KU LEUVEN

FACULTY OF MEDICINE

Mapping depression and non-adherence to anti-HIV therapy to uncover common treatment targets

Master Thesis proposed to achieve
the degree of master in medicine by

De Vis EVA

Unit: Clinical and Epidemiological Virology

Department of Microbiology and Immunology

Promotor: Prof. dr. Vandamme ANNE-MIEKE
Mentor: Kiekens ANNELEEN

Leuven, 2018-2019

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Dear Sir/Madam, editor in chief

The challenges in the field of HIV have always been huge. Over 60% of all people living with HIV or AIDS are living in sub-Saharan Africa, a geographical region with poor resources to deal with public health problems. However, as a result of recent advances in access to antiretroviral treatment (ART), important steps towards successful prevention, treatment and support have been taken. But, even before these targets are fully reached we are facing another upcoming threat. Concern is rising about the growing resistance of the virus against first-line drugs. Millions of people risk to lose effective treatment against HIV and the WHO target to reach viral suppression in 90% of treated patients by 2020 will be undermined.

Therefore, action is urgently needed. One of the problems contributing to HIV drug resistance is poor adherence and retention in care of patients receiving ART. Many people living with HIV suffer from mental health problems, like depression, further complicating adherence.

Since previous efforts to improve adherence by treating depression yielded variable results, we took a step back and mapped the determinants of adherence and depression as well as their interconnectivity in HIV-positive patients. This way, we could take into account the interactions shaping the relationship between depression and adherence and make proper recommendations for further research about types of depression treatment having most impact on adherence.

To our knowledge, this kind of review has never been published before. Therefore, I kindly ask you to consider its publication for a broader public.

Sincerely,

Eva De Vis

ABSTRACT

In 2017, approximately 36.9 million people were living with HIV/AIDS, of which more than 60% in sub-Saharan Africa. As a result of the WHO's 'treat all' policy, an increasing number of patients currently receives antiretroviral therapy (ART). Low adherence rates, however, are contributing to the development of HIV drug resistance, which will complicate treatment effectiveness and precede further spread of the virus. Since depression is an important barrier to adherence, we aimed to define possible antidepressant treatment targets simultaneously improving adherence and thus recommended to be subject of further research. We performed two literature searches to visualize determinants of adherence and depression in two separate systems maps. Subsequently, we compared both maps to determine common factors playing a key role in the development of both depression and non-adherence. Afterwards, we examined if these variables could be possible targets of first-line antidepressant treatment. Analysing both maps, we identified 4 possible targets for depression treatment which we suggest to be included in further research. These are addressing stigma, relieving perceived stress, promoting a positive therapeutic alliance and improving cognitive functioning. We believe to provide useful information for further research, since effective interventions to bring about a certain behaviour change can only be developed after considering the underlying mechanisms shaping the behaviour. Nevertheless, the fact that mental health care resources in SSA are poor should be taken into account if one wishes to integrate mental health care into primary care.

SAMENVATTING

In 2017 waren er naar schatting 36,9 miljoen mensen geïnfecteerd met HIV, waarvan ruim 60% in sub-Saharisch Afrika. Meer en meer patiënten krijgen tegenwoordig antiretrovirale therapie (ART), als gevolg van het nieuw ingevoerde beleid van de WHO om iedereen die geïnfecteerd is te behandelen. Slechte therapietrouw echter draagt bij tot het ontstaan van resistentie van het virus tegen de behandeling. Dit zal leiden tot slechtere doeltreffendheid van de medicatie en een verdere verspreiding van het virus. Aangezien depressie bij HIV-patiënten een belangrijke barrière is voor de therapietrouw, was het ons doel aangrijpingspunten voor antidepressieve interventies te bepalen die tegelijkertijd de therapietrouw verbeteren. Deze zijn dan ideale kandidaten om verder onderzoek op te verrichten. We voerden hiervoor 2 literatuurstudies uit om determinanten van therapietrouw en depressie bij HIV-patiënten in kaart te brengen door middel van 2 verschillende 'systems maps'. Door vervolgens beide systemen te vergelijken bepaalden we de belangrijkste factoren die een rol spelen in het ontstaan van zowel depressie als slechte therapietrouw. Vervolgens werd onderzocht of deze factoren ook aangepakt kunnen worden met een bepaald type eerstelijns antidepressieve behandeling. Na analyse van beide systemen konden we 4 interessante aangrijpingspunten voor antidepressieve therapie identificeren: stigma, een positieve therapeutische relatie, ervaringen van stress en cognitief functioneren. We hebben er vertrouwen in relevante informatie aan te brengen voor toekomstig onderzoek, gezien de ontwikkeling van gedragsveranderende interventies enkel tot stand kan komen na rekening te houden met de onderliggende mechanismen die aan de basis van het betreffende gedrag liggen. Desondanks zal men rekening moeten houden met de beperkte beschikbaarheid van middelen voor mentale gezondheidszorg in SSA bij de integratie ervan in de algemene eerstelijns zorg.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS[a]

APR	Adjusted Prevalence Ratio
ART	Antiretroviral Treatment
BMI	Body Mass Index
CBT	Cognitive Behavioural Therapy
CSA	Childhood Sexual Abuse
HIVDR	HIV Drug Resistance
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard Ratio
IPT	Interpersonal Therapy
IPV	Intimate Partner Violence
LMIC	Low- and Middle- Income Countries
MSM	Men having Sex with Men
NK-cell	Natural Killer cell
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NS	Non-significant
OR	Odds Ratio
PLWH	People Living With HIV or AIDS
QOL	Quality Of Life
SNRI	Serotonin-Noradrenalin-reuptake inhibitor
SSRI	Selective Serotonin-reuptake inhibitor
TB	Tuberculosis
TCA	Tricyclic Antidepressiva
VL	Viral Load

[a] Abbreviations both used in the article and in the online systems maps

INTRODUCTION

At the end of 2017, 36.9 million people were suffering from HIV or AIDS worldwide. More than 60% of them is living in sub-Saharan Africa (SSA).[1] The number of people living with HIV or AIDS (PLWH) in SSA receiving antiretroviral therapy (ART) has increased from 758 000 in 2005 to 15.3 million in 2017, which is an estimated 60% of all patients in this region.[2] In 2014, The UNAIDS has set the 90-90-90 targets for 2020, which means by then, 90% of PLWH should know their HIV-status, 90% of those should receive treatment and 90% of those treated should have no detectable virus in their blood anymore. The WHO recommendations of September 2015 to treat all patients diagnosed with HIV, regardless of their CD4 cell-count are fully in support of these goals.

These target values are also expected to decrease HIV drug resistance (HIVDR), as is happening in most developed countries. However, in SSA, simultaneously with this increasing coverage of antiretroviral treatment, the proportion of the virus that has become resistant is growing. *This master's thesis is written within the context of a larger PhD on all the variables contributing to HIVDR in SSA*. This will become a serious problem when the common drugs used as first-line treatment (Tenofovir, Lamivudine and Efavirenz) can no longer be relied on. Eastern Africa and Southern Africa present the quickest rise, with an estimated annual incremental increase of resistance to NNRTI (non-nucleoside reverse transcriptase inhibitors, like Efavirenz) of 29% and 23% respectively.[3]

Drugs active against the most common resistant variables are available, but due to economic and financial burdens, they are not easily implemented in low- and middle- income countries (LMIC). An important focus should therefore be put on preventing the further development of resistance. This can be managed by improving therapy adherence of the treated patients, improving healthcare management, resolving supply chain issues etc. This will not only be favourable for the outcome of the individual patient. It will also prevent the further development of drug resistance and the spread of resistant strains throughout the population.

An important barrier preventing patients from adhering to therapy is the presence of mental problems, most often depression or depressive symptoms. The risk for HIV-positive patients to develop a depressive disorder is two times higher than in an HIV-negative comparison

population.[4] In high-income countries, several studies have examined the association between depressive symptoms or major depression and therapy adherence and different studies found a negative correlation.[5] In SSA, evidence is less convincing, but still in line with these findings. According to a systematic review of 11 studies, patients with significant depression symptoms are less likely to be adherent than patients without these symptoms, with a pooled OR of 0.45.[6]

Efforts to improve mental health of PLWH are therefore thought to improve adherence to therapy and viral suppression. Evidence for this hypothesis is however limited. A systematic review and meta-analysis of 29 studies examining the effect of depression treatment on ART adherence in high- and low-income countries revealed a small but significant overall result (non-weighted mean effect size *r* of 0.15 (95 % CI = 0.06, 0.23)).[7] However, the effect of depression treatment was quite variable and 8 studies detected no significant or even a negative effect. Another narrative review suggests that mental health treatment may reduce transmission risk behaviour and improve adherence to HIV care and treatment.[8] Nevertheless, the limited number of quality studies conducted on the topic was an important limitation in the article. Therefore, they concluded that further research is needed to more thoroughly explore the potential benefits of mental health treatment on adherence. Reasons given for the limited quality of evidence are methodological issues in both interventional and observational studies. For example, some studies only describe ART adherence as a secondary outcome, risking their sample to be underpowered for the detection of any effect. Similarly, not all studies use a diagnosis of depressive disorder or low baseline adherence as inclusion criterion, which might be the reason for not detecting any substantial effect. Others might investigate treatments of too short duration, despite the fact that it can take a long time before a mental health intervention succeeds in reducing depressive symptoms. These and other limitations necessitate caution when interpreting the results.

One specific inconsistency between studies hampering the comparison of results, is the use of different mental health interventions. One group of studies uses antidepressant drugs, whereas another examines the effect of various types of psychotherapy. Within the last group, there are studies specifically targeting depressive symptoms and others including an

extra adherence component in their intervention. Different types of interventions can act through different pathways and different mediators to achieve adherence change.

In order to make proper recommendations for future research, it can be helpful to identify the underlying mechanisms causing depression and poor adherence in PLWH. When defining the main mediators in both processes, interventions can be effectively tailored to maximize their benefits on both depression and adherence.

Systems mapping is a useful tool to improve our understanding of the complex interplay between different variables. It puts together different actors within a certain system and visualizes the various interactions between them. It has been used as a platform to conceptualize mental models, develop hypotheses and reveal (unexpected) feedback loops between variables or possible gaps in a proposed concept. Our aim is to make proper suggestions for future prospective interventional research by defining the targets an antidepressant treatment should focus on in order to effectively improve adherence in depressed PLWH. We will, therefore, create two systems maps visualizing depression and adherence mechanisms in PLWH.

