An adapted intervention for problematic alcohol use in people living with AIDS and its impact on alcohol use, general functional ability, quality of life and adherence to HAART: A cluster randomized control trial at Opportunistic Infections Clinics in Zimbabwe.

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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third-party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Preface

This dissertation is a synthesis of research work I carried out in Zimbabwe. The research entailed development and piloting of a treatment for problematic alcohol use in people living with HIV. The dissertation includes published and manuscripts that are at various stages of publications as follows

Chapter two -Systematic review page (19-63) under review and ready for resubmission

Chapter three- Published page (64-75)

Chapter four – Under review, pages (76-101)

Chapter five-published, pages (102-115)

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SUMMARY

With the advent of antiretroviral therapy, the HIV pandemic has become a chronic illness requiring lifelong treatment. The 90-90-90 strategy, adopted by UNAIDS, aims for (i) 90% of HIV infected persons knowing their status, (ii) 90% on antiretroviral therapy; and (iii) 90% achieving viral suppression. The goal is to reach these aims by 2020. Alcohol use affects the attainment of the 90-90-90 goals. Research shows that people living with HIV (PLWH) drink twice as much as their HIV negative counterparts. Alcohol use disorders (AUD) in PLWH are associated with poor adherence to ART. Recommendations have been made to include interventions for AUDs in HIV prevention and treatment strategies. Brief interventions are recommended for hazardous alcohol use; however, for alcohol dependence a stepped care model incorporating behavioural/psychological treatments and pharmacological interventions may be required. Pharmacological treatments may lead to a higher pill burden and psychological interventions are, therefore, the treatment of choice. Psychological

interventions have traditionally been delivered by a highly skilled workforce. However, in low and medium income countries (LMIC) where the HIV prevalence is high, there is a shortage of a skilled workforce. Task sharing has been recommended as a way of scaling up the delivery of services.

The aim of this study was to adapt an evidence-based intervention for HIV and AUDs in Zimbabwe and to assess its effectiveness

in a cluster randomized controlled trial (RCT). To achieve this, we first conducted a systematic review of the evidence for the effectiveness of psychological interventions. Second, a qualitative study was done to understand knowledge and perceptions of AUDs among PLWH and potential barriers and facilitators of interventions for AUDs. Third, we conducted a pilot and feasibility study in preparation for the RCT.

The systematic review found limited evidence for the effectiveness of psychological interventions for AUDs, particularly on the frequency of drinking. Motivational interviewing (MI) alone and in combination with mobile technology, and cognitive behavioural therapy (CBT) were found to be effective. Additionally, MI was effective in reducing risky sexual behaviour, adherence to ART, other substance use disorders, viral load reduction, and increase in CD4 count. The qualitative study found that PLWH had adequate knowledge of the direct and indirect effects of alcohol use on HIV transmission and adherence to treatment, and were concerned about the stigma faced by PLWH who have and AUDs.

Furthermore, participants were concerned about the stigma faced by PLWH who have AUDs. They called for stigma reduction strategies to be implemented and were receptive of the idea of interventions for AUDs.

Following a pilot study which indicated that an intervention for AUDs was feasible, a cluster RCT was carried out at 16 HIV care clinics. The adapted intervention included motivational interviewing blended with cognitive behavioural therapy (MI/CBT). The comparator intervention was

the alcohol use section of the World Health Organisation (WHO) mental health Gap Action Program Intervention Guide (mh GAP IG). The MI/CBT and mh GAP IG interventions were delivered by registered general nurses (RGN) embedded in HIV care clinics. The primary outcome was a reduction in alcohol use as measured by the Alcohol Use Disorders Identification Test (AUDIT) score. Secondary outcome measures included: (i) HIV disease parameters, as measured by the viral load and CD4 count; (ii) functionality, as assessed by the WHO Disability Assessment Schedule (WHODAS 2.0); and (iii) quality of life, as measured by the WHO Quality of Life HIV (WHOQOL HIV).

The cluster RCT demonstrated that RGNs can be trained to deliver an MI/CBT intervention for AUDs in PLWH. Additionally, the MI/CBT intervention significantly reduced alcohol consumption in PLWH. While the reduction in alcohol consumption was maintained in the MI/CBT arm at 6 months, this effect was only maintained in the mh GAP IG arm up to 3 months. Additional improvements were seen in HIV treatment outcomes (especially viral load), functionality, and quality of life. Finally, it was feasible to deliver an MI/CBT intervention using a task sharing model. In terms of implementation, this can be done with a modest increase in staffing. Given the negative role AUDs play in the HIV treatment cascade, reduction in alcohol use can help in achieving the UNAIDS' 90-90-90 goals.

