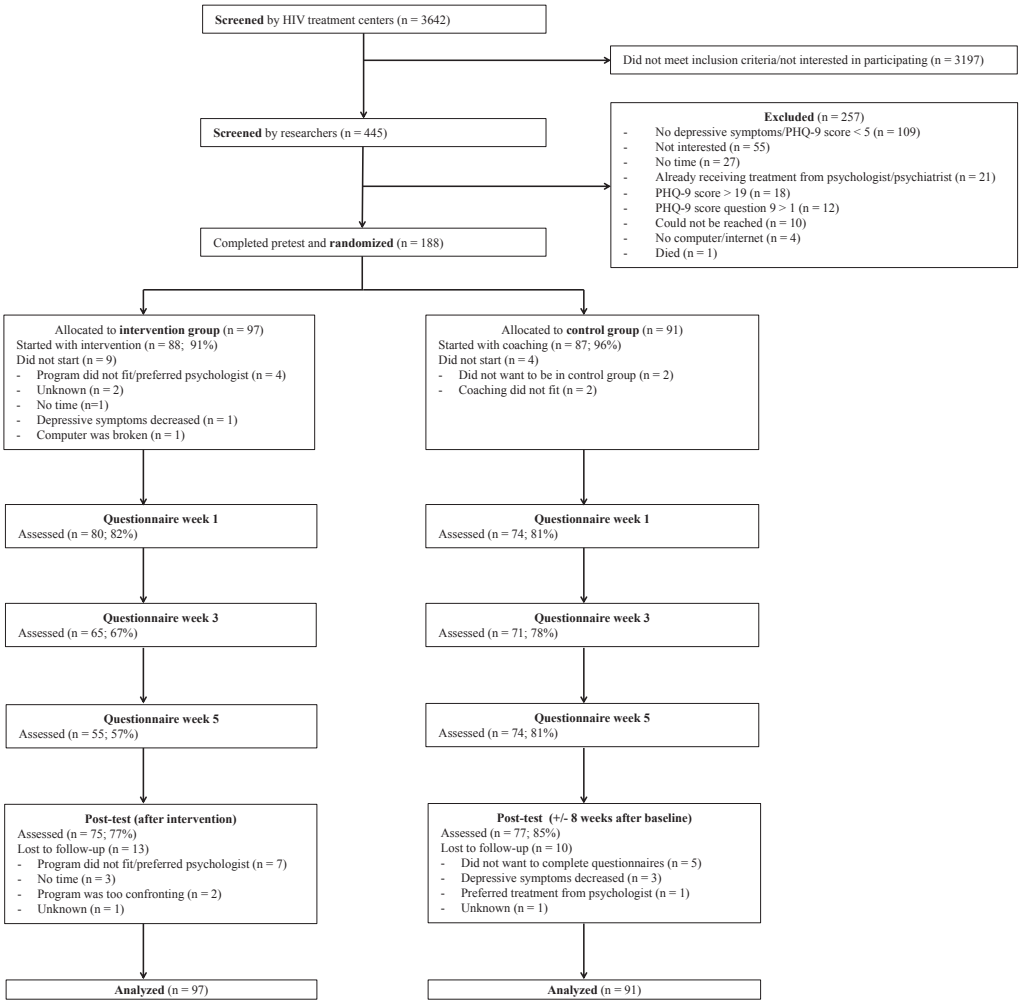


Figure 1. Flow of participants through the study.

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.

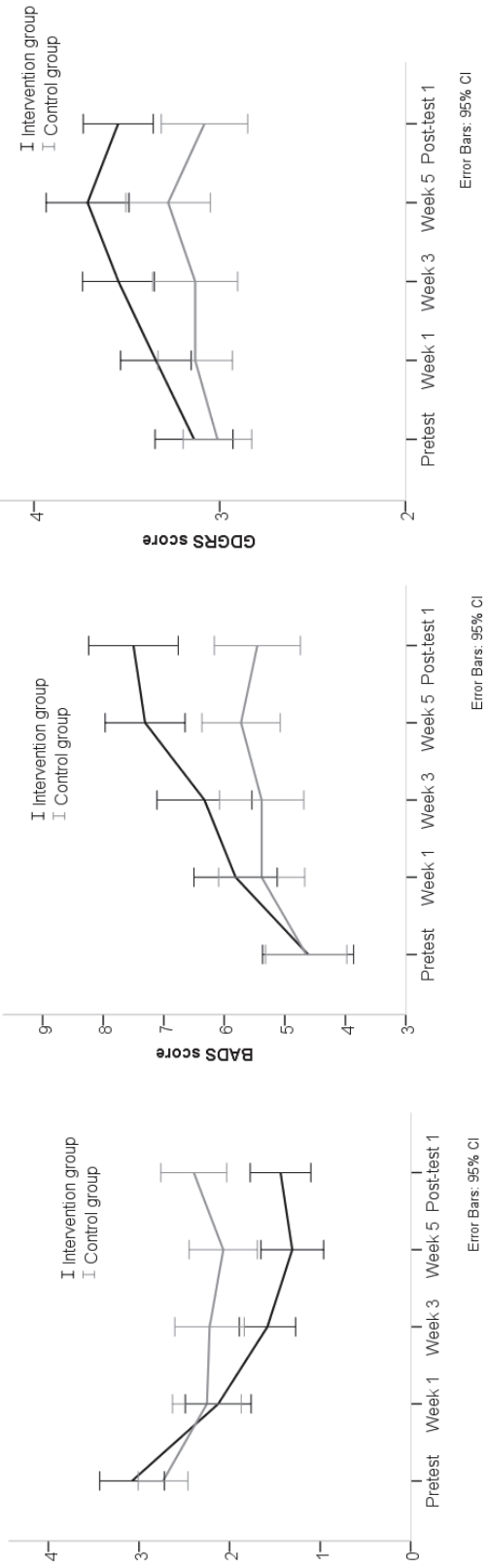


Figure 2. Course of the mean PHQ-2 score, BADS score, and GDGRS score over time for both groups.

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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Chapter 8

Cost-utility of a guided Internet-based intervention in comparison with attention only for people with HIV and depressive symptoms: A randomized controlled trial.

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Abstract

Objective: The aim of this study was to evaluate the cost-utility of a guided Internet-based intervention for people living with HIV and depressive symptoms, compared to attention only (control condition). It was previously found that the intervention was effective in decreasing depressive symptoms, compared to the control group.

Methods: This economic evaluation was conducted alongside a randomized controlled trial. The control group received attention only and was put on a waiting list. Quality adjusted life years were calculated over six months. The study was conducted from a societal perspective and included intervention costs, healthcare costs, and non-healthcare costs. Participants completed a pretest, a post-test after two to three months, and a second post-test after six months. Cost-utility acceptability curves were constructed and two sensitivity analyses were conducted.

Results: No differences between the intervention and the control group were found in quality adjusted life years and total societal costs. The results indicate that the intervention is likely to be cost-effective, compared to attention only. The findings of the sensitivity analyses point in the same direction.

Conclusion: More research with larger samples is necessary to confirm the findings. The outcomes of this study may inform policy makers to decide which interventions will be included in policies. The guided Internet intervention may improve psychological care for people living with HIV and depressive symptoms, against low costs.

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

Keywords: HIV; depression; Internet intervention; cost utility; quality of life; economic evaluation.

Introduction

People living with HIV (PLWH) often suffer from depressive symptoms (1). Next to a negative influence of depressive symptoms on the quality of life of PLWH (2, 3), the symptoms are also associated with high healthcare costs (4-6). These healthcare costs, such as inpatient and outpatient services and use of medication, for PLWH with depression (or other psychiatric diseases) varied a lot between studies, from $17,911 to $33,037 per person per year in the USA between 1995 and 2010 (4-6). In addition to direct healthcare costs, more indirect costs related to losses in productivity from work due to illness may be present. As far as we know, no research is available regarding these indirect costs of PLWH with depressive symptoms. Though, it has been found that the reported annual indirect costs for PLWH, irrespective of depressive symptoms, range from €1,353 per person in 2010 in Italy (7), to €19,786 per person in 2002 in Switzerland (8). For people with depression, irrespective of HIV, the annual indirect costs have been investigated in 2010 in 30 European countries and were found to be €1,782 on average per person (9).

Because of the effect of depressive symptoms on quality of life and the high costs, it is important to treat PLWH. Several psychological interventions were found to be effective in reducing depressive symptoms in PLWH, such as cognitive behavioral therapy (CBT) and mindfulness (10-15). In addition to studying the effectiveness, it is also important to conduct economic evaluations of psychological interventions. Health insurance companies and policy makers are interested in the results of economic evaluations, to decide which interventions will be reimbursed and included in health care policies. Economic evaluations of psychological interventions for PLWH with depressive symptoms are scarce. One study found that collaborative care, including education, activation, and self-management, for depression in PLWH was likely to be cost-effective compared to usual care (16).

Internet-based interventions are used more and more often for people with depressive symptoms. Previous meta-analyses have found that Internet-based interventions are effective to treat depressive symptoms (17-19), also in people with a chronic somatic disease (20). Mixed results were found in previous studies regarding the cost-effectiveness of Internet-based interventions for depression, compared to different conditions. Two systematic reviews have found that guided Internet-based interventions for depression are likely to be cost-effective when compared to wait-list, treatment as usual, attention only, and unguided Internet-based CBT (21, 22). However, the results of an individual-participant data meta-analysis suggested that guided Internet interventions for depression were not cost-effective compared to care as usual, psychoeducation, or wait-list (23). Only a few studies were included in these reviews and meta-analysis, since many RCTs only investigated the effectiveness of Internet interventions, and not their cost-effectiveness. Therefore, more economic evaluations of Internet interventions on depression are needed.