METHODS

Search strategy and eligibility criteria

We used the WHO's definition of treatment adherence: “the extent to which a person’s behaviour – taking medications, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider”.[9] In practice, it is operationalized as the percentage of the prescribed tablets that is taken at the right time and at the right dose. Another way to quantify adherence is to measure the amount of missed doses over a given period. Since there was little literature about depression and adherence to ART in SSA, we broadened our search to include countries all over the world.

First, we performed a literature search on the different factors influencing adherence to ART in PLWH. We assumed there would already be a large body of evidence, so we focused on systematic reviews assessing different barriers and facilitators to adherence based on

original studies published between 2000 and 2018. Exclusion criteria were inclusion of patients aged 18 and below, language other than English and systematic reviews about the use of ART for prevention of mother to child transmission (PMTCT), since treatment here is confined to the pre- and perinatal period instead of being a lifelong commitment.

Secondly, we searched for articles describing the relationship between infection with HIV and depression. We included studies of all kinds of design that met the following inclusion criteria: studied patients were HIV-positive adults (aged 19 and above) who were diagnosed with or assumed to have a depressive disorder (including depressive symptoms, minor or major depressive disorder and dysthymia). We excluded studies assessing children or adolescents, written in a language other than English or published before 2008.

Articles reporting on HIV risk behaviour as a risk factor for contracting the disease in depressed patients were excluded after the initial selection because of lack of time to analyse the bidirectional relationship between depression and HIV. Only causes of depression in HIV-infected patients were studied, not the reasons for depressed patients to be more susceptible to infection.

We searched the online MEDLINE database on different days from February 2018 until the 4th of November 2018. Following search terms were used for the different maps: (adherence OR compliance) AND (ART OR HAART), filtering according to publication date (2000-2018) and article type (systematic review); (Depression OR "Depressive Disorder") AND "HIV Infections", filtering according to language (English), age (adult: 19+ years) and publication date (2008-2018). The website of the WHO was also consulted for guidelines and worldwide data about HIV, on different days from February 2018 until August 2018. Bibliographies from extracted articles were screened for relevant references.

Data analysis

Systems mapping is a visualization method to summarize and better understand relationships within a certain system and how different variables influence each other. We used KUMU software for this purpose. This software was chosen out of practical reasons, since this was the software used for this type of projects at the Institute for the Future, where an introductory workshop was organized.

In order to make these systems maps, variables possibly explaining poor adherence and depression in PLWH were extracted from the selected articles. Data were summarized in tables (*supplementary table 1* for adherence determinants and *supplementary table 2* for depression determinants, see *Appendix I*). Subsequently, two causal loop diagrams were drawn, called 'Determinants of adherence to ART' and 'Determinants of depression in PLWH'. For more information on the process of creation and further guidance to read the map, we refer to *Appendix II: Process of creating the systems maps and guide to read them*.

In order to make proper recommendations for future research, we searched for variables determining both depression and adherence to ART in PLWH that were at the same time a possible target for antidepressant treatment (as marked in *supplementary table 2*). To define the latter criteria, we used the WHO mental Health gap intervention guide 2016 to get an overview of the common types of treatment available in first line care. Subsequently, we selectively searched PubMed and UpToDate for articles suggesting the use of these treatments to reduce the impact of the selected variables on depression.

RESULTS

Our first literature search for determinants of adherence to ART yielded 395 articles, of which 7 systematic reviews were retained in the final selection (*figure 1*).[10–16] Searching for determinants of depression in PLWH, 1607 reports were screened, resulting in 107 articles (*figure 2*).[17–26][27–36][37–46][47–56][57–66][67–76][77–86][87–96][97–106][107–116][117–123] After extraction of data, we constructed two causal loop diagrams as a tool to interpret our findings (see *figure 3 and 4* with the corresponding links to the interactive online map[b]).

[b] Note: given the poor readability of the figures, they are only meant as a surrogate for the map. We recommend using the interactive online map as a tool to visualize the results.

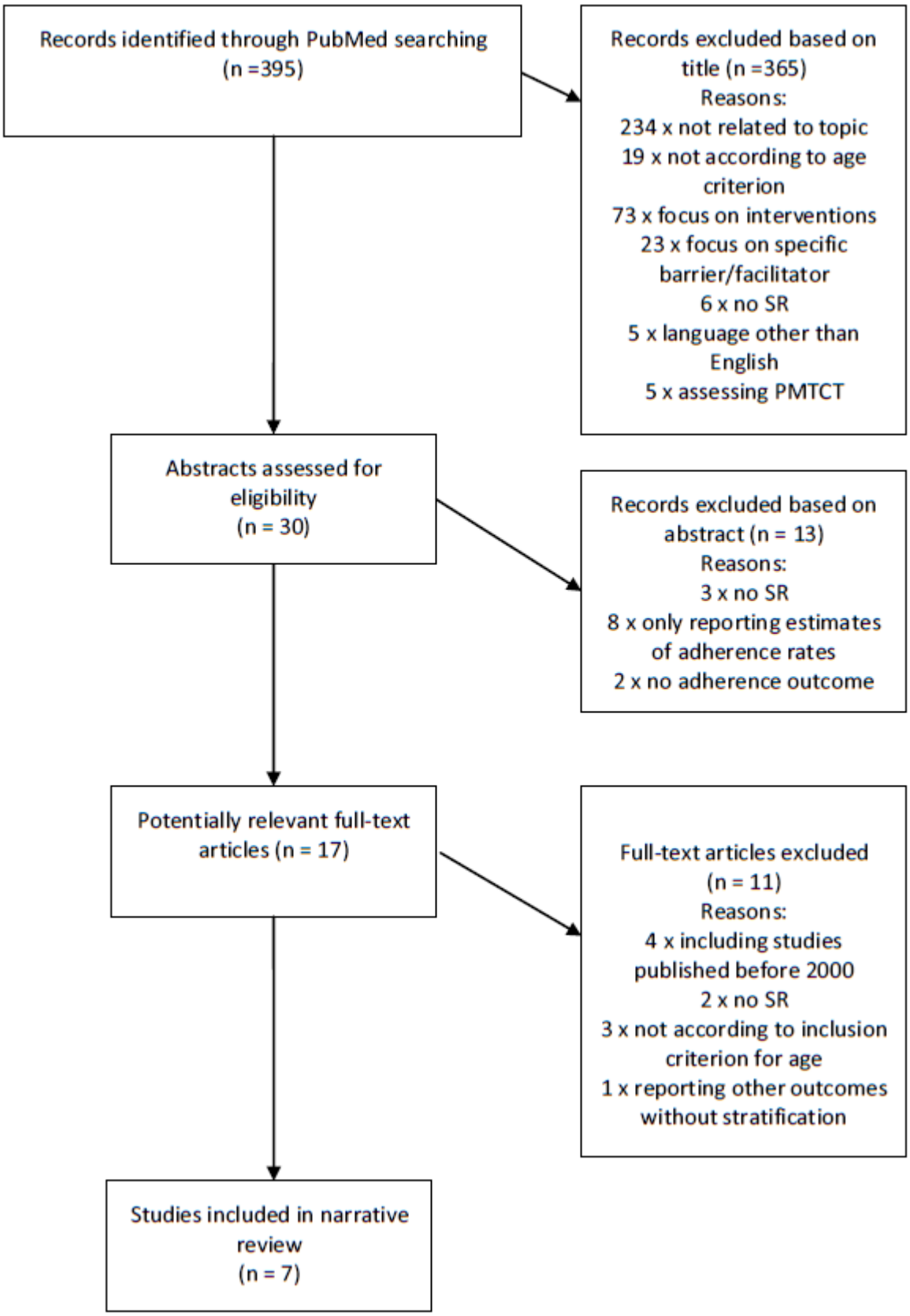

Figure 1: Flowchart of article selection for the adherence map based on 2009 PRISMA guideline
Legend: SR = Systematic Review, PMTCT = Prevention of Mother to Child Transmission

