Living positive: eHealth for people with HIV and depressive symptoms

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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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