In 2015, we have developed an Internet-based CBT intervention for PLWH with depressive symptoms: Living positive with HIV (24). In a randomized controlled trial (RCT), we have found that the intervention including telephone coaching was effective in reducing depressive symptoms, compared to a control condition that received attention only and was put on a waiting list (25). The aim of the current study was to evaluate the cost-utility of the intervention, compared to attention only. Therefore, an economic evaluation has been conducted alongside the RCT. We expected that effects would be larger in the intervention group compared to the control group. Costs were expected to be lower in the intervention group than in the control group, as intervention costs are low and PLWH in the intervention group will feel better over time, make less use of healthcare services and experience less decreases in productivity at work. The outcomes of this economic evaluation are important for policy makers; when it is found that the intervention is cost-effective compared to attention only, chances are higher that it will be included in health care policies.

Methods

Participants and procedure

This study was part of an RCT with an intervention and a control condition. The methods of this study are explained in detail elsewhere (24). Between February and December 2015, PLWH in 23 of the 26 HIV treatment centers in the Netherlands were screened on depressive symptoms with the Patient Health Questionnaire-2 (PHQ-2) (26) by their nursing consultants and doctors during regular consultations. The PHQ-2 contains the first two questions of the Patient Health Questionnaire-9 (PHQ-9) (27). When patients had a PHQ-2 score > 0 they were informed about the study and referred to the researchers after permission.

Subsequently, the researchers called the patients to inform and screen them on the inclusion criteria of the study: > 17 years old; HIV diagnosis > 6 months; good understanding of Dutch or English; available for eight weeks to work on the intervention; having Internet access and an e-mail address; no severe cognitive impairments; no current treatment from psychologist/psychiatrist; PHQ-9 (27) score > 4 and < 20 (mild to moderate depressive symptoms); PHQ-9 score question nine < 2 (none or few suicidal thoughts); and no use of antidepressants, or use for more than three months without a change in dosage or kind of antidepressants in the past three months. Patients with severe depressive symptoms and/or suicidal thoughts were referred to their general practitioner or nursing consultant/doctor at the HIV treatment center.

When patients were eligible and willing to participate they signed online informed consent. Thereafter, they completed the pretest and were randomly allocated to one of the two conditions. Randomization was stratified by treatment center and gender in blocks of six participants. An

independent researcher used random number tables to create the sequence, which was hidden from the main researcher. When participants were finished with the intervention (maximum ten weeks after the pretest) or after eight weeks in the control group, they received the first post-test. The second post-test was completed three months later. Participants that completed all questionnaires during the study received €25. The study was approved by the medical ethics committee of the Leiden University Medical Center (LUMC; nr. P14.091).

Study conditions

Guided Internet-based intervention

The intervention 'Living positive with HIV' was provided on a secured website. It contains CBT and consists of psychoeducation and exercises. The four main components are activation, relaxation, changing negative cognitions, and goal attainment. The intervention consists of eight lessons, which may be completed in eight weeks, one to two hours per week. In addition, participants received telephone support from a coach of about 15 minutes per week. Participants were asked how they were doing and how they progressed with the intervention. Furthermore, coaches motivated the participant to continue with the intervention by using motivational interviewing. Coaching was provided until participants completed the intervention, with a maximum of ten weeks. Coaches were Master students in clinical psychology or graduates with a Master's degree in psychology. They were trained to provide the coaching and they followed a manual with guidelines. In the beginning of the study, supervision sessions with coaches and the main researcher were arranged (later individual supervision via e-mail and phone).

Control condition

Participants in the control condition received attention only from a coach and were put on a waiting list. The coach called them for about five minutes per week during the first eight weeks of the waiting period. The well-being of participants was checked and they were motivated to continue with the study. When depressive symptoms worsened and became severe, participants were referred to their general practitioner or HIV treatment center. A couple of participants (see Table 1) started with psychological treatment before the first post-test was completed, e.g. treatment from a psychologist or psychiatrist. Participants were invited to start with the intervention after the second post-test. This control condition was different from standard care. PLWH with depressive symptoms in the Netherlands are often treated by a psychologist, psychiatrist, or general practitioner. In addition, mild to moderate depressive symptoms are not always recognized and treated in PLWH. Thus it could also be argued that standard care may be that they would not have received any treatment.

Assessments

All assessments were completed online.

Quality of life

The research question regarding the cost-utility analysis was added in a later stage of the study. Therefore, the PHQ-9 was used to indirectly measure quality of life as it was already included in the assessments to measure depressive symptoms. The PHQ-9 consists of nine items that are scored on a scale from zero to three, and higher scores indicate more depressive symptoms. Psychometric properties of the PHQ-9 are adequate (28). PHQ-9 scores were converted to Short-Form Six-Dimension (SF-6D) utilities (29), using a mapping algorithm. Mapping algorithms transform outcomes of disease specific measures into health-related quality of life utilities. Item specific weightings from the PHQ-9 mapping table of Brazier et al. (2014) (29), were used to convert PHQ-9 item scores to an SF-6D utility. The original PHQ-9 has nine questions and one extra question that is scored differently (If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?). This last question was not included in our assessment. However, to apply the item specific weighting from the PHQ-9 mapping table (29), also the individual score on question ten was needed. Therefore, the mean score of the nine PHQ-9 questions (per participant, per assessment) was used as the score on question ten. Thereafter, the SF-6D utilities were calculated; they range from zero (death) to one (perfect health). With the SF-6D utilities, Quality Adjusted Life Years (QALYs) were calculated over six months with the area-under-the-curve method. Higher QALYs point to more improvement in quality of life. The duration between completing the pretest and the post-tests varied between participants. The mean duration from pretest to post-test 2 was six months, therefore we adjusted all QALYs and costs to a duration of six months.

Costs

The economic evaluation was conducted from a societal perspective and included intervention costs, healthcare costs, and non-healthcare costs (e.g. productivity losses). All costs were adjusted to the year 2017 with the Consumer Price Index (30). The cost-effectiveness of the intervention compared to attention only was not a pre-specified outcome of the RCT. During the study we decided to include this outcome.

Intervention costs

The costs of the intervention consisted of costs for the website, coaching, training, and supervision of coaches. Website costs included costs related to updates, domain, and security. The fixed costs for the development of the website (€13,102) were not included in the analysis. These costs were not included

because they were one-off and they do not play a role when the intervention is further implemented. Coaches received a volunteer fee of €20.13 for the whole trajectory of coaching of one participant in the intervention group, and €12.58 for the whole trajectory of coaching of one participant in the control group. The costs related to training and supervision of coaches included the time investment of the main researcher multiplied by the hourly pay rate of the researcher (€21.00). The total costs for training and supervision were divided by the total number of participants to calculate the costs per participant.

Healthcare costs

Use of healthcare services during the study was measured with the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) (31) at post-test 2. This questionnaire measures the amount of visits to healthcare providers (e.g. general practitioner), day treatments, hospital admissions, and medication use since the start of the study (i.e. period of six months). The use of healthcare services was multiplied by the standard costs of these services, according to Dutch tariffs (32). The reference price for a consultation with the general practitioner was for example €33.41, for a session with a physiotherapist €33.41, and for a hospital outpatient doctor visit €92.14. Medication use (including dosage and amount) was multiplied with medications costs (33).

Non-healthcare costs

Non-healthcare costs are related to being absent from work due to illness (absenteeism), being less productive at work due to mental or physical problems (presenteeism), and the inability to perform unpaid work such as domestic tasks or voluntary work due to mental or physical problems. Absenteeism, presenteeism, and the inability to perform unpaid work since the start of the study (i.e. period of six months) were assessed with the TiC-P at post-test 2. The friction cost method was used to calculate costs associated with absenteeism. This method assumes that after a certain period of time (the friction period; 85 days) the productivity loss due to an absent employee should be resolved. The number of hours that one was absent within the friction period was multiplied by the standard productivity costs per hour, based on gender (€38.37 for males and 31.99 for females) (32). The Osterhaus method was used to calculate costs related to presenteeism (31). The productivity loss due to presenteeism (in hours) was calculated by: number of days with productivity losses * number of hours worked per day * one minus the efficiency on these days ranging from zero (could not do anything) to one (able to do as much as normal). The productivity loss due to presenteeism was multiplied by the standard productivity costs per hour, based on gender (32). To calculate costs related to the inability to perform unpaid work, the number of hours that would be spend by others to take

over the work were multiplied by the standard replacement costs for domestic help (€14.17 per hour) (32).

Statistical analysis

The analyses were based on the intention to treat sample. The pretest was completed by 188 PLWH, which were randomized to the intervention group (n= 97) or control group (n = 91). Seventy-five participants (77%) in the intervention group completed post-test 1 and 64 (66%) completed post-test 2. In the control group, 77 participants (85%) completed post-test 1 and 67 (74%) completed post-test 2. The number of participants that completed the TiC-P questionnaire is smaller (n = 38 in the intervention group and n = 41 in the control group), because this questionnaire was added to the assessment at a later stage. We investigated differences in baseline characteristics between the participants that completed the TiC-P and the participants that did not receive the TiC-P. No differences between the groups were found, except on age. Participants that completed the TiC-P had a mean age of 44.09 (*SD* = 9.73) and participants that did not receive the TiC-P had a mean age of 48.75 (*SD* = 10.21).

Missing data were imputed by conducting multiple imputation by chained equations (MICE) in Stata /IC 14.2. A total of 100 imputed datasets were generated, which were pooled according to Rubin's rules (34) for the analyses. Multiple imputation involves filling in the missing values multiple times, creating multiple "complete" datasets. Missing values are imputed based on the observed values for a given individual and the relations observed in the data for other participants, by including the observed variables in the imputation model. The following variables were used in the model: group (intervention or control), age, gender, time since HIV diagnosis, nationality, marital status, sexual orientation, education, AIDS diagnosis, time between pretest and post-test 1, time between pretest and post-test 2, scores on the Crandell Cognitions Inventory (CCI) (35), scores on generalized Anxiety Disorder-7 (GAD-7) (36) questionnaire, scores on relaxation questionnaire (self-designed), SF-6D utilities, and all cost variables. Questionnaire scores on the pretest, post-test 1 and post-test 2 were used as predictors. To assess values to impute, a series of regression models are run whereby each variable with missing data is modeled conditional upon the other variables in the data. This means that for the participants that did not complete the TiC-P, the relation between TiC-P outcomes and age observed in the data for other participants was taken into account by imputing missing values for the individuals without TiC-P data. In this way, MICE reduces bias due to selectively missing values, without ignoring the uncertainty of the imputation.