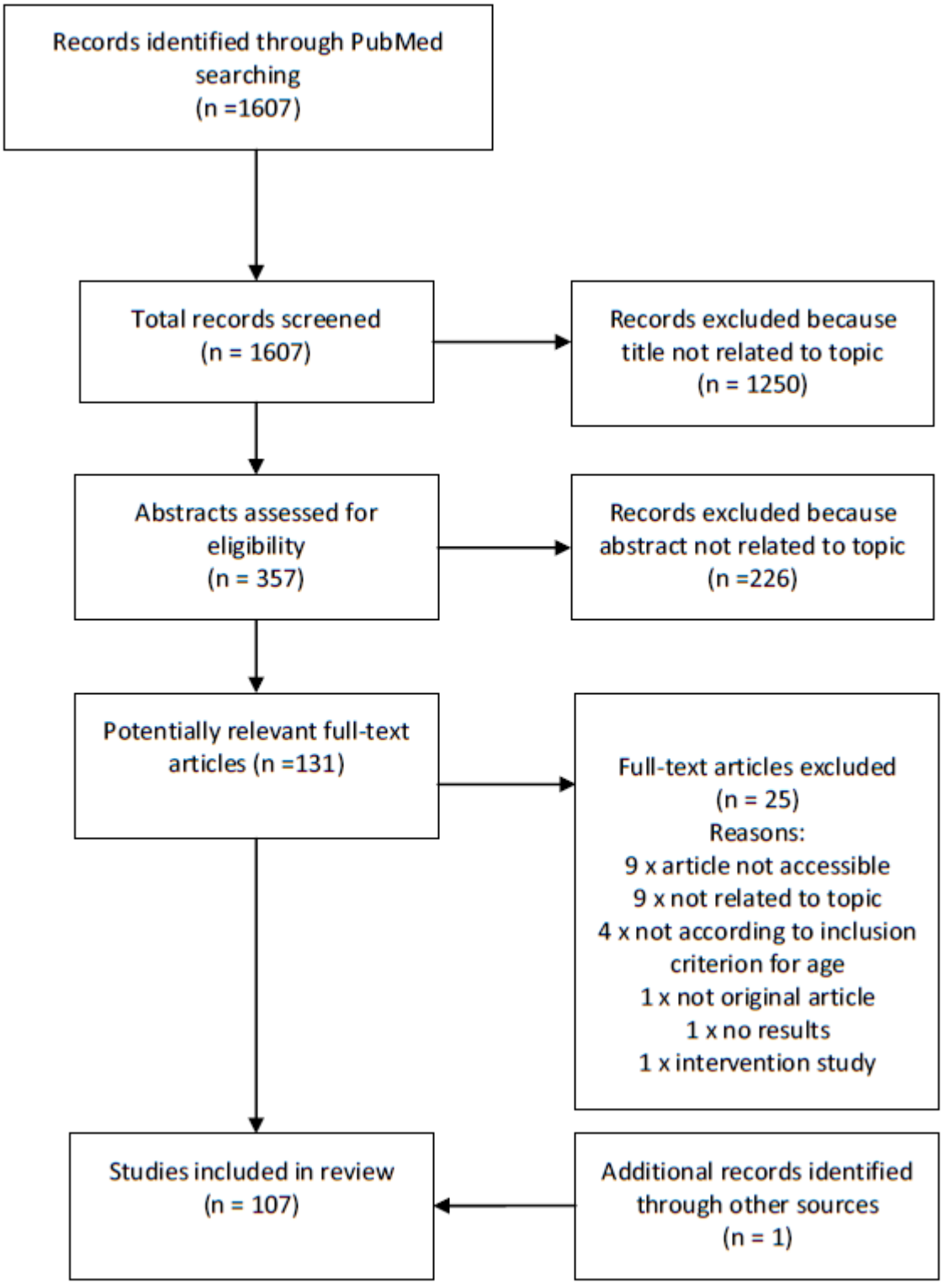

Figure 2: Flowchart of article selection for the depression map based on 2009 PRISMA guideline

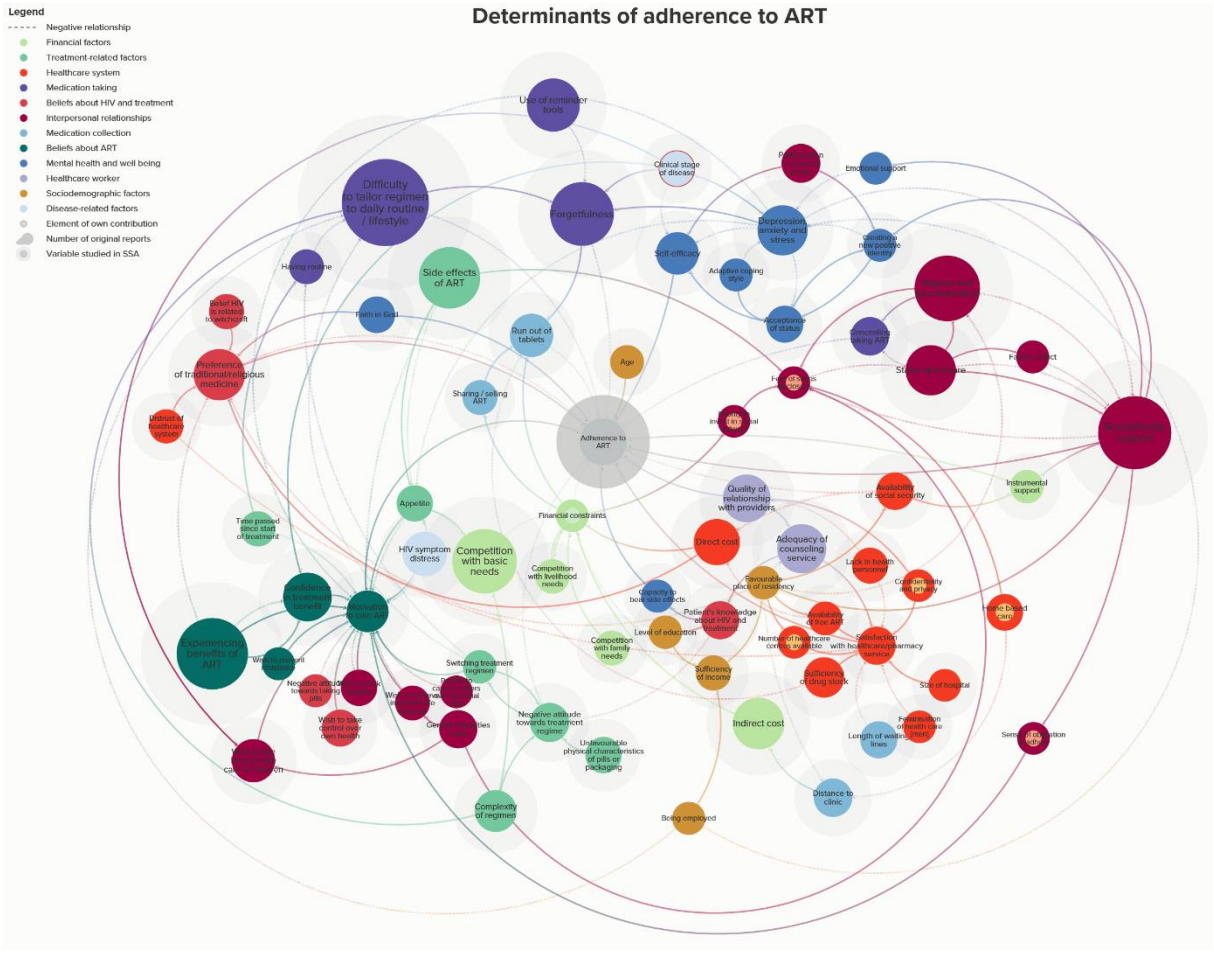

Figure 3: overview of the adherence map (see* https://evadevis.kumu.io/determinants-of-adherence-to-art *for the interactive online map.)

Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of original studies reporting on the variable, ranging from 1 to 150; Elements surrounded by a grey shadow represent variables studied in SSA; Elements with a 'bulls eye' in the centre are variables of own contribution to visualize a relationship between two other variables; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.

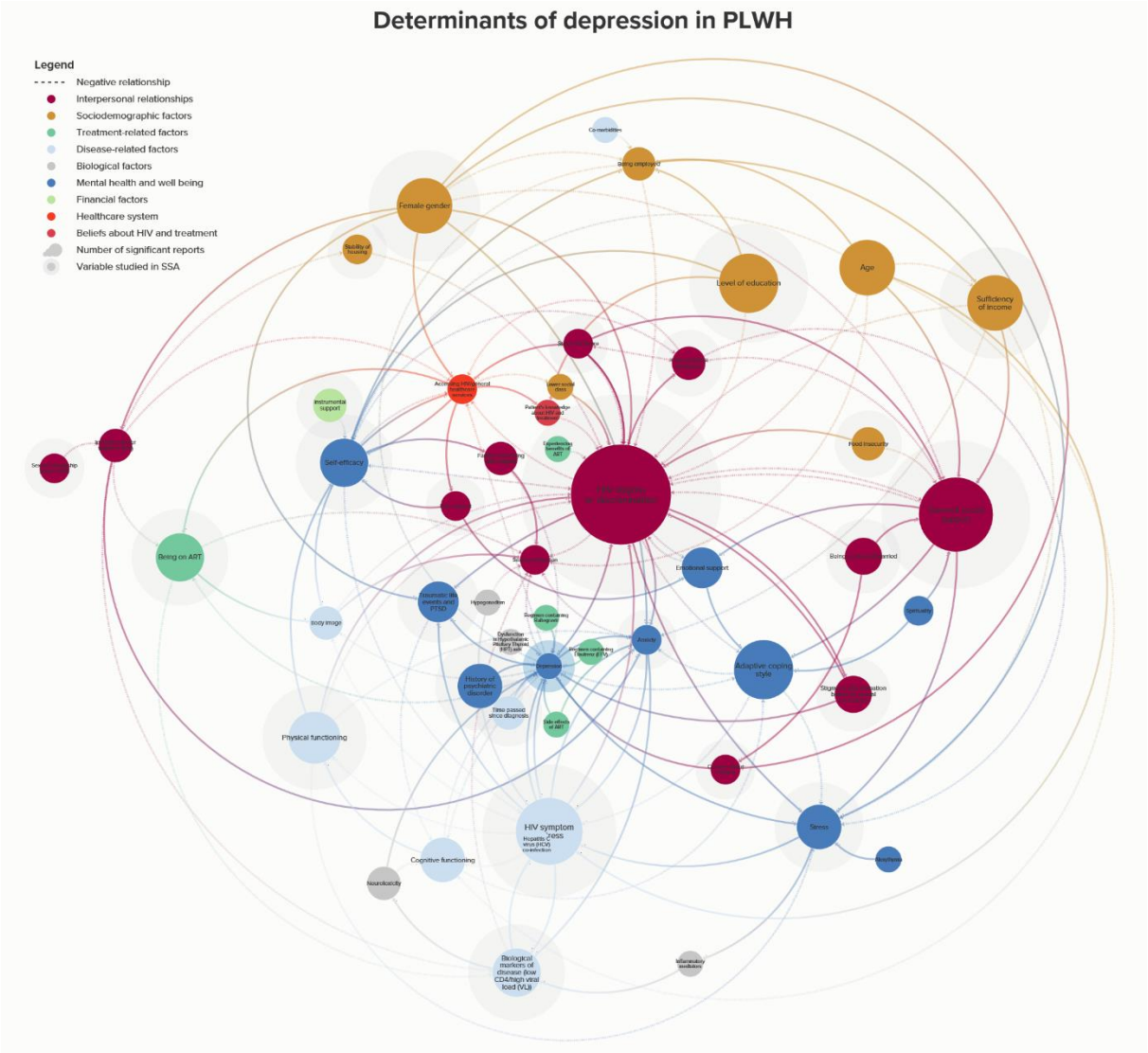

Figure 4: overview of the depression map (see* https://evadevis.kumu.io/determinants-of-depression-in-plwh *for the interactive online map)

Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 21; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively

We focused on predictors to depression and adherence specifically associated with HIV infection, since this is our main population of interest facing a very own variety of stressors and depression-provoking factors. Since we originally aimed to concentrate on SSA, factors considered less informative for the region were excluded from our discussion. These are ethnicity, racial discrimination and substance abuse. Analysing both the adherence and depression map, we identified 4 possible targets for depression treatment which we suggest to be included in further research. Considering their common role in both the development of depression and adherence behaviour, these subsets of the system are expected to have the highest impact on improving adherence when approached effectively with antidepressant treatment.