Further, effectiveness trials are needed in LMIC with a high prevalence of HIV. When conducting these trials, attention should be paid to patient experiences, such as the 'double' stigma of HIV and AUDs.

OPSOMMING

HIV het ’n kroniese siekte geword as gevolg van antiretrovirale tarapie. UNAIDS het die 90-90-90 strategie begin. Die strategie beoog dat: (i) 90% van HIV-positiewe mense hulle status moet ken; (ii) 90% moet antiretrovirale terapie (ART) ontvang; en (iii) 90% moet virale-onderdrukking bereik. UNAIDS beoog om die doelwitte teen 2020 te bereik. Alkoholgebruik beïnvloed die 90-90-90 strategie. Navorsing toon that mense wat met HIV leef (MHL) twee keer soveel alkohol drink as mense wat HIV-negatief is. Alkoholmisbruikversteurings (AMVs) word met swak nakoming vir antiretroviralebehandeling (ARB) geassosieer. Intervensies vir AMVs, as deel van HIV voorkoming en behandeling, word aanbeveel. Kort intervensies word vir gevaarlike alkoholgebruik aanbeveel, maar vir alkoholafhanklikheid is ’n trap-vir-trap versorgings model wat gedrags/sielkundige- en farmakologiesebehandeling insluit moontlik nodig. Tog mag farmakologiesebehandeling tot ’n hoër medikasie-lading lei. Geveloglik, is sielkundige intervensies ’n beter keuse. Sielkundige intervensies word grotendeels deur hoogs-geskoolde werkers, wat nie in lae-middel inkomste lande (LMIL) waar HIV baie voorkom, volop beskikbaar is nie, aangebied. Taakdeling word aanbeveel as oplossing om die tekort aan hoogs geskoolde werkers aan te spreek.

Hierdie studie beoog om ’n bewys-gebasseered intervensie vir HIV en AMVs vir Zimbabwe aan te pas, sowel as om die effektiwiteit daarvan deur middel van ’n groepe-ewekansige-beheerde-toets (GEBT) te bepaal. Om dit te doen het ons eerste ’n sistematiese-literatuuroorsig oor die effektiwiteit van sielkundige intervensies gedoen. Dit is gevolg deur ’n kwalitatiewe studie met die doel om die kennis en persepsies van AMVs, sowel as moontlike hindernisse en fasiliteerders van AMVs; onder MHL te verstaan. Ten derde het ons ’n toets- en proefstudie in voorbereiding vir die GEBT gedoen.

Die sistematiese-literatuuroorsig het weinige bewyse vir die effektiwiteit van sielkundige intervensies vir AMVs, veral in terme van die frekwensie van gebruik, getoon. Motiversingonderhoudvoering (MO), met en sonder die gebruik van selfoontegnelogie, en

kognitiewegedragsterapie (KGT) is gevind om effektief te wees. Verdermeer is MO effektief in die vermindering van gevaarlike seksuele gedrag, die nakoming van ART, behandeling van ander substansmisbruikversteurings, die vermindering van viralelading, en die verhoging van CD4 tellings. Die kwalitatiewestudie het gevind dat MHL voldoende kennis van die direkte en indirekte invloed van alkoholverbruik op HIV oordrag en behandeling, het. Verdermeer het deelnemers daarop gedui dat hulle oor die stigma van MHL wat ook AMVs het, besorg is. Hulle het gevra dat strategieë wat die stigma verminder geimplimenteer moet word. MHL was ontvanklik in terme van AMV intervensies.

Nadat die proefstudie daarop gedui het dat ’n intervensie vir AMVs doenbaar is, is ’n GEBT by 16 HIV-versorgingsklinieke uitgevoer. Die studie intervensies het gemengde motiveringsonderhoudvoering/kognitiewe gedragsterapie (MO/KGT) en die WHO se mh GAP intervensiegids (mh GAP IG) ingesluit. Geregistreerde algemene verpeegsters (GAV) by HIV-versorgingsklinieke het die intervensies aangebied. Die vermindering van alkoholverbruik, soos deur die *Alcohol Use Disorders Identification Test* (AUDIT) gemeet, het as primêre uitkomste gedien. Die volgende het as sekondêre uitkomstes gedien: (i) HIV parameters, soos deur die viralelading en CD4 telling gemeet; (ii) funksionaliteit, soos deur die *WHO Disability Assessment Schedule* weergawe 2 (WHODAS 2.0) gemeet; en (iii) lewenskwaliteit, soos deur die *WHO Quality of Life HIV* (WHOQOL HIV) gemeet.