The cost-utility of the intervention group compared to the control group was evaluated with bootstrapping. A new intervention is cost-effective compared to an alternative when the extra cost of one extra QALY is less than the decision maker's willingness to pay (WTP) for it (37). In the current

cost-utility analysis the WTP was varied from €0 to €100,000. Using Microsoft Excel, 1000 bootstrap samples were created. The net benefit was calculated for different values of WTP for each sample: net benefit = WTP *Δ QALY – Δ total societal costs (37). When the net benefit is > 0, the intervention is cost-effective compared to the control condition for that sample. Thereafter, a cost-utility acceptability curve was constructed, which displays the probability of the intervention being cost-effective compared to attention only for a range of WTP values, i.e. the proportion of bootstrap samples for which the net benefit > 0. Cost-effectiveness is likely when the probability that the intervention is cost-effective is above 0.5 for a given WTP.

Two sensitivity analyses were conducted to investigate the robustness of the results. The first sensitivity analysis included only healthcare costs and no non-healthcare costs. This analysis was conducted to inform policy makers that are mainly interested in the healthcare perspective, instead of the societal perspective. The second sensitivity analysis included antiretroviral therapy (ART) costs on top of the costs of other medication. We expected no differences in use of ART between groups, as they should use ART during their whole life, but conducted this sensitivity analysis to be sure about this.

Results

Sample characteristics

In HIV treatments centers 3642 PLWH were screened, of which 445 were screened by the researchers. Thereafter, 188 PLWH completed the pretest and were randomized. Figure 1 presents a flow chart of participants during various stages in the study.

The majority of the sample was male (n = 166, 88%), and the mean age was 46.30 years (*SD* = 10.63). Ninety-five participants (51%) were employed and participants had HIV for 9.87 years on average (*SD* = 6.58). A minority of the participants had AIDS (n = 23, 12%), 184 (98%) participants used ART, and 22 (12%) used psychotropic medication. Participants suffered from moderate depressive symptoms at baseline (PHQ-9 score: *M* = 11.44, *SD* = 4.50). More information regarding baseline characteristics of the sample can be found elsewhere (25).

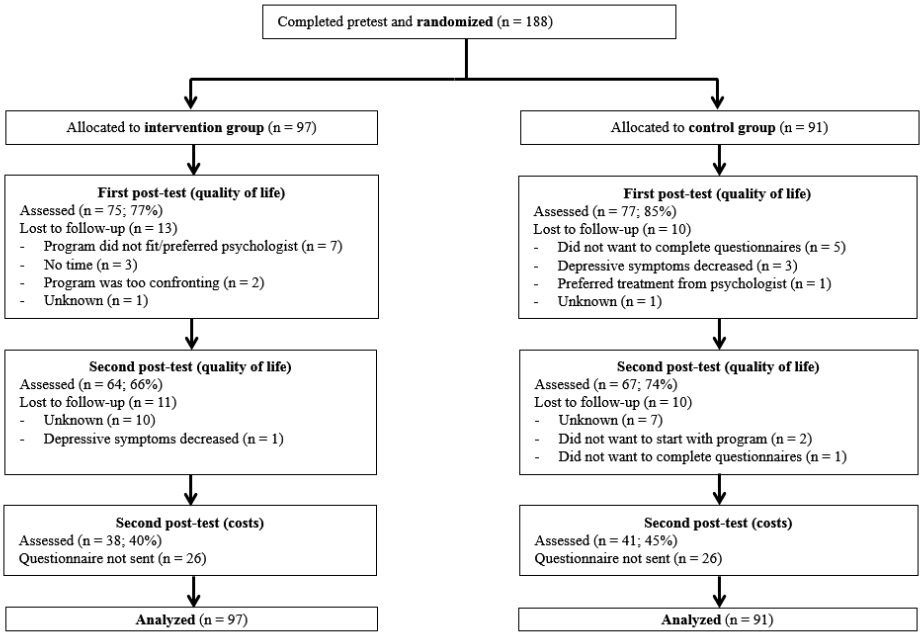


Figure 1. Flow chart of participants in the study.

Quality of life

Figure 2 presents the mean SF-6D utilities over the course of the study. The utilities of the intervention group were significantly higher than the utilities of the control group at post-test 1 (difference: 0.03; 95% CI [0.001, 0.05]). There were no significant differences between groups on the SF-6D utilities at post-test 2. Though, utilities increased from pretest to post-test 2 in both groups. In addition, mean QALYs over the course of the study were 0.34 (SEM = 0.003) in the intervention group and 0.33 (SEM = 0.003) in the control group, with no significant difference between groups (difference: 0.008; 95% CI [-0.0009, 0.018]).

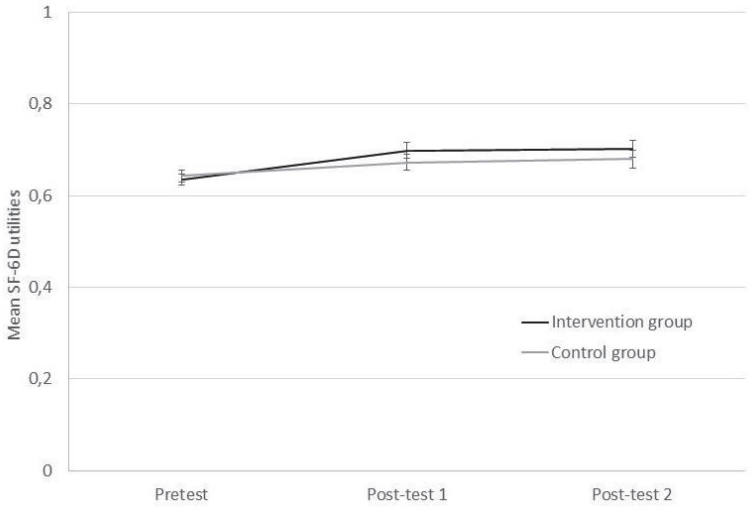


Figure 2. Mean SF-6D utilities over the course of the study in both groups. The data are based on the pooled results of 100 multiple imputed datasets. Error bars: 95% CI.

Costs

Table 1 shows the societal costs, divided into healthcare and non-healthcare costs in both groups. In addition, the number of participants that made use of each item was shown. Except for the costs for the website and the coaching, no significant differences in costs between groups were found.

Cost-utility

Figure 3 presents the cost-utility acceptability curves of the base case analysis and the two sensitivity analyses. The results of the base case analysis indicate that for all values of WTP, the intervention demonstrates a higher probability of being cost-effective, compared to attention only. The cost-utility acceptability curve of the sensitivity analysis with only healthcare costs included shows that for all values of WTP > €5,000, the intervention demonstrates a higher probability to be cost-effective, compared to attention only. Including ART costs in the medication costs, leads to mean additional costs of €2,802 (SEM = 391) in the intervention group and €3,657 (SEM = 442) in the control group, with no significant differences between groups (difference: -856; 95% CI [-2005, 294]). The results of the sensitivity analysis including ART costs indicate that the intervention has a higher probability of being cost-effective for all values of WTP, compared to attention only.

Table 1. Mean healthcare and non-healthcare costs per patient over six months (2017, in €) and the number of participants that made use of each item. The data are based on the pooled results of 100 multiple imputed datasets.

	Intervention group %[a]	Intervention group (n = 97) *M* (*SEM*)	Control group %[a]	Control group (n = 91) *M* (*SEM*)	Difference (95% CI)
Intervention					
Website	100%	3 (0)	-	-	3 (3, 3)[b]
Coaching	100%	20 (0)	100%	13 (0)	8 (8, 8)[b]
Training coaches	100%	3 (0)	100%	3 (0)	0 (0, 0)
Supervision coaches	100%	5 (0)	100%	5 (0)	0 (0, 0)
General practitioner	73%	87 (15)	70%	77 (15)	10 (-30, 49)
Social worker	8%	13 (7)	14%	20 (8)	-7 (-27, 12)
Physiotherapist	20%	62 (23)	18%	62 (24)	-1 (-63, 61)
Ergo therapist	0%	0 (1)	2%	1 (1)	-1 (-3, 2)
Dietitian	0%	0 (0)	2%	1 (1)	-1 (-2, 1)
Homeopath	7%	29 (15)	8%	34 (17)	-5 (-50, 39)
Ambulatory mental health service	6%	22 (13)	3%	6 (6)	17 (-12, 45)
Psychologist / psychiatrist / psychotherapist private practice	16%	78 (30)	13%	75 (37)	3 (-86, 93)
Psychologist / psychiatrist / psychotherapist hospital outpatient department	10%	15 (8)	14%	28 (10)	-13 (-37, 12)
Alcohol and drug rehab clinic	2%	0 (0)	0%	0 (0)	0 (-1, 1)
Self-help group	5%	12 (8)	5%	13 (8)	-2 (-24, 20)
Occupational health doctor	5%	6 (3)	4%	4 (3)	2 (-7, 11)
Domestic help	5%	75 (44)	3%	47 (37)	28 (-80, 135)
Medication[c]	45%	84 (25)	54%	107 (25)	-22 (-91, 46)
Hospital outpatient doctor visit	48%	123 (28)	50%	138 (32)	-15 (-98, 67)
Daycare treatment hospital	5%	29 (17)	5%	26 (17)	3 (-44, 50)

	Intervention group %[a]	Intervention group (n = 97) *M* (*SEM*)	Control group %[a]	Control group (n = 91) *M* (*SEM*)	Difference (95% CI)
Emergency room visit	14%	34 (13)	15%	63 (28)	-28 (-87, 31)
Hospital stay	7%	55 (30)	4%	24 (21)	32 (-37, 100)
Total healthcare costs	**100%**	**757 (103)**	**100%**	**747 (103)**	**11 (-271, 292)**
Absenteeism	15%	250 (123)	15%	362 (159)	-111 (-497, 275)
Presenteeism	23%	519 (264)	31%	907 (377)	-388 (-1229, 452)
Replacement unpaid work	28%	558 (248)	36%	800 (273)	-242 (-931, 446)
Total non-healthcare costs	**52%**	**1327 (394)**	**60%**	**2069 (494)**	**-742 (-1898, 415)**
Total societal costs[d]	**100%**	**2084 (426)**	**100%**	**2815 (517)**	**-731 (-1969, 507)**

[a] percentage of participants that made use of this item; [b] $p < .001$; [c] costs without ART; [d] total societal costs = total healthcare costs + total non-healthcare costs.