1) Stigma

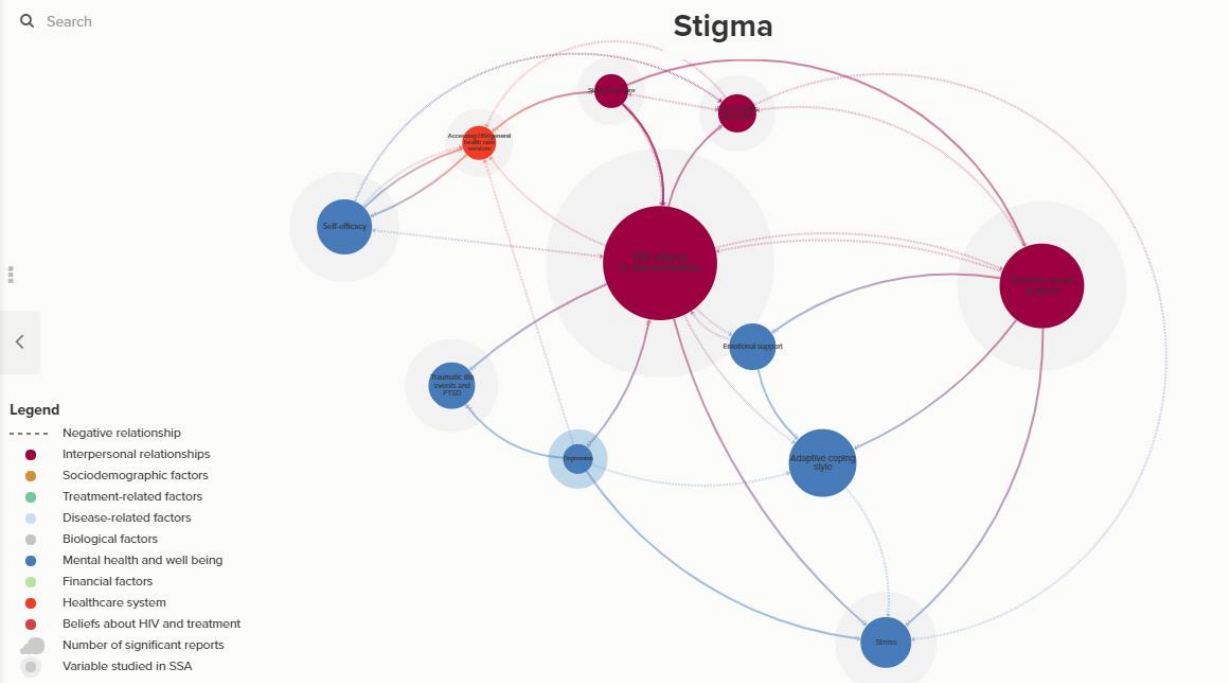

Figure 5: focus of depression map showing interactions between variables related to stigma
Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 21; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.

Stigma clearly is an important factor in our system (*figure 5*). Antidepressant interventions mainly focus on internalized stigma and felt normative stigma.[c] A possible intervention targeting stigma is the use of Cognitive Behavioural Therapy (CBT) to correct distorted cognitions. This therapy is based on the idea that particular negative ways of thinking predispose individuals to develop and maintain depression in stressful situations. These can be both a negative view of the self (seeing oneself as worthless, inadequate, unlovable, deficient ...) and the environment (seeing it as overwhelming, filled with obstacles and failure).[124] According to a prospective study conducted in Uganda, treatment with either Fluoxetine or Imipramine may also help to restore cognitive factors such as self-acceptance and self-confidence.[125]

According to our depression map, restoring one's self-esteem and correcting a negative perception of public attitudes against PLWH will reduce fear of status disclosure.[79,88,105] Disclosure avoidance poses an extra challenge to adhere properly due to the need to take tablets without anyone seeing and reduced likeliness to receive social support *(figure 6).* Besides that, it is an important predictor to depression given the consequential mental burden of secrecy and reluctance to visit healthcare centres. Depending on infrastructure and organization of healthcare services, privacy will not always be guaranteed. This may cause problems in communities with high prevalence of stigma. Out of fear of status disclosure and subsequently being target of stigma, PLWH will avoid going to appointments and will be lost to follow up. In some regions, discrimination of often economically poor, illiterate, marginalized patients at the centre can directly discourage people to come back for further care.[25] Furthermore, stigma is an important risk factor for depression,[20-38] which in turn will impair coping with stigmatizing experiences, hence further complicating patients' willingness to seek care. Also, negative affect and lack of motivation will directly contribute to a decreased attendance to healthcare services.

[c] *According to the definitions in the stigma framework adopted from Steward W. et al. 2011*[105]

Internalized stigma is the fear of being stigmatized and personal endorsement of stigmatizing beliefs. People feel guilty and ashamed about being HIV positive.

Felt normative stigma is the patients' perception of the prevalence of negative attitudes against people with HIV in the community.

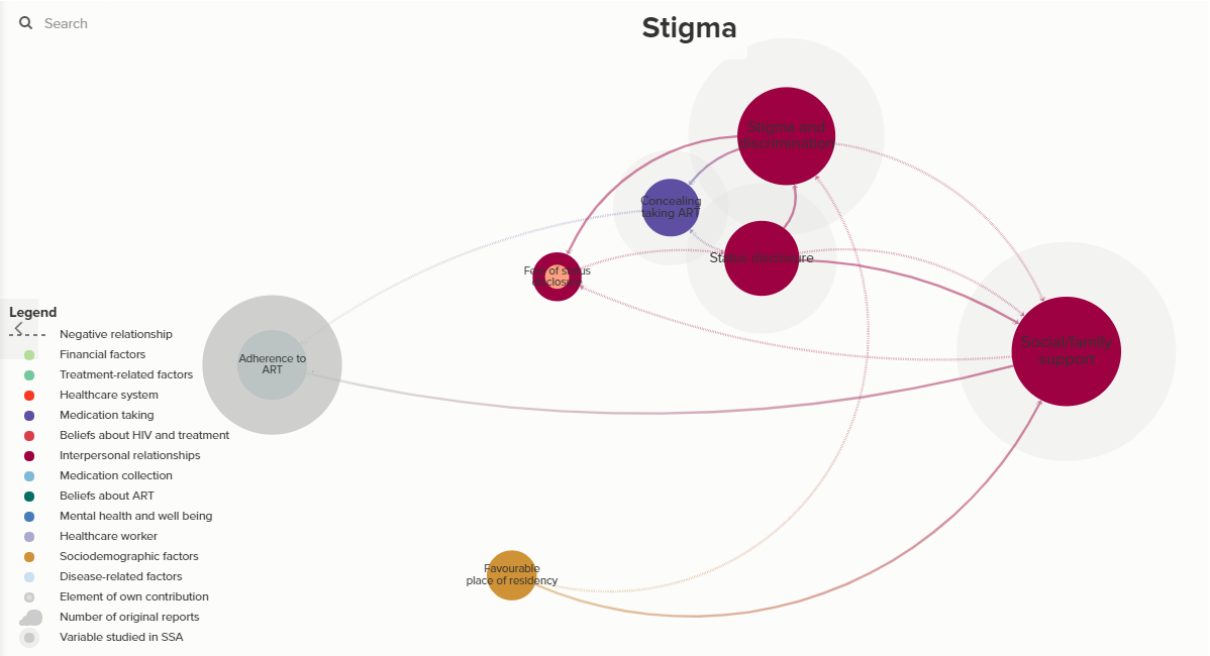

Figure 6: focus of adherence map showing interactions between variables related to stigma *Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 150; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.*

Therefore, interventions to improve linkage to care in PLWH (cf. infra) should be combined with actions enhancing self-efficacy and resilience of the patients to deal with possible reactions of stigma following disclosure of status at the healthcare centres. This could be attained through CBT-enhanced problem solving, emotion regulation and development of a greater sense of confidence in one's own abilities.[126–128] Furthermore, the behavioural component of CBT could also be useful to guide the process of status disclosure by learning to face one's fears instead of avoiding them and to prepare for potentially problematic interactions with others.[127] Access to care will be made easier when patients don't have to conceal their status.

Relieving stigma will simultaneously facilitate social support given the tendency of stigmatized people to hide in isolation and the facilitation of status disclosure allowing others to offer support. In turn, social support will promote further disclosure and buffer against stigma. Empathy, understanding, affection, listening ... provided by emotional support in particular will help patients cope with their disease and other stressors.[32] This is

especially interesting since internalized stigma will negatively influence a patient's coping abilities.[31,33]

Another pathway possibly guiding the beneficial effect of reduced stigma is through alleviation of the traumatic experience stigma can be. For many patients, being diagnosed with HIV means a real trauma to their lives, so experiencing stigma and discrimination merely based on that diagnosis will be a constant reminder to that trauma.[21]

We need to acknowledge our lack of power to change stigma within a community merely by treating depression. Nevertheless, considering our finding that internalized and felt normative stigma have a primary role to play in this system, we can make the hopeful conclusion that community stigma itself doesn't need to be changed in order to achieve beneficial effects on mental well being and adherence of PLWH. Empowering patients by addressing their mental problems can create more resistance against the detrimental effects of stigma experiences.

2) Perceived stress

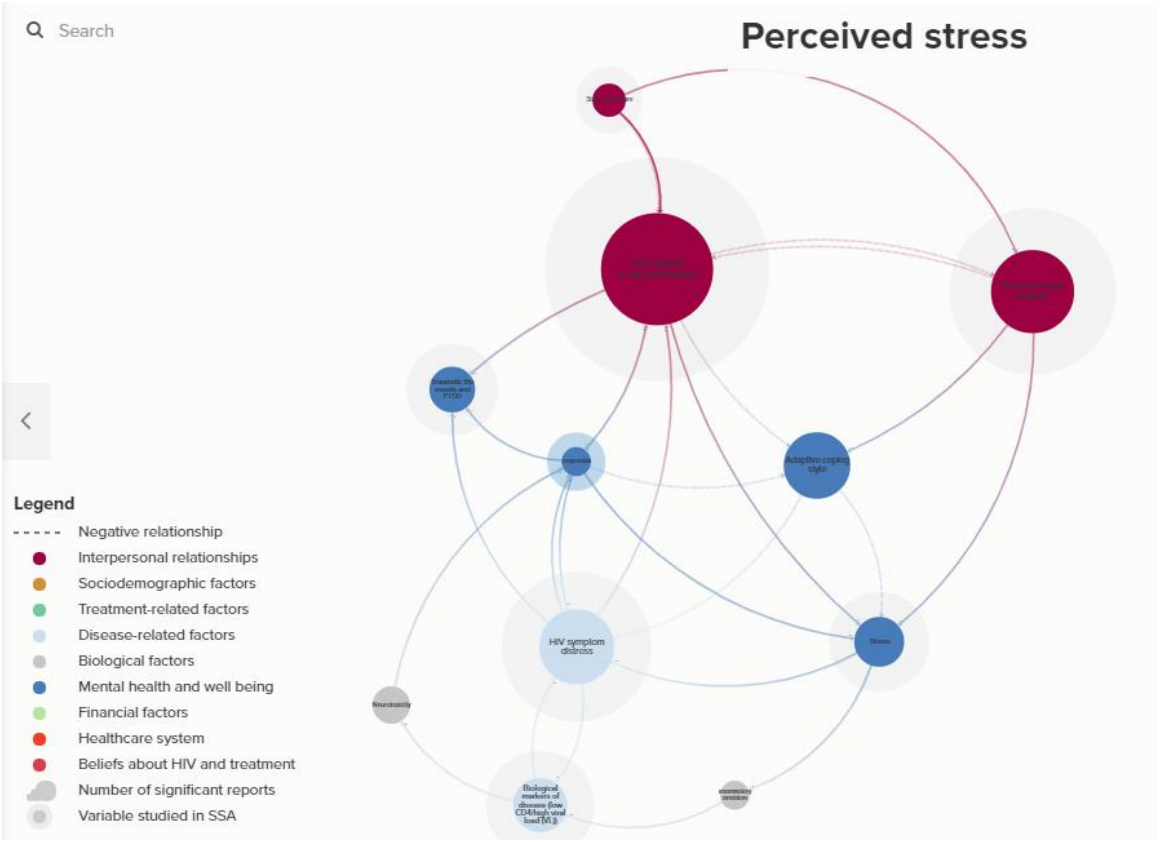

Figure 7: focus of depression map showing interactions between variables related to perceived stress
Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according

to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 21; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.

Being HIV-positive imposes certain very specific psychosocial stressors to patients often being part of a generally vulnerable population. Interpersonal therapy (IPT) aims to improve problematic relationships or circumstances that are directly contributing to the current depressive episode. It focuses on some predefined problem areas.[129] In patients living with HIV, this could be the problem of stress related to role transition when confronted with a life-changing diagnosis like HIV positivity. The goal of therapy is to establish a realistic view of both the old and new role and provide strategies to cope with one's new role. Another focus could be on helping patients going through a normal grief process and moving on with their life, after having experienced the death of a friend or relative due to HIV.

Chronic stress activates the sympathetic nervous system and Hypothalamic-Pituitary-Adrenal (HPA) axis *(figure 7)*. Continuous exposure of the immune system to cortisol causes desensitisation to the inhibitory effects of corticosteroids, thereby resulting in a constantly activated immune system.(40,46) Pro-inflammatory cytokines (CK) can directly facilitate HIV replication and disease progression. Furthermore, modulation of cellular immunity will indirectly impair the body's defences against HIV infection and replication.[46,92] Disease progression precedes more HIV symptom distress and worsens the mental burden because of the threatening implications of a low CD4 count.[130] Viral neurotoxicity, in addition, can directly cause a worsening of depressive symptoms.[58,101,114] By reducing stress and all its downstream effects, lower levels of depression will automatically decrease levels of stress, as depression itself is an important psychological stressor (reinforcing loop).[108,120] Also, adherence will be improved, since better acceptation of the life-changing diagnosis and slower disease progression will improve adherence self-efficacy *(figure 8).*

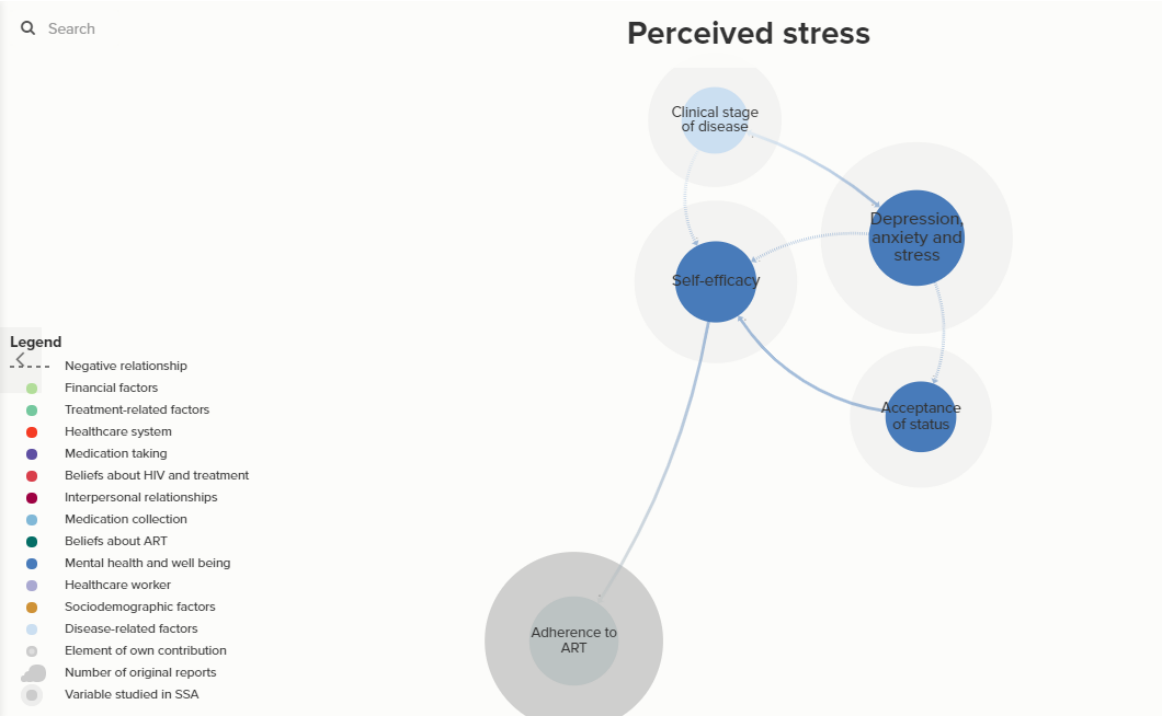

Figure 8: focus of adherence map showing interactions between variables related to perceived stress *Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 150; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.*

Following our depression map, another important variable capable of relieving the detrimental effects of stress as well as HIV symptom distress is an adaptive coping style.[68,102,123] This is a tendency to use adaptive responses to adversities or chronic stress, facilitating their processing. Problem solving and emotion regulation are two examples of adaptive coping styles which are often trained during CBT.

Remarkably, social support appears to not only have beneficial effects in our systems map. In some cases, it can increase stress.[121] This might be due to a mismatch between the amount of support patients perceived they needed and the support they actually received. Well meant but rather insensitive support can also have a harmful effect. Patients might perceive the reception of support as a prove of their incapability to deal with daily tasks.

3) therapeutic alliance

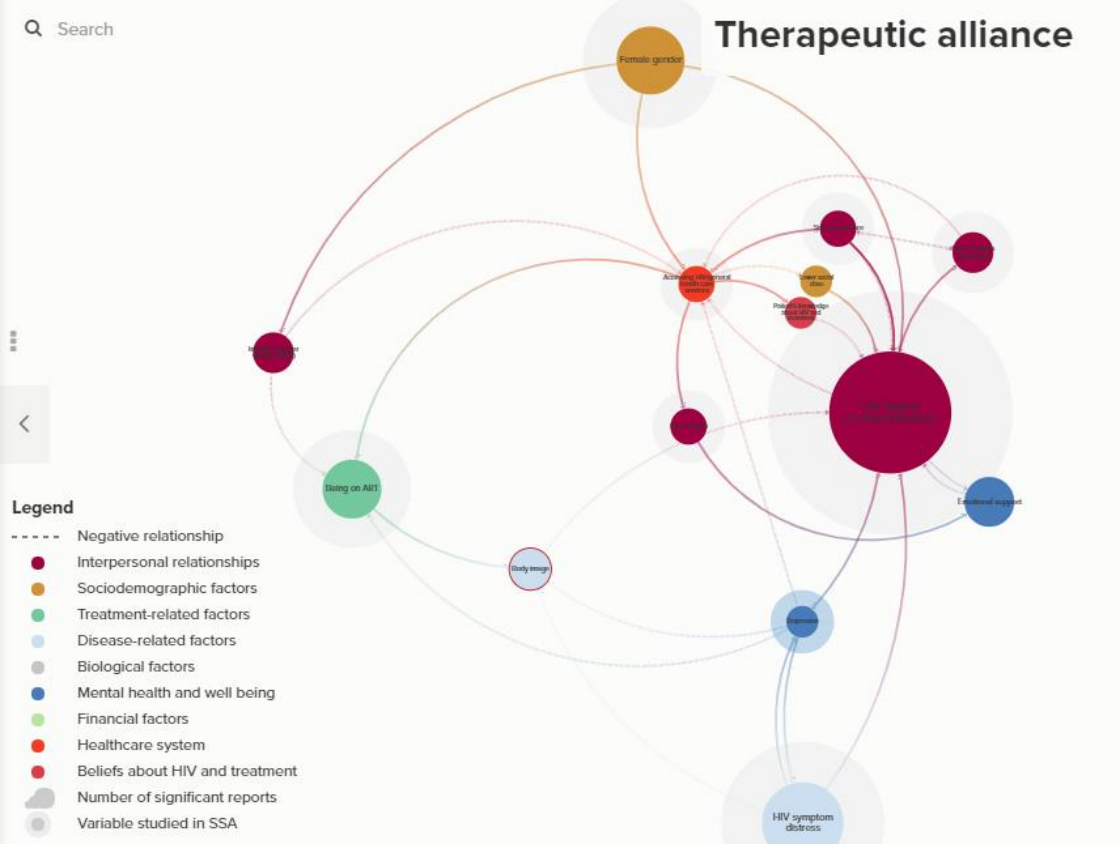

Figure 9: focus of depression map showing interactions between variables related to therapeutic alliance *Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 21; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.*

Common to all types of psychotherapy is the promotion of a positive therapeutic alliance by conveying interest, respect, acceptance and approval of the patient.[(129)] It is of paramount importance that the psychologically ill patient feels safe with and cared for by his/her treatment providers in order to achieve successful antidepressant treatment. At the same time, a good patient-provider relationship will increase satisfaction with healthcare service and thereby adherence. Moreover, integration of mental health services and HIV care can facilitate both the recognition and management of mental disorders as well as follow up of HIV treatment in mentally ill patients.