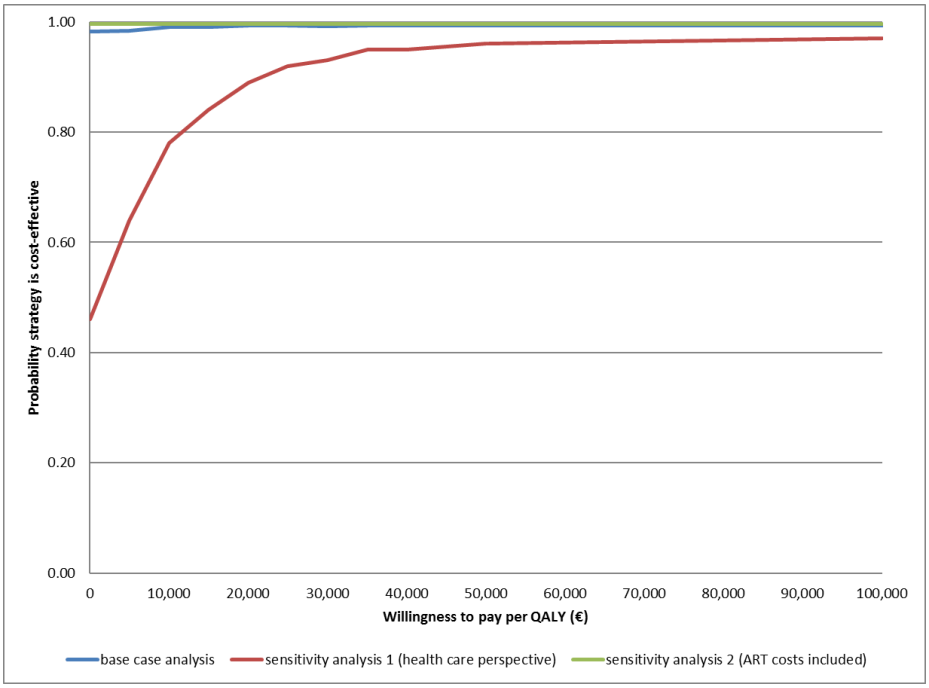


Figure 3. Cost-utility acceptability curves showing the probability that the guided online intervention is cost-effective compared to attention only for different values of willingness to pay.

Discussion

The current study aimed to investigate the cost-utility of a guided online intervention for PLWH with depressive symptoms, compared to attention only. We found no significant difference between groups in QALYs and total societal costs. The results indicate that for all values of WTP, the guided online intervention is likely to be cost-effective compared to attention only. In addition, the results of the two sensitivity analyses point in the same direction.

It has been found previously that collaborative care for PLWH with depressive symptoms was likely to be cost-effective compared to usual care (16). This is in line with our findings. Previous reviews (21, 22) and a meta-analysis (23) found mixed results regarding the cost-effectiveness of Internet interventions for depression, compared to different control conditions. The number of economic evaluations of Internet interventions for depression is small, especially in PLWH with depression. More of these economic evaluations are recommended.

In contrast to expectations, QALYs were not significantly different between groups. QALYs were calculated from the SF-6D utilities, and these were obtained by converting PHQ-9 scores. The SF-

6D is a general measure of quality of life, which also includes e.g. physical functioning. Hence, when PHQ-9 scores are converted into SF-6D utilities, differences between groups on mental health may have been weakened. A difference between groups on the SF-6D (and QALYs) is therefore more difficult to find in evaluating the effect of an intervention specifically targeting mental health. Though, it was previously found that the intervention was effective in decreasing depressive symptoms, compared to the control group (25).

We expected that costs would be higher in the control group than in the intervention group, but we have not found this. Healthcare and non-healthcare costs were not significantly different between groups. It is not clear what the costs would have been when participants would not have received any treatment (no coaching calls and waiting list), because we did not include a no-treatment control group. Furthermore, this study had not enough power to detect differences in costs between groups, because of the wide confidence intervals around the costs. This is the case in many economic evaluations that are conducted alongside clinical trials, because the sample size is too small; the power calculation is based on the clinical outcomes and not on the cost outcomes (38).

This study had some strengths and limitations. An important strength was that we performed an intention to treat analysis, with all participants that were randomized at baseline. Furthermore, the economic evaluation was conducted from a societal perspective and also included non-healthcare costs, in contrast to economic evaluations that only include healthcare costs. Lastly, two sensitivity analyses were conducted and these provided similar results as the main analysis. A first limitation is that there was a lot of missing data, especially on the costs, that needed to be imputed. This is related to the fact that cost-effectiveness was not a pre-specified outcome of the trial. Second, we did not administer the tenth question of the PHQ-9 and therefore the answer to this question was estimated by calculating the mean over the other nine items, before converting PHQ-9 scores into SF-6D utilities. Third, the costs were estimated retrospectively at the second post-test. Participants had to remember their healthcare use and productivity losses during the last six months, which is quite a long period and may have led to recall bias. Last, in the current study the comparison group was an attention only waiting list control condition, instead of usual care. When usual care would be used as comparison group, it may be investigated if the intervention is more cost-effective than usual care. Because of these limitations, the results should be interpreted with caution. Future studies with larger samples can investigate the cost-effectiveness of the intervention, compared to face-to-face interventions (usual care) for PLWH with depressive symptoms. In addition, longer follow-up measurements may be included to study the long term effects and cost-effectiveness of the intervention compared to a control condition.

In conclusion, this study investigated the cost-utility of a guided Internet intervention for PLWH with depressive symptoms, compared to attention only. It was previously found that the intervention

was effective in decreasing depressive symptoms compared to the control group (25). We found no differences between groups in QALYs and total societal costs. However, the results indicate that the intervention is likely to be cost-effective compared to attention only. When future studies find similar results, policy makers may use this information to include the intervention in health care policies. Furthermore, the intervention may be implemented in the healthcare for PLWH with depressive symptoms.

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Chapter 9

Summary and general discussion

As depressive symptoms are frequently reported by people living with HIV (PLWH) (1-3), it is important to treat them adequately. Treatments for depressive symptoms in PLWH include mostly face-to-face Cognitive Behavior Therapy (CBT). eHealth interventions are upcoming in the last years and may have advantages compared to face-to-face interventions. For example, more people may be reached, perceived stigma may be reduced because of the anonymity of eHealth interventions, and the interventions are in general easily accessible. The first aim of this dissertation was to study and summarize the effects of psychosocial interventions for PLWH to improve mental health and antiretroviral therapy (ART) adherence. The second aim was to evaluate the effectiveness of the eHealth intervention 'Living positive with HIV' which was developed for PLWH with depressive symptoms. In addition, moderators and mediators of intervention effect were investigated, as well as the cost-utility of the intervention compared to attention only (control condition).
In this chapter, the results of all chapters are summarized and discussed. Strengths and weaknesses of the studies are addressed, just as implications for clinical practice. The discussion ends with directions for future research and an overall conclusion.

Summary of main findings

Chapter 2 contains a systematic review and meta-analysis of the effectiveness of psychosocial interventions for PLWH to improve mental health. Several characteristics that may influence the effectiveness of interventions were investigated (e.g. treatment provider). Depression, anxiety, quality of life, and psychological well-being were the outcome measures in this study. The meta-analysis included 62 studies. It was found that psychosocial interventions had a small positive effect on the mental health of PLWH. There was evidence for publication bias; the effect size was smaller when it was corrected for publication bias. No differences were found between diverse intervention types, so CBT may for example be as effective as mindfulness in improving mental health. Six characteristics that influenced the effect of the intervention on depression were found. For example, studies that had psychologists as treatment providers had larger effect sizes than studies with other treatment providers. Additionally, larger effects have been found for studies that only included PLWH with depressive symptoms, instead of all PLWH. Previous meta-analyses mostly have found small to moderate effect sizes of psychosocial interventions on the mental health of PLWH (4-6). These differences in effect sizes between this meta-analysis and previous meta-analyses may be explained by the primary focus of the included interventions. Most previous meta-analyses included interventions with a primary focus on improving mental health. This meta-analysis was more broad, and also included interventions that measured mental health outcomes, but did not have mental health as the primary focus of the intervention. As expected, larger effects were found in this meta-analysis for interventions with the primary focus on improving mental health. We can conclude that

psychosocial interventions are of importance for PLWH to improve their mental health, and they should be incorporated in healthcare.

Chapter 3 consists of a systematic review and meta-analysis that aimed to study the effectiveness of psychosocial interventions to improve ART adherence in PLWH. Forty-three RCTs were included in the meta-analysis. The results indicated that psychosocial interventions had a small to moderate positive effect on ART adherence in PLWH. There was no evidence for publication bias. It was found that various intervention types may be effective for various PLWH groups. The results of this study are in line with most previous meta-analyses and reviews, which also found that psychosocial interventions may have a positive effect on medication adherence in PLWH (7-10). Improving medication adherence in PLWH is important, because it promotes their health and the public health, as it decreases transmission risk. Therefore, the use of psychosocial interventions for PLWH with adherence difficulties should be encouraged.