By optimizing linkage to care, one must keep in mind the possible downstream effects mediated by HIV stigma, as discussed above. A possible way to bypass these negative

consequences of stigma is to optimize peer support from the centre. By setting up peer support groups or connecting PLWH to each other, the emotional encouragement provided by peers can create more resilience to stigmatizing situations *(figure 9).*[64]

Interestingly, access to care is also described to reduce stigma through different mechanisms.[24,79] First, proper HIV care and resolution of external symptoms can transform a disfiguring disease into a manageable condition that is invisible to others. Secondly, integration in a community program with comprehensive care aids to improve living standards and reduce stigma. Thirdly, appropriate counselling and teaching of the patients about HIV and AIDS will lead to better knowledge and understanding of their disease and protect them from being mislead by other's opinions or attitudes. It will put an end to their own misconceptions about for example transmission of HIV (fear to spread the disease by holding other people's child, cooking for others, sharing plates).

Important to note is the difference in accessing care between men and women. Female dominated health services can represent a barrier to men's attendance. Furthermore, because of maternal health care, women have always been linked closer to the healthcare system. Therefore, extra efforts should be made to reach HIV-positive men. However, if women experience intimate partner violence, threats to their safety or possible violent repercussions of engagement in care will make linkage to HIV care less of a priority.

Looking at the adherence map, organizational aspects of accessible and quality health care, like proper amount of health personnel, sufficient drug stocks, length of waiting lines,... should also be taken into account to maximize impact on adherence *(figure 10).*

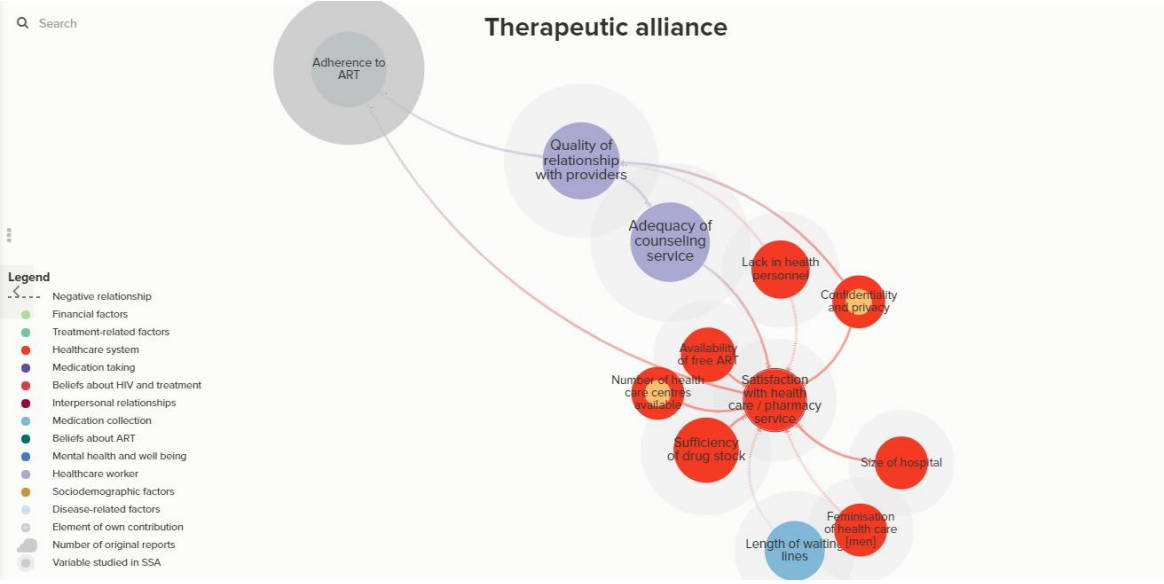

Figure 10: focus of adherence map showing interactions between variables related to perceived stress *Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 150; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.*

4) Cognitive functioning

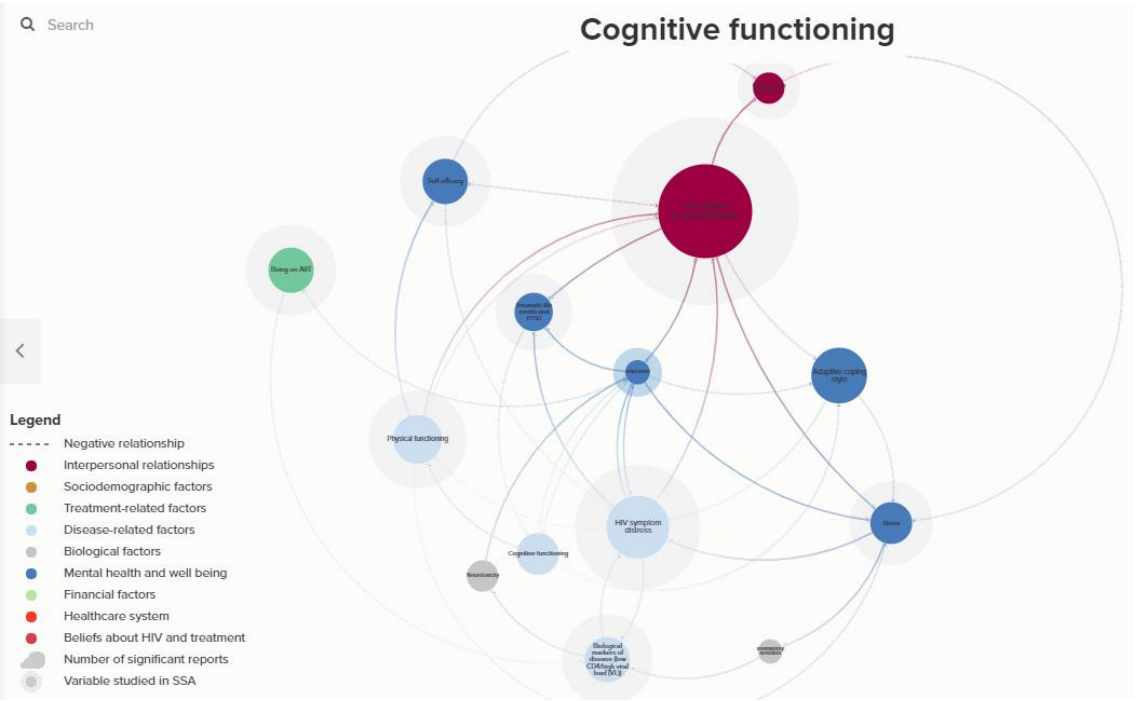

Figure 11: focus of depression map showing interactions between variables related to cognitive functioning *Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 21; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.*

In a patient cohort receiving 12 sessions of CBT, significant improvements in cognitive function (in this case executive function and attention) were seen, independently of changes in depression score.[131] Furthermore, specific brain regions within the cognitive control network showed increased activity in a sample of 31 patients after 12 weeks of CBT.[132] Cognitive control is the capacity to modulate cognitive and emotional systems, for the purpose of goal-directed behaviour, task flexibility, reorienting attention and behavioural inhibition. In addition, chronic treatment with monoamine reuptake inhibitors has shown to restore normal cognitive activity in the brain and increase levels of Brain-Derived Neurotrophic Factor (BDNF).[133]

Cognitive dysfunction is a direct risk factor for depression due to the disturbance of affective processing and hence the activation of negative self-referenced schemes and thoughts.[23,38,39,73,75,115] Indirectly, a decline in cognitive reserves impairs memory and cognitive flexibility required for the process of adaptive coping.[75] In more advanced stages, it will have substantial impact on physical functioning at work, in the family, in daily life ... This will be an extra enhancer to depression *(figure 11)*.

Apparently, improving cognitive function will only have beneficial effects. Moreover, the subsequent reduction in depressive symptoms interrupts the feedback loop worsening cognition, since depression itself causes cognitive dysfunction.[97] However, mechanisms causing cognitive dysfunction following depression might be different from these resulting from HIV-related neurotoxicity. Therefore, interventions for depression addressing cognitive functioning might not alleviate cognitive dysfunction due to HIV infection. Behavioural therapy, a variant of CBT, can partly address this problem by improving physical functioning despite poor cognition. Behavioural therapy encourages patients to maintain their usual activities, which include household duties, work, self-care, maintaining regular sleeping and waking times, social events, etc. Setting up small goals the patient will likely achieve will improve the patient's mood, sense of achievement and confidence. Thus, motivation to continue engaging in daily activities and community life will grow, even though physical symptoms might not have changed.[134]

According to the adherence map, poor memory in particular is a possibly fruitful target of treatment, since a lot of studies reported 'simply forgetting to take their medication' as a

barrier to adherence *(figure 12).* Practical assistance comprising tips to match the regimen to their daily lives and useful reminder tools can provide additional support to overcome the barrier of poor memory.

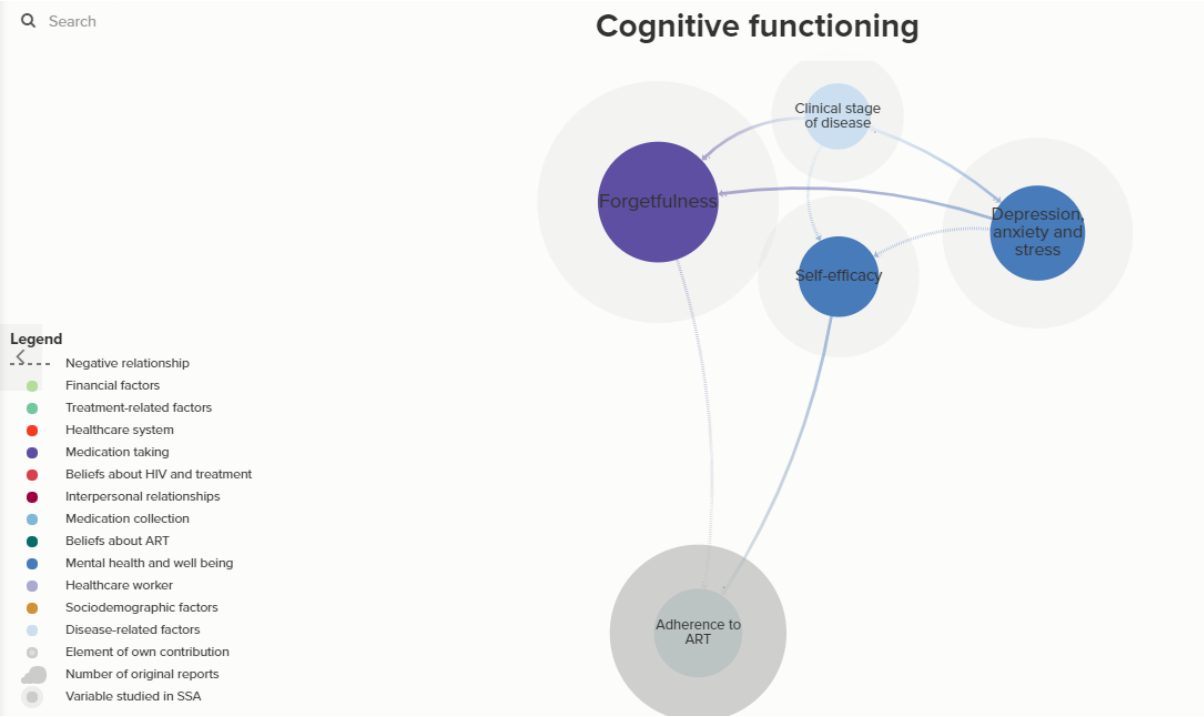

Figure 12: focus of adherence map showing interactions between variables related to cognitive functioning *Legend: colours represent different variable categories, as explained in the legend; Size of the elements is adapted according to the number of studies reporting on a direct connection between the variable and depression, ranging from 1 to 150; Elements surrounded by a grey shadow represent variables studied in SSA; Dashed or solid arrows represent relationships with negative or positive polarity, respectively.*

DISCUSSION

To introduce interventions to bring about a certain behaviour change, it is of paramount importance to understand the underlying mechanisms that shape the behaviour. As stated in a proposed framework for interventions on medication adherence, the development of an intervention should be grounded in theory and evidence in order to be effective.[135] Initially our aim was to define the main mediators shaping the relationship between depression and adherence, such that interventions targeting depression could then be effectively tailored to maximize their benefits also for adherence. Since the context of this work was to reduce HIV drug resistance in SSA, we wanted to identify the underlying mechanisms linking depression to poor adherence in PLWH in SSA through creating a systems map. A literature search and

preliminary analysis of data yielded insufficient information to create a systems map and make proper conclusions. Therefore, we changed our strategy. To define possibly interesting targets of antidepressant treatment, we first visualized adherence and depression mechanisms in PLWH separately with the help of two different maps and then compared these two maps.

Surprisingly, we could not find a pre-existing systems map about the different determinants of adherence in spite of the large amount of research conducted on the topic. The literature on adherence is vast, such that within the time frame of this work, we decided to focus on systematic reviews. To retain enough useful information to create a systems map, we did not restrict our search to SSA only. Therefore, we made a first attempt to map different factors affecting adherence of PLWH worldwide. Our next goal was to create a similar systems map for the determinants of depression in PLWH. There is virtually no literature on depression in PLWH in SSA, so also for this goal we widened our search to any geographic area. The creation of a systems map is partially based on personal interpretation and formulation of hypotheses. As such, different maps can be constructed by different researchers, despite the use of identical original data. Nevertheless, we believe that our map can provide useful information for further research.

The original aim of this review was to focus on strategies to treat depression and thus improve adherence in SSA. However, across the region, there is an extreme shortage of mental health resources and professionals. According to the WHO, more than 45% of the world population in 2014 lived in a country with less than 1 psychiatrist for every 100,000 people.[136] Therefore, we confined our proposed possible antidepressant treatment types to these interventions possible in primary care. Nevertheless, even the integration of mental health care in primary HIV care will be a serious challenge given the often overburdened and understaffed healthcare centres and the need for additional training and supervision of health personnel.

Comparing the two maps and restricting to common elements that can be targeted in primary care, we found four potential targets for treatment that could alleviate depression and at the same time improve adherence: addressing stigma, reducing perceived stress, promoting a positive therapeutic alliance and improving cognitive functioning. These

elements are not independent of each other, so any treatment should take into account their interaction. We suggest possible methods for such treatments, but acknowledge that this is not within our area of expertise, and these should be considered mere suggestions.

This review has some important limitations. First, the inclusion of studies conducted worldwide neglects important cultural differences. Some predictors of depression may be more or less important depending on culture- or country- specific factors: presence of poverty, food insecurity, difficult access to care, availability of free medical treatment, degree of HIV-stigma in the community, political instability, exposure to trauma, acceptability of Men having Sex with Men (MSM)/other minority groups ... Furthermore, in view of our focus on mental health, the expression, attribution and description of depression symptoms often are culture-specific. Moreover, when choosing a certain treatment, one must keep in mind the degree to which depression is stigmatized within a given population, differences in utilization of psychiatric care services, preferences for and availability of a certain treatment and different biologic reactions to pharmacologic treatment.[128] Secondly, the connections in our systems map are based either on personal interpretation, or on the results of mostly cross-sectional research. Therefore, we cannot guarantee the causality, nor directionality of the associations. Based on the information gathered throughout the process, we aimed to describe the different relationships as accurately as possible. Still, the synthesis of variables and connections in these systems maps is not exhaustive. Additional connections can be made and additional variables can be added. Thirdly, across different studies included in this review there was a lot of inconsistency in measurement of our two main variables of interest: adherence and depression. Apart from using different cut-offs to define adherence and depression, measurements were both based on self-report as well as more objectively clinician-assessed or electronically monitored. This can have important implications for the eventual results.[137] Depressed patients have a tendency to negatively evaluate their own capability and selectively recall negative memories. Furthermore, depressed patients may have difficulties recalling due to decreased cognitive functioning. As a result, self-reported assessments tend to overestimate depression severity or non-adherence. Some depression scales contain items overlapping with the symptoms of HIV itself or its co-morbidities (like fatigue, poor appetite, lack of energy, poor concentration, poor sleep), hence rendering the depression scores even less reliable. Also, using a screening

method rather than a diagnostic interview is likely to reveal higher rates of depression. Fourthly, in order to assign a certain weight to the elements in our systems maps, we adjusted their size based on the number of reports suggesting a significant direct relationship to adherence or depression. We acknowledge this only is a weak surrogate for the importance of the element. The amount of reports on a certain variable depends on how we pooled the original data into the eventual variables used in the map. In the adherence map, for example, 'being employed' is a separate variable notwithstanding it could be included in 'difficulty to tailor regimen to daily routine/lifestyle' as well, since this one also includes work constraints. Of course, the number of reports published on a certain variable also depends on which topics are most popular in the field of research. Lastly, both alcohol and intravenous drug use (IDU) were pooled under the variable 'substance abuse', which we considered less important given the smaller prevalence of IDU in SSA. However, alcohol (over-)consumption does exist in some regions in SSA, so it could be an important predictor to both depression and non-adherence.

In conclusion, we want to underscore the potential value of integrating mental health care into general HIV care, despite the difficulties that need to be faced in SSA. In order to obtain optimal adherence in depressed PLWH, we believe further research should be done to evaluate interventions addressing stigma of PLWH, relieving perceived stress, promoting a positive therapeutic alliance and improving cognitive functioning. After gathering more evidence about the public health benefits of depression treatment, such evidence may be key to moving the policy debate regarding allocation of mental health resources.

CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE

None.

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APPENDICES

Appendix I. Supplementary tables

Supplementary table 1 is an excel file containing original data on the determinants of adherence. It sums the variables as originally described in the studies, the number of original studies discussing on the variable, references to the systematic reviews based on the original studies and the pooled variable referring to the original variables.

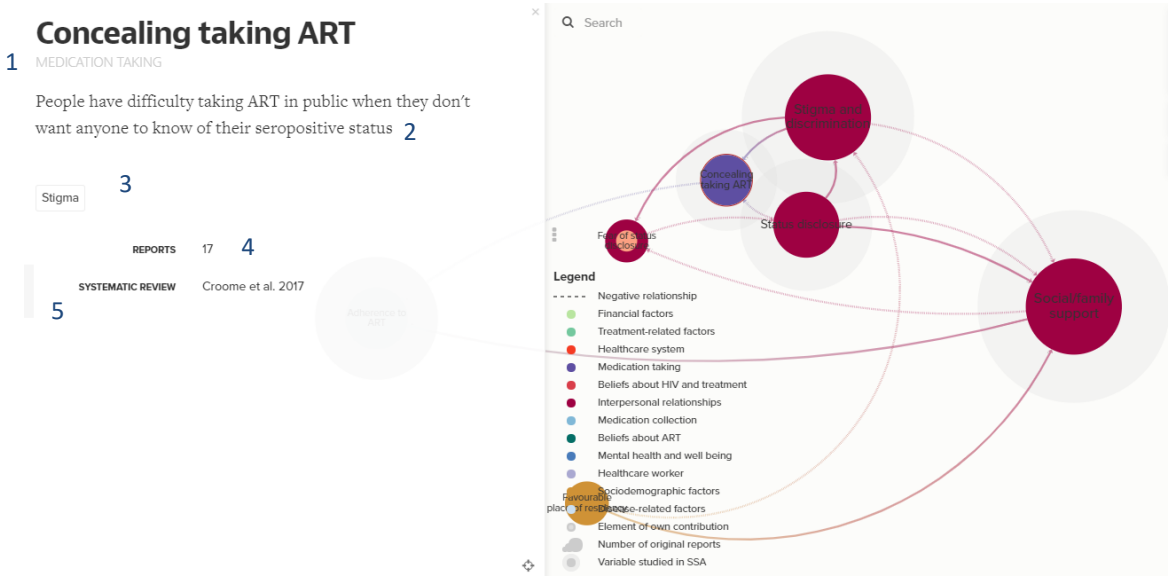
Supplementary table 2 is an excel file containing original data on the determinants of depression. It consists of different sheets. The first sheet shows the unpooled variables directly associated with depression with additional information on the study, country/region where it was conducted, effect size of the association if published and explanation for the relationship if given in the report. The second sheet is a pooling of the results from the first sheet. A third sheet reports on relationships between variables, with their respective study references, country/region, effect sizes and explanations. The final sheet shows which variables could be a target for first-line antidepressant treatment and a short description of the treatment.