In **Chapter 4** the study protocol for the RCT on the effectiveness of the eHealth intervention 'Living positive with HIV' for PLWH with depressive symptoms was described. The intervention group was compared to a control group that was on a waiting list and received weekly attention only from a coach via telephone. The online CBT intervention was based on a self-help booklet that was found to be effective in previous research. Thereafter, the booklet was adapted and converted into the online intervention which consists of four components: activation, relaxation, changing negative cognitions, and goal attainment. Participants worked on the intervention for approximately eight weeks, one to two hours a week. Participants in the intervention group also received telephone support from a coach for about 15 minutes per week. PLWH with mild to moderate depressive symptoms were included in the study. The RCT included a pretest, three measurements during the intervention/waiting period, and three post-tests. Chapters 5 to 8 report on the results of the RCT.

The effectiveness of the guided eHealth intervention 'Living positive with HIV' was investigated in **Chapter 5**. Participants were 188 PLWH with mild to moderate depressive symptoms, of which 97 were randomly allocated to the intervention group and 91 to the control group. It was found that the intervention was effective in decreasing depressive symptoms on the short and long term, compared to the attention only control group. Furthermore, the intervention was effective in reducing anxiety symptoms, compared to the control group. Significantly more participants in the intervention group reached the criteria for clinically significant change in depressive symptoms than in the control group. Lastly, the intervention and the coach were positively evaluated by the participants. In the past, only four studies (11-14) investigated the effectiveness of computerized/Internet interventions for PLWH

with depressive symptoms, and three were not effective (11-13). The results described in Chapter 5 are comparable to the large body of literature that found that eHealth interventions are effective for people with depressive symptoms (15-20), also for people with a comorbid chronic somatic disease (21). As eHealth interventions have certain advantages compared to face-to-face interventions, and were found to be effective, they may be used more frequently in the future for PLWH with depressive symptoms. It is important to pay attention to specific factors that were found to contribute to the effectiveness of eHealth interventions, such as the addition of guidance (16, 19, 20).

In **Chapter 6** moderators of change of the Internet-based intervention for PLWH with depressive symptoms were examined. Many possible moderators were investigated: demographic characteristics (e.g. gender), HIV characteristics (e.g. duration of having HIV), and psychological characteristics (e.g. baseline anxiety symptoms). One moderator of intervention effect was found: coping self-efficacy. That is, participants with low coping self-efficacy improved more in the intervention group than in the control group, and participants with high coping self-efficacy improved in both groups. The aim of this study was to find out who benefits the most from the intervention. It can be concluded that the intervention may be effective for all PLWH with mild to moderate depressive symptoms, regardless of certain demographic characteristics, HIV characteristics, or psychological characteristics. It may be especially important to treat PLWH with low coping self-efficacy, as they do not improve with only minimal attention. However, some participants did not improve after following the intervention. This was not related to any of the investigated characteristics. Though, it is important to examine in future studies why some participants do not improve and what could be done to address this.

In **Chapter 7** the results of the mediation analysis were presented. The aim was to explore mediating variables that could help to identify mechanisms of change of the intervention 'Living positive with HIV'. Potential mediators that were included in the study were changes in behavioral activation, relaxation, the cognitive coping strategies catastrophizing and positive refocusing, goal reengagement, and coping self-efficacy. It was found that increases in behavioral activation and goal reengagement were significant mediators of intervention effect. The mediation effect occurred probably between week three and five for behavioral activation and between week one and three for goal reengagement. The mediation effect of behavioral activation seemed to be slightly stronger than that of goal reengagement. The mediators that were found in this study may suggest possible mechanisms of change of the intervention. More research is necessary to find these possible mechanisms of change to have an indication of how the intervention works. After these studies have been conducted the intervention may be optimized and may help decrease depressive symptoms among PLWH even more effectively.

Chapter 8 includes a cost-utility analysis of the guided online intervention for PLWH and depressive symptoms, compared to attention only. The outcome quality of life was operationalized as Quality Adjusted Life Years (QALYs) over six months. The economic evaluation was conducted from a societal perspective and included intervention costs, healthcare costs, and non-healthcare costs (e.g. losses in productivity) over six months. Results demonstrated that there were no significant differences in QALYs and healthcare and non-healthcare costs between groups. We found that it is very likely that the online intervention is cost-effective compared to attention only. That is, the intervention is preferred over attention only to decrease depressive symptoms in PLWH. As the sample that completed questionnaires about costs was small, more research regarding the cost-utility of the intervention is needed.

General discussion

The results of our study add to the literature that eHealth interventions may be effective for PLWH with depressive symptoms. These results are in line with previous research, which found that eHealth interventions may decrease depression (15-20). Additionally, previous studies found that eHealth interventions for people with chronic somatic conditions, such as tinnitus, irritable bowel syndrome, chronic pain, and diabetes, may be effective in decreasing depressive symptoms (21). The between-group effect sizes in our study were medium, and mostly larger than reported in previous studies (19, 21). In addition, the results may be meaningful for clinical practice, as many participants in the intervention group showed clinically significant improvement in depressive symptoms, compared to the control group.

Furthermore, it was found that the effects of the intervention were enduring. This is important, since many studies (see also chapter 2 of this dissertation) found positive effects of psychological interventions on the short term, that were not maintained on the long term (4). Hence, longer follow-up measurements are necessary to investigate the effects of the intervention after six months. In addition, long term moderator effects may also be investigated.

Besides an effect on depressive symptoms, participants also showed a reduction in anxiety symptoms after following the intervention. The aim of the intervention was to reduce depressive symptoms, but some components may also have an effect on anxiety symptoms. For example, the assignments where participants identified and changed negative thoughts into more positive thoughts may also be used to change anxious thoughts, which is an effective strategy in CBT for anxiety (22, 23). It was previously found that interventions for depressive symptoms may also enhance quality of life (see also chapter 2 of this dissertation) (6) and medication adherence of PLWH (chapter 3) (8, 24). Consequently, following this intervention may contribute to an improved physical health, next to an improved mental health.

Implementation of the intervention

The results of this thesis show that the online intervention may be effective, so we are ready to implement the intervention in routine care. Implementation of the intervention is important, but there are some challenges. Many effective eHealth interventions for people with mental health problems are not successfully implemented in routine care (25-27). Research regarding the implementation of eHealth interventions is scarce, compared to the many effectiveness trials that have been conducted (27, 28). Barriers in implementation are for example that health care professionals and patients have a lack of experience and confidence in eHealth interventions, and a lack of availability and appropriateness of resources such as personnel and funding to implement and deliver eHealth interventions (29, 30). Since we already have contact with almost all HIV treatment centers in the Netherlands, we will approach them for implementation. Some of the treatment centers already showed interest in implementation and almost all doctors and HIV nursing consultants are enthusiastic about our intervention. We assume that this will facilitate the implementation process.

During implementation, the provider of the coaching is a topic of consideration. In the current study, coaches were Master students and graduates in clinical psychology. Master students and graduates may also be coaches when the intervention is implemented. However, coaching may also be provided by others, e.g. nursing consultants in HIV treatment centers. This may increase the scalability of the intervention. It was previously found that there was no difference in effectiveness between studies with experienced (e.g. psychologists) or less experienced (e.g. students) coaches (18, 31). Though, it is important that the coaches are trained and supervised (32).

Two questions regarding our eHealth intervention that often arise are: 1) is it possible to use this intervention in people with depressive symptoms, but no HIV?; and 2) can PLWH also use a general eHealth CBT intervention for depressive symptoms? When answering these questions, it is important to note that our intervention was specifically designed for PLWH with depressive symptoms. Therefore, many examples are provided in the text and exercises that are related to living with HIV. In addition, we developed our intervention after preparatory studies to investigate the specific needs of PLWH with depressive symptoms and correlates of depressive symptoms in PLWH. Yet, PLWH may also use a general eHealth CBT intervention for depressive symptoms, but our intervention may be more adjusted to their needs and wishes. Regarding the use of this intervention in people without HIV, it is possible to adapt this intervention for use in people with depressive symptoms without HIV. Though, studies are necessary then to investigate the needs of the population and the correlates of depressive symptoms, after which the intervention can be adapted.

Participants in our study were asked to provide feedback on the intervention. Most participants were satisfied with the intervention, but they also had suggestions for improvement. For example, comments that were mentioned sometimes were that the intervention was too much

focused on HIV, that there was too much text, and that the lesson concerning changing negative cognitions into more positive cognitions was difficult. Before implementation, we will adapt the intervention by taking into account these comments. People with low eHealth literacy - that have less abilities to seek, find, and understand digital health information and use this information to solve a health problem (33) - may help us to adapt the intervention and make it suitable for everyone. In addition, at the moment, our intervention is standardized and the same for each participant. In the future, the intervention may be individually tailored to the needs and wishes of participants. For example, some participants already used relaxation exercises. Hence, these participants may skip the lesson concerning relaxation exercises. It was previously found that tailored eHealth interventions for depression may be effective (34, 35).

The importance of coaching

The coaching in our study seemed to be important. The control group was put on a waiting list and received attention only from a coach. Depressive symptoms of participants in the control group improved, as was found in previous studies with attention only control conditions (36, 37). Several participants in the control group of our study valued the contact with the coach, as was also reflected in the high grades for the coaches. The fact that the coach called participants each week, listened to their stories, and kept an eye on them may lead to a decrease in depressive symptoms, as was also suggested by others (38-40). Participants in the intervention group indicated that they valued the support from the coach, it helped them to continue with the intervention, and they evaluated the coach as friendly and caring. In addition, coaches received high satisfaction grades of the participants.

Previous meta-analyses have found that guided eHealth interventions showed larger effects than unguided interventions (16, 19, 20), and resulted in less attrition during the study (19, 31). However, in our study, it was not possible to determine the effectiveness of the intervention and the coaching separately, as they were provided together. To explore this, in future research the effectiveness of the following three active conditions compared to no treatment might be investigated: a condition that receives the eHealth intervention, a condition that receives coaching, and a condition that receives both.

Decreasing drop-out in eHealth interventions

The drop-out rate in our study was 19%. That means that almost one out of five participants did not complete the first post-test, which is comparable to other eHealth interventions (19, 21). In our previous study regarding the effectiveness of an unguided self-help booklet for PLWH with depressive symptoms, there was a drop-out of 40% (41). In the current study, coaching was added to decrease drop-out and this seemed to be effective, as drop-out decreased to 19%. In addition, in the meta-

analysis described in Chapter 2 on the effectiveness of (mostly face-to-face) psychosocial interventions on mental health of PLWH, the average drop-out was 18%. So, drop-out is also a problem in face-to-face interventions. It was previously investigated which barriers may be experienced to continue with an eHealth intervention for people with depressive symptoms and risk factors for cardiovascular disease, and which motivating factors may influence adherence (42). It was found that barriers for persistence were not valuing the intervention as a benefit for self, forgetfulness, increasing distress from following the intervention, and completing the intervention was not experienced as a priority. Some of these factors were also mentioned by participants in our study. The most common reasons for drop-out were preference for face-to-face treatment, intervention did not fit needs, not enough time, intervention was too confronting, and depressive symptoms decreased.

On the other hand, motivating factors that were previously found were perceived benefit for self and/or others, commitment to the researchers, and dependence on reminders (42). Recommendations to improve adherence to eHealth interventions may include optimizing intrinsic motivation and overcoming the barriers mentioned above. This can be done by educating users about the benefits of eHealth interventions in general and this intervention in particular. In addition, habit forming strategies may be imbedded in the intervention, such as planning when to work on the intervention. Reminders can be sent to increase adherence. Last, personal feedback on improvements may also benefit adherence to the intervention (42). Most of these recommendations were included in our study. An important aim of the coaching was to reduce drop-out. Therefore, coaches used motivational interviewing to motivate participants to continue with the intervention. In addition, coaches also discussed the planning of lessons with participants and reminders were sent. Last, coaches gave feedback on improvements during the intervention period. We can conclude that we incorporated many different strategies in our study to decrease drop-out. Still, drop-out cannot be prevented completely and more research is necessary on how to improve adherence to eHealth interventions for people with mental health problems.

What is the best control condition?

In our study we used an attention only waiting list control condition. There is much debate about which control conditions are most suitable in RCTs evaluating psychological interventions (43-46). In no treatment control conditions, participants do not expect to benefit over time and they may start looking for other treatments when they feel they need it. To the contrary, in waiting list control conditions participants wait until they can start with the intervention and in general do not look for other treatments. Therefore, studies with no treatment control conditions may find smaller effect sizes than studies with waiting list control conditions, because some participants in no treatment control conditions start with treatment during the study (45, 46). In our study, participants in the control group

were free to start with treatment, and some also actually did that. Hence, the effect size in our study may be smaller than expected.

All types of control conditions have advantages and disadvantages. It was previously argued that attention control conditions may not be useful in pragmatic behavioral trials, but usual care or another effective intervention may be more appropriate as a comparison condition (43). Attention may be difficult to provide without any content and therapeutic elements, so most of these attention control conditions are actually interventions. These 'attention interventions' may only exist in research and are not generally provided in clinical practice. However, the advantage of an attention control condition is that it may be useful for investigating possible mediators of intervention effect (47). In this way, it is possible to control for non-specific mediators. Studying mediation effects was a major aim of our study. In addition, when one uses an attention control condition, it is important to describe both the intervention and control procedures clearly in a manual, monitor the behavior of the therapists in both conditions, and provide equivalent supervision to the therapists in both conditions. These suggestions were all followed in our study.

Usual care as control condition may also have disadvantages, it may not be adequately described at the start of the study what usual care is, for example (47). As a consequence, it is possible that usual care is provided differently between therapists or institutions. It can be concluded that each control condition has advantages and disadvantages. The choice of which control condition is suitable in an RCT depends among other things on the phase of the trial, the research question, and the available resources (45, 47).

Strengths and limitations

A strength of the meta-analyses in this dissertation is that a high statistical power was obtained, due to a large amount of included studies (62 and 43). Additionally, a variety of psychosocial interventions was included in the meta-analyses, and differences between intervention types were investigated. An important strength of the RCT in this dissertation is that PLWH throughout the Netherlands were included in the study. We had collaborations with almost all HIV treatment centers. Since there may be differences in the HIV population between regions, this large coverage increases the generalizability of the findings. Another strength is that we investigated many different characteristics of the intervention. Next to the effectiveness, also moderators, mediators, and the cost-effectiveness of the intervention have been studied. The moderator analysis indicated that the intervention may be effective for all participants, regardless of specific characteristics. When implementing the intervention, it is useful to know that it may be provided to all PLWH. Additionally, it is valuable that we found two mediators of the intervention effect, behavioral activation and goal reengagement. This may give us more information about possible working mechanisms of the intervention, which should be

investigated further. And from an economical perspective it is important that it is likely that the intervention is cost-effective compared to attention only, which may convince policy makers to include the intervention in health care policies. In addition, the program was available in Dutch and English, which allowed English speaking PLWH to participate in the study. The intervention can now be adapted for use in other countries, because it is already translated. Lastly, we used two outcome measures for depressive symptoms, the PHQ-9 and the CES-D. The intervention was found to be effective on both outcome measures, which increases the strength of our findings.

A limitation of the meta-analysis regarding the effectiveness of psychosocial interventions on mental health is that there was evidence of publication bias. Furthermore, the meta-analysis regarding the effectiveness of psychosocial interventions on medication adherence only investigated short-term effects. A limitation of the RCT is that we did not investigate the long-term effect of the intervention after six months. It is possible that the effect of the intervention on depressive symptoms decreases over time. The meta-analysis in Chapter 2 also found that the effects of psychosocial interventions diminished over time (follow-ups longer than nine months were included). Furthermore, a limitation is that there was a lot of missing data regarding costs, because only at a later stage we decided to study the cost-effectiveness. However, multiple imputation was used to impute missing data and an intent to treat analysis was conducted. In addition, only self-report measures were used in our study. Other measures such as interviews may provide more information about symptoms and the presence of a depressive disorder. On the other hand, interviews are also time consuming and we investigated the effect of the intervention on the severity of depressive symptoms and not on the presence of a depressive disorder. Last, PLWH with severe depressive symptoms and/or suicidal ideation were excluded from this study. In general, people with severe depressive symptoms are offered face-to-face treatment (48, 49). Yet, it was found previously that an online self-help intervention for depression and anxiety was especially effective for patients with high levels of baseline symptoms (50).

Clinical implications

In the meta-analyses in Chapter 2 and 3 we found that psychosocial interventions in general were effective in improving depression, anxiety, quality of life, psychological well-being, and medication adherence. Therefore, it is important that these interventions are incorporated in the healthcare for PLWH to improve their physical and mental health.

The results of this dissertation show that the guided online self-help intervention ‘Living positive with HIV’ was effective in decreasing depressive symptoms. In addition, participants were generally satisfied with the intervention and the coaching. This indicates that the intervention may be implemented in routine mental healthcare in the Netherlands for PLWH with mild to moderate depressive symptoms. With eHealth interventions many PLWH can be reached, also PLWH that may

not use face-to-face interventions. As eHealth interventions seem promising for PLWH with mental health problems and have certain benefits compared to face-to-face interventions, they may be more widely implemented.

A couple of participants indicated that the intervention did not fit their needs completely and that they preferred face-to-face treatment from a psychologist. Furthermore, the intervention was not effective for every participant, some participants showed (almost) no change in depressive symptoms. It is important to pay attention to the preferences of each patient and monitor progress during the intervention. When the personal needs are not completely met or when the intervention does not lead to sufficient progress, other treatment options should be offered (51, 52).

The findings of the moderator analysis indicate that (in theory) the intervention may be effective for all participants. This implicates that the intervention may be provided to all PLWH, regardless of certain demographic characteristics, HIV characteristics, or psychological characteristics. In addition, we found that behavioural activation and goal reengagement may be mediators of the intervention effect. In future research, mechanisms of change of the intervention may be investigated and the intervention may be optimized. Furthermore, we found that it is likely that the intervention was cost-effective compared to attention only. These findings may inform policy makers that decide which interventions will be included in health care policies. As our intervention seems to be effective against low costs, it may be included in health care policies.

Recommendations for future research

As HIV is very prevalent in other parts of the world, such as Africa, it is recommended to adapt the intervention to the local culture of these countries and investigate its effectiveness there (53). At the end of the study participants gave feedback on the intervention and the coaching. The intervention may be adapted according to this feedback. Thereafter, the intervention may be implemented and the effectiveness and the implementation may be investigated. The long-term effect of the intervention may also be studied. Additionally, the cost-effectiveness of the intervention compared to usual care may be examined in a larger sample. Since depressive symptoms may have an influence on adherence to ART and quality of life, it is interesting to investigate the effect of the intervention on these outcomes. Furthermore, the effect of the intervention may be compared to the effect of face-to-face CBT for PLWH.

In addition, more research may be conducted in specific subgroups, such as PLWH with more severe depressive symptoms and/or suicidal ideation. We did not include these patients in our study, but they may be included in a follow-up study with more intensive monitoring or coaching. Also, more studies may be conducted into deterioration after the intervention; which patients are most vulnerable for deterioration and how can it be prevented.