Appendix II. Process of creating the systems maps and guide to read them

1) Adherence map:

We extracted the determinants of adherence reported in the selected systematic reviews (SR) together with the number of original studies that found these determinants to be significantly linked with adherence. If any of the original studies was discussed in more than one SR, we only counted it once. Equivalent variables were pooled together under the same name and one predictor was dropped because of unclear meaning, even after consulting the original article. Finally, we remained with 65 determinants to include in our systems map. Connections were formed based on personal interpretation and relationships proposed in one of the reviews(15), which not merely summarized the determinants involved, but also connected findings from different studies providing a synthesis (a so-called meta-ethnography). To be able to clarify the link between certain variables, we included 8 more, indicated by a 'bulls eye' in the map. The eventual result is a systems map with 73 variables all related to 'Adherence to ART'. These variables were grouped in 12 different categories (called 'element type' in KUMU), based on the themes used in one of the reviews.[16] Categories are represented by a specific colour, clarified in the legend. For variables needing some additional clarification, we added a short description of their meaning and/or role in the system. The size of the corresponding element in the map was adjusted according to the number of original studies reporting on it. Given our original aim to focus on adherence and depression in SSA, variables studied in this region were marked with a shadow.

Using the link to the interactive online map, you will get access to a presentation about this systems map consisting of 5 slides: an overview slide of the whole map and 4 slides focussing on the discussed treatment targets. You can switch slides by clicking on the arrows on the left and right side of the screen. Zooming in or out is possible by scrolling up or down with your mouse or using the '+' and '-' buttons in the right upper corner of the screen. To read the information about a certain variable, click on the corresponding element in the map. A side panel will open from the left containing all the information about that variable. To leave the side panel again, click on any free space in the map. *Supplementary figure a* shows how information about a certain variable is displayed in the adherence map.



Supplementary figure a: Information about a certain variable as displayed in the adherence map
1: element type/theme
2: description of the element or its role in the system
3: tag(s) added to link the variable to one of the four depression treatment targets
4: number of original reports that found this variable to be a significant barrier/facilitator to adherence
5: reference(s) to the systematic review(s) reporting on the variable

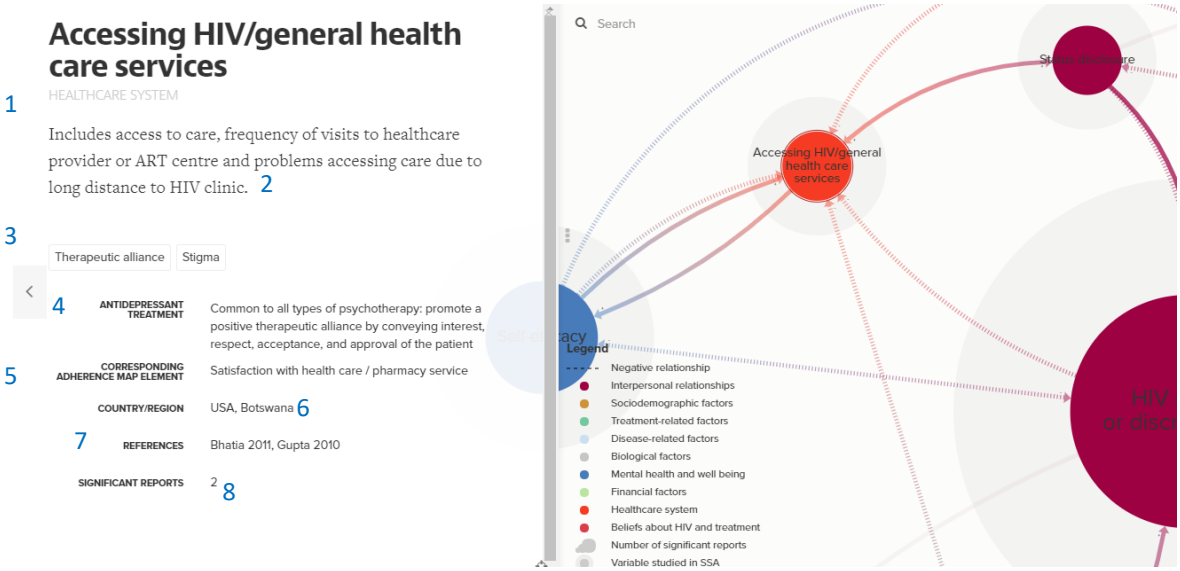
Arrows represent hypothesized relationships between two variables with positive or negative polarity, indicated as a '+' or '-' next to the corresponding solid or dashed arrow, respectively. Positive polarity means an increase in cause indicates an increase in the effect as well; similar for a decrease in cause. Negative polarity means there is an inverse relationship, whereby the two variables change in opposite directions.

2) Depression map:

We extracted data about the determinants of depression from 107 selected reports. Direct as well as indirect relationships to depression and interconnectivity between variables were found and summarized in tables *(see supplementary table 2)*. Equivalent variables were pooled together under the same name. Finally, we remained with 49 determinants to include in our systems map. Variables were grouped in the same categories (or 'element types' in KUMU) as used in the adherence map and represented by the same colours, clarified in the legend. We added a short description of their meaning for those variables needing some additional clarification. The size of the corresponding element in the map was adjusted according to the number of significant reports directly linking that variable to depression. Like in the adherence map, variables studied in SSA were marked with a shadow.

Connections were formed based on reported findings and own interpretation. To enhance readability of the map, some direct connections to depression were not added to the map if they could be explained by at least one indirect pathway through another variable in the map. Polarity of a connection was based on the direction reported by the majority of studies. Trends reported in non significant studies were also considered to make decisions about the global direction of a given relationship. If there were studies reporting contradictory results, relevance of the contradicting studies was estimated. Studies considering their results as unexpected without the possibility of explaining the finding were considered as outliers and ignored. Contradicting studies reporting on specific populations were ignored if these populations were considered non-informative to make conclusions about patients in SSA (e.g. use of drugs, since this is less common in SSA). If both directions were considered plausible, then they were both added to the map. The variable "race/ethnicity" and "racial discrimination" was excluded from the results, since this variable would not yield any interesting information regarding SSA.

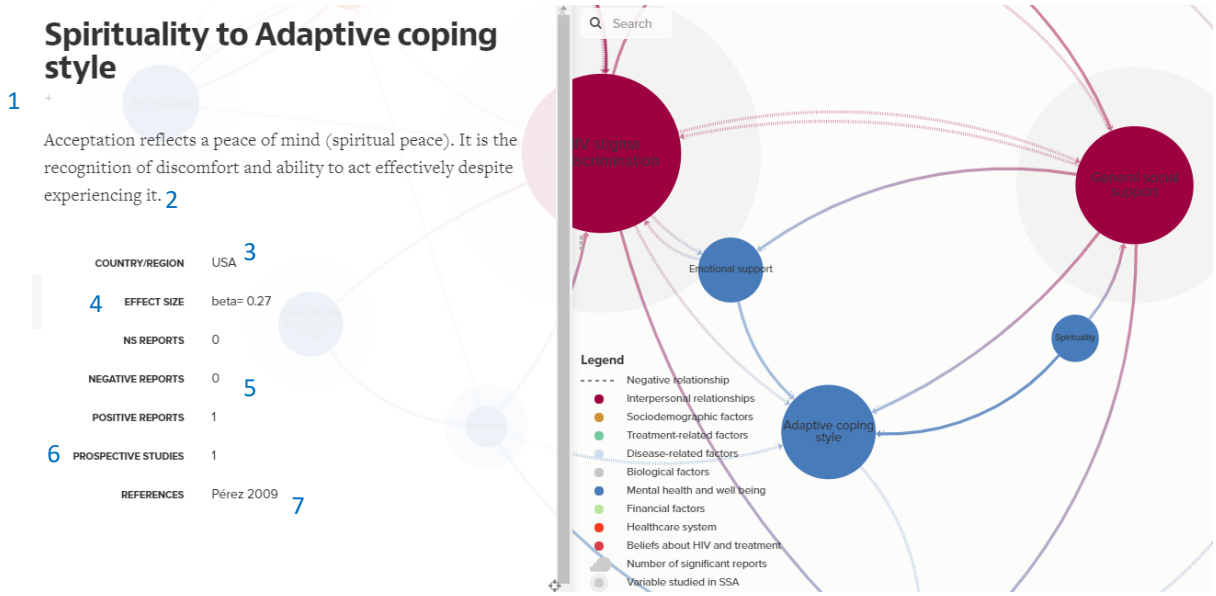
Supplementary figure b shows how information about a certain variable is displayed in the depression map.



Supplementary figure b: Information about a certain variable as displayed in the depression map
1: element type / theme
2: description of the variable
3: tags added to link the variables to one of the four depression treatment targets
4: description of a possible antidepressant treatment targeting this variable
5. variable in the adherence map corresponding to this variable
6: countries / regions were the studies reporting on this variable were conducted
7: references to the studies reporting on this variable
8: number of significant reports indicating this variable as a direct determinant of depression

In the depression map, information explaining a relationship between 2 variables is assembled under the specific connection in the map, which can be accessed by clicking on the corresponding arrow.

Supplementary figure c shows how information about a certain connection is displayed in the depression map.



Supplementary figure c: Information about a certain connection as displayed in the depression map
1: polarity of the relationship (positive or negative)
2: explanation of the link between the two variables
3: country / region where the study reporting on this connection is conducted
4: effect size found in the study (shown here if there was only one study reporting on the relationship)
5: number of reports suggesting a non-significant (NS), negative or positive relationship
6: number of prospective studies that found a significant result for this relationship
7: references to studies reporting on this relationship and concluding the direction to be as displayed for this connection

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