In many HIV treatment centers in the Netherlands PLWH are not screened on mental health problems, so these problems often remain undetected and untreated (54). We recommend to compose and implement a screening instrument for prevalent mental health problems among PLWH such as depressive symptoms, anxiety symptoms, posttraumatic stress symptoms, and substance use (55). When mental health problems are detected, PLWH may be referred to effective interventions. The effect of this screening instrument may be studied in the future.

Last, the role of the coach on the effectiveness of the eHealth intervention and adherence may be investigated. Three conditions may be compared in such a study: the intervention with coaching, the intervention without coaching, and only coaching.

Conclusion

The results of the meta-analyses in this dissertation point to the effectiveness of psychosocial interventions to improve depressive symptoms, anxiety symptoms, quality of life, psychological well-being, and medication adherence. The results of the RCT in this dissertation indicate that the eHealth intervention 'Living positive with HIV' was effective in decreasing depressive symptoms, compared to a control group that received attention only. It was also found that (in theory) the intervention may be effective for all PLWH, regardless of certain baseline characteristics. Especially PLWH with low coping self-efficacy may start with the intervention, as they do not improve with attention only. Furthermore, behavioral activation and goal reengagement were found to be mediators of the intervention effect. Also, the intervention is likely to be cost-effective compared to attention only. As eHealth interventions have certain benefits compared to face-to-face interventions, they may be more widely implemented in the mental healthcare for PLWH.

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Nederlandse samenvatting (Dutch summary)

Publications

Curriculum Vitae

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Nederlandse samenvatting (Dutch summary)

Hoofdstuk 1 is de inleiding van dit proefschrift. Depressieve klachten komen vaak voor bij mensen met hiv en hebben een grote impact op individuen en op de maatschappij. Psychologische interventies voor mensen met hiv en depressieve klachten werden in eerder onderzoek effectief bevonden. Vooral cognitieve gedragstherapie (CGT) blijkt effectief te zijn. Er is echter behoefte aan interventies waar men minder last heeft van stigma, die flexibeler zijn in tijd en plaats om de interventie te volgen, meer mensen kunnen bereiken en goedkoper zijn. eHealth interventies kunnen op deze behoeften inspelen en bleken in eerder onderzoek effectief te zijn bij mensen met depressieve klachten. Er is tot nu toe echter niet veel onderzoek gedaan naar eHealth bij mensen met hiv en depressieve klachten, terwijl dit een groep is die veel baat kan hebben bij eHealth interventies. Daarnaast zijn studies naar moderatoren en mediatoren van het effect van eHealth interventies schaars, evenals economische evaluaties van eHealth interventies.
Een aantal jaren geleden is er een zelfhulpboek ontwikkeld voor mensen met hiv en depressieve klachten. Het zelfhulpboek is onderzocht en bleek effectief te zijn. Vervolgens is er een eHealth interventie ontwikkeld: 'Positief leven met hiv', gebaseerd op het zelfhulpboek. Het doel van dit proefschrift was om de effectiviteit te onderzoeken van 'Positief leven met hiv' op het verminderen van depressieve klachten.

Hoofdstuk 2 bevat een systematische review en meta-analyse van de effectiviteit van psychosociale interventies voor mensen met hiv die als doel hebben om de mentale gezondheid te verbeteren. Verschillende kenmerken die de effectiviteit van interventies kunnen beïnvloeden werden onderzocht (bijvoorbeeld type behandelaar en duur van de interventie). Depressie, angst, kwaliteit van leven en psychisch welbevinden waren de uitkomstmaten in dit onderzoek. De meta-analyse bevatte 62 studies. Het bleek dat psychosociale interventies een klein positief effect hadden op de mentale gezondheid van mensen met hiv. We vonden bewijs voor publicatiebias; het effect was kleiner wanneer hiervoor werd gecorrigeerd. Er werden geen verschillen gevonden tussen diverse typen interventies, CGT kan bijvoorbeeld even effectief zijn als mindfulness bij het verbeteren van de mentale gezondheid. Er werden zes kenmerken gevonden die het effect van de interventie op depressie beïnvloedden. Studies met psychologen als behandelaars vonden bijvoorbeeld grotere effecten dan studies met andere behandelaars. Daarnaast zijn er grotere effecten gevonden in onderzoeken die alleen mensen met hiv en depressieve klachten hebben geïncludeerd, in vergelijking tot studies die alle mensen met hiv includeerden. In eerdere meta-analyses werden meestal kleine tot matig positieve effecten van psychosociale interventies op de mentale gezondheid van mensen met hiv gevonden. Deze verschillen

in effectgroottes tussen deze meta-analyse en eerdere meta-analyses kunnen worden verklaard door de focus van de interventies. De meeste eerdere meta-analyses bevatten interventies met als belangrijkste focus het verbeteren van de mentale gezondheid. Deze meta-analyse was breder en omvatte ook studies met als secundaire uitkomstmaat mentale gezondheid, maar waar het verbeteren van de mentale gezondheid niet het voornaamste doel van de interventie was, maar bijvoorbeeld het verhogen van de therapietrouw. Zoals verwacht werden grotere effecten gevonden in deze meta-analyse voor interventies met als belangrijkste focus het verbeteren van de mentale gezondheid. We kunnen concluderen dat psychosociale interventies van belang zijn voor mensen met hiv om hun mentale gezondheid te verbeteren, en adviseren om ze op te nemen in de gezondheidszorg.

Hoofdstuk 3 bestaat uit een systematische review en meta-analyse gericht op de effectiviteit van psychosociale interventies ter verbetering van de medicatietrouw van antiretrovirale therapie (ART) bij mensen met hiv. In de meta-analyse werden 43 RCT's opgenomen. De resultaten gaven aan dat psychosociale interventies een klein tot matig positief effect hadden op de medicatietrouw van mensen met hiv. Er was geen bewijs voor publicatiebias. Het bleek dat diverse interventietypen (b.v. CGT en sociale steun) effectief kunnen zijn voor diverse groepen mensen (b.v. risicogroep voor problemen met medicatietrouw en groep die al problemen heeft). De resultaten van dit onderzoek zijn in lijn met de meeste eerdere meta-analyses en reviews, die ook hebben aangetoond dat psychosociale interventies een positief effect kunnen hebben op de medicatietrouw van mensen met hiv. Het verbeteren van de medicatietrouw in deze groep is belangrijk, het kan hun gezondheid en de volksgezondheid bevorderen, omdat het transmissierisico vermindert. Daarom moet het gebruik van psychosociale interventies bij mensen met hiv die moeite hebben met medicatietrouw worden aangemoedigd.

In **Hoofdstuk 4** werd het studieprotocol voor de RCT beschreven met betrekking tot de effectiviteit van de eHealth interventie 'Positief leven met hiv'. De interventiegroep wordt vergeleken met een controlegroep die op een wachtlijst staat en wekelijks alleen een kort telefoontje krijgt van een coach. De online CGT interventie is gebaseerd op een zelfhulpboek dat in eerder onderzoek effectief bleek te zijn. Het boek is aangepast en omgezet in de online interventie die bestaat uit vier componenten: activering, ontspanning, het veranderen van negatieve gedachten en het werken aan doelen. Deelnemers werken ongeveer acht weken aan de interventie, één tot twee uur per week. Deelnemers in de interventiegroep krijgen ook ongeveer 15 minuten per week telefonische ondersteuning van een coach. Mensen met hiv en lichte tot matige depressieve klachten worden in het onderzoek geïncludeerd. De RCT omvat een pretest, drie metingen tijdens de interventie / wachtperiode en drie post-tests. Hoofdstukken 5 tot en met 8 rapporteren over de resultaten van de RCT.

De effectiviteit van de begeleide eHealth interventie 'Positief leven met hiv' werd onderzocht in **Hoofdstuk 5**. Deelnemers waren 188 mensen met hiv en lichte tot matige depressieve klachten, waarvan er 97 random werden toegewezen aan de interventiegroep en 91 aan de controlegroep. We vonden dat de interventie effectief was in het verlagen van depressieve klachten op de korte en lange termijn (tot zes maanden na afronding), in vergelijking met de controlegroep die alleen aandacht kreeg. Bovendien was de interventie effectief in het verminderen van angstklachten, vergeleken met de controlegroep. Aanzienlijk meer deelnemers in de interventiegroep bereikten de criteria voor klinisch significante verandering in depressieve klachten dan in de controlegroep. Ten slotte werden de interventie en de coach positief beoordeeld door de deelnemers. In het verleden onderzochten slechts vier studies de effectiviteit van computer / internetinterventies voor mensen met hiv en depressieve klachten en drie ervan waren niet effectief. De beschreven resultaten in hoofdstuk 5 zijn in lijn met de grote hoeveelheid literatuur die aantoonde dat eHealth interventies effectief zijn voor mensen met (een chronische somatische ziekte en) depressieve klachten. Omdat eHealth interventies bepaalde voordelen hebben in vergelijking met face-to-face interventies en effectief bleken te zijn, kunnen ze in de toekomst vaker worden gebruikt voor mensen met hiv en depressieve klachten.

In **Hoofdstuk 6** werden moderatoren van verandering op de online interventie voor mensen met hiv en depressieve klachten onderzocht. Moderatoren zijn factoren die de effectiviteit van een behandeling beïnvloeden. Veel mogelijke moderatoren werden bestudeerd: demografische kenmerken (bijvoorbeeld geslacht), kenmerken gerelateerd aan hiv (bijvoorbeeld tijd sinds hiv diagnose) en psychologische kenmerken (bijvoorbeeld angstklachten). Er is één moderator van interventie effect gevonden: zelfvertrouwen in het omgaan met hiv. De resultaten lieten zien dat deelnemers met weinig vertrouwen in hun coping vaardigheden in de interventiegroep meer verbeterden dan in de controlegroep, en dat deelnemers met veel vertrouwen in hun coping vaardigheden in beide groepen evenveel verbeterden. Het doel van deze studie was om erachter te komen wie het meeste baat heeft bij de interventie. Er kan worden geconcludeerd dat de interventie effectief kan zijn voor alle mensen met hiv met lichte tot matige depressieve klachten, ongeacht bepaalde demografische kenmerken, hiv kenmerken of psychologische kenmerken. Het kan met name belangrijk zijn om mensen met hiv met weinig vertrouwen in hun coping vaardigheden te behandelen, omdat zij over het algemeen niet verbeteren met slechts minimale aandacht. Sommige deelnemers verbeterden echter niet na het volgen van de interventie. Dit was niet gerelateerd aan een van de onderzochte kenmerken. Het is echter belangrijk om in toekomstige studies te onderzoeken waarom sommige deelnemers niet verbeteren en wat er gedaan kan worden om dit aan te pakken.

In **Hoofdstuk 7** werden de resultaten van de mediatie analyse gepresenteerd. Het doel was om variabelen te identificeren die wijzen naar mechanismen van verandering tijdens de interventie 'Positief leven met hiv'. Mogelijke mediatoren die we hebben onderzocht waren componenten van de interventie: veranderingen in gedragsactivering, ontspanning, de cognitieve coping strategieën catastroferen en positieve heroriëntatie, doelen stellen en vertrouwen in eigen coping vaardigheden. Het bleek dat toenames in doelen stellen en gedragsactivering een belangrijke mediator waren voor het interventie effect. Het mediatie effect trad waarschijnlijk op tussen week 1 en 3 voor doelen stellen en tussen week 3 en 5 voor gedragsactivering. Het mediatie effect van gedragsactivering leek iets sterker dan dat van doelen stellen. De mediatoren die in deze studie werden gevonden, kunnen mogelijke mechanismen voor verandering van de interventie suggereren. Meer onderzoek is nodig om deze mogelijke mechanismen van verandering te vinden om een indicatie te krijgen van hoe de interventie werkt. Nadat deze onderzoeken zijn uitgevoerd, kan de interventie worden geoptimaliseerd en kunnen depressieve klachten van mensen met hiv nog beter worden verminderd.

Hoofdstuk 8 bevat een kostenutiliteitsanalyse van de begeleide online interventie voor mensen met hiv en depressieve klachten, in vergelijking met alleen aandacht. Kwaliteit van leven werd gemeten als voor kwaliteit gecorrigeerde levensjaren gedurende zes maanden. De economische evaluatie werd uitgevoerd vanuit een maatschappelijk perspectief en omvatte interventiekosten, medische kosten en niet-medische kosten (bijvoorbeeld productiviteitsverlies) gedurende zes maanden. De resultaten toonden aan dat er geen significante verschillen waren tussen de groepen in voor kwaliteit gecorrigeerde levensjaren en medische en niet-medische kosten. We hebben vastgesteld dat het zeer waarschijnlijk is dat de online interventie kosteneffectief is in vergelijking met alleen aandacht. Dat wil zeggen dat de interventie de voorkeur heeft boven alleen aandacht om depressieve klachten bij mensen met hiv te verminderen. Deze bevindingen kunnen beleidsmakers informeren over welke interventies zouden kunnen worden opgenomen in het zorgaanbod. Omdat onze interventie effectief lijkt te zijn tegen lage kosten, zou deze kunnen worden opgenomen in het zorgaanbod. Aangezien het aantal mensen dat vragenlijsten over de kosten invulde klein was, is meer onderzoek nodig naar de kostenutiliteit van de interventie.

Hoofdstuk 9 is de discussie van dit proefschrift. Hier worden de resultaten samengevat en sterktes en zwaktes van de studies besproken. Tevens worden de klinische implicaties van het proefschrift weergegeven, gevolgd door aanbevelingen voor vervolgonderzoek en een conclusie.

Implementatie van de interventie

De resultaten van dit proefschrift laten zien dat de begeleide online zelfhulpinterventie 'Positief leven met hiv' effectief was in het verminderen van depressieve klachten. Bovendien waren de deelnemers over het algemeen tevreden over de interventie en de coaching. Dit geeft aan dat de interventie kan worden geïmplementeerd in de reguliere geestelijke gezondheidszorg in Nederland voor mensen met hiv met lichte tot matige depressieve klachten. Met eHealth interventies kunnen veel mensen met hiv worden bereikt, ook mensen die geen gebruik maken van face-to-face interventies. eHealth interventies lijken veelbelovend voor mensen met hiv met psychische problemen en hebben bepaalde voordelen in vergelijking met face-to-face interventies, zoals meer flexibiliteit in tijd en plek om de interventie te volgen en lagere kosten. Om die reden kunnen ze op bredere schaal worden geïmplementeerd.

Implementatie van 'Positief leven met hiv' is belangrijk, maar er zijn enkele uitdagingen. Veel effectieve eHealth interventies voor mensen met psychische problemen worden niet succesvol geïmplementeerd in de reguliere zorg. Onderzoek naar de implementatie van eHealth interventies is schaars, vergeleken met de vele effectiviteitsstudies die zijn uitgevoerd. Belemmeringen bij de uitvoering zijn bijvoorbeeld dat zorgprofessionals en patiënten een gebrek aan ervaring en vertrouwen hebben in eHealth interventies en een gebrek aan beschikbaarheid en geschiktheid van middelen zoals personeel en financiering om eHealth interventies te implementeren. Omdat we al contact hebben met bijna alle hiv behandelcentra in Nederland, zullen we ze benaderen voor implementatie. Sommige behandelcentra hebben al belangstelling getoond voor implementatie en bijna alle artsen en hiv consulenten zijn enthousiast over deze interventie. We nemen aan dat dit het implementatieproces zal vergemakkelijken.

Een aantal deelnemers in onze studie gaf aan dat de interventie niet volledig aan hun behoeften voldeed en dat zij de voorkeur gaven aan een face-to-face behandeling door een psycholoog. Bovendien was de interventie niet effectief voor elke deelnemer, sommige deelnemers vertoonden (bijna) geen verandering in depressieve klachten. Het is belangrijk om aandacht te besteden aan de voorkeuren van de patiënt en de voortgang tijdens de interventie te bewaken. Wanneer niet aan de persoonlijke behoefte wordt voldaan of wanneer de interventie niet tot voldoende vooruitgang leidt, moeten andere behandelingen worden aangeboden.

Toekomst

Omdat hiv veel voorkomt in andere delen van de wereld, zoals Afrika, is het aan te bevelen om de interventie aan te passen aan de lokale cultuur van deze landen en daar de effectiviteit te onderzoeken. Verder gaven deelnemers aan het einde van de studie feedback over de interventie en de coaching. De interventie kan aan de hand van deze feedback worden aangepast. Omdat depressieve klachten

invloed kunnen hebben op therapietrouw en kwaliteit van leven, is het interessant om het effect van de interventie op deze uitkomsten te onderzoeken.

Bovendien kan meer onderzoek worden uitgevoerd in specifieke subgroepen, zoals mensen met hiv met ernstige depressieve klachten en/of zelfmoordgedachten. We hebben deze patiënten niet geïncludeerd in onze studie, maar ze kunnen worden geïncludeerd in een vervolgonderzoek met intensievere monitoring of coaching.

In veel hiv behandelcentra in Nederland worden mensen met hiv niet gescreend op psychische problemen, dus deze problemen blijven vaak onopgemerkt en onbehandeld. We raden aan om een screeningsinstrument te ontwikkelen en implementeren voor veelvoorkomende mentale gezondheidsproblemen bij mensen met hiv, zoals depressieve symptomen, angstsymptomen, posttraumatische stresssymptomen en middelengebruik. Wanneer psychische problemen worden ontdekt, kunnen mensen met hiv worden verwezen naar effectieve interventies. Het effect van dit screeningsinstrument kan in de toekomst worden onderzocht.

Ten slotte kan de rol van de coach op de effectiviteit van de eHealth interventie en therapietrouw worden onderzocht. Drie condities kunnen in een dergelijke studie worden vergeleken: de interventie met coaching, de interventie zonder coaching en alleen coaching.

Conclusie

De resultaten van dit proefschrift wijzen erop dat (online) psychologische interventies effectief kunnen zijn voor mensen met hiv en depressieve klachten. De online interventie ‘Positief leven met hiv’ is klaar voor implementatie. Online interventies zijn veelbelovend in de (geestelijke) gezondheidszorg en zouden meer ingezet kunnen worden in de psychologische zorg voor mensen met hiv om ervoor te zorgen dat iedereen de zorg krijgt die hij nodig heeft en bij hem past.

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Curriculum Vitae

Sanne van Luenen was born in Breda on the 19th of August, 1985. She completed secondary education (HAVO) in 2002 at the Ashram College in Alphen aan den Rijn. In 2006, she obtained her Bachelor's degree in Nursing at the University of Applied Sciences in Leiden (Hogeschool Leiden). From 2006 to 2007 Sanne worked as a nurse at Leiden University Medical Center (LUMC). In 2010 she obtained her Bachelor's degree in Psychology at Leiden University. She was a research assistant at the Department of Clinical, Health and Neuropsychology of Leiden University for three months in 2011. She started with the Research Master Clinical and Health Psychology at Leiden University in 2011 and graduated in 2013. From 2007 to 2013 Sanne worked part-time as a nurse at Activite home care and in 2013 she was a research assistant at the Department of Psychiatry of the LUMC for four months. In 2014 she started with her PhD project at the section of Clinical Psychology of Leiden University: "Living positive: eHealth for people with HIV and depressive symptoms". She has also taught several Bachelor and Master Psychology courses during her PhD. She received training and a certificate of the Dutch-Flemish post-graduate school Experimental Psychopathology (EPP) and the Graduate School of Social and Behavioural Sciences of Leiden University. Sanne now works as a postdoctoral researcher at Leiden University (section of Clinical Psychology) and LUMC (department of Public Health and Primary Care). She has started with the implementation of the online intervention that she studied during her PhD and she conducts several eHealth projects.

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