Die GEBT het getoon dat GAV opgelei kan word om die MO/KGT intervensie vir MHL met AMV aan te bied. Verdermeer het die MO/KGT intervensie ’n beduidende effek op die verminering van alkoholverbruik van MHL gehad. Die effek van die mh GAP IG intervensie is vir 3 maande volgehou, terwyl die effek van die MO/KGT vir 6 maande volgehou is. Daar is ook gevind dat ’n vermindering in alkoholverbruik HIV terapie uitkomste verbeter, veral soos aangedui deur die vermindering in viralelading. Funksionaliteit en lewenskwaliteit het ook as gevolg van die intervensie verbeter. Laastens is dit bevind dat die lewering van ’n MO/KGT intervensie deur middel van taakdeling, geldig is. Die implementasie van ’n MO/KGT kan met ’n matige vermeedering van die

werksmag gedoen word. Gegewe die negatiewe effek van AMVs op die behandeling van MHL kan die vermindering van alkoholverbruik help om die UNAIDS se 90-90-90 doelwit te bereik.

Verdere kliniese toetsings van die effektiwiteit van intervensies in LMIL met ’n hoë HIV voorkoms, is nodig. Wanneer die toetsings toegepas word, moet daar aandag aan die dubbele-stigma van beide HIV en AMVs verleen word.

DEDICATION

I dedicate this dissertation to my late mother Khuthalani Esther for enduring and consistent love and my family for their love and patience. To the Almighty God be the honour and glory.

ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretrovirals
AUD	Alcohol Use Disorders
AUDIT	Alcohol Use Disorders Identification Test
CBT	Cognitive Behavioural Therapy
CONSORT	CONsolidated Standards of Reporting Trials
DSM-5	Diagnostic statistical manual version 5
DTS	Davidson Trauma Scale
DUDIT	Drug use disorders identification test
EtG	Ethyl glucuronide
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
IHDS	International HIV Dementia Scale
LMIC	Low- and Medium-Income Countries
MD	mean difference
mh GAP IG	mental health GAP Action Program Intervention Guide
MI	Motivational Interviewing
MI/CBT	motivational interviewing/ cognitive behavioural therapy
PE	phosphatidyl ethanol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QoL	Quality of life
SBI	Screening and Brief Interventions
SSA	Sub-Saharan Africa
UNAIDS	The Joint United Nations program on AIDS
WHO	World Health Organisation
WHODAS	World Health Organisation Disability Assessment Schedule
WHOQoL	World Health Organisation Quality of Life

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CHAPTER ONE

INTRODUCTION

Background

Since the beginning of the HIV pandemic in the 1981, it has caused 35 million deaths, 37 million are living with the infection, 1.9 million were infected in 2016 alone, 20.9 million were on antiretroviral therapy as at June 2017, and by 2020 US$ 26.2 billion will be required to address HIV/AIDS in low and middle income countries(1). Although the first HIV infection was documented among injection drug users and gay men in the USA (2), in Sub-Saharan Africa the main mode of infection is through heterosexual contact with prevalence higher in females (3). Sub Saharan Africa has two thirds of all infections at 25 million(4). Zimbabwe has 1.6 million PLWH with 75% cognisant of their HIV status; 75% of those infected are on antiretroviral treatment and 64% have achieved viral suppression according to a recent population based survey (5, 6).

Mental illness is associated with poor HIV disease treatment outcomes according to research(7). PLWH are at increased risk of mental illness, with more than twice the risk of depression, alcohol and substance use and anxiety disorders among this population (8-10). Mental illness has been shown to have adverse effects on adherence to antiretroviral therapy resulting in poor treatment outcomes (11). Alcohol and substance use disorders have been implicated particularly in non-adherence more than other mental disorders (12). Research suggests that a hazardous alcohol use relationship with poor HIV treatment outcomes is through lack of adherence to treatment and exacerbated by nutrition insufficiency among other factors (13, 14).

Alcohol Use and HIV transmission

Drinking increases the risk of HIV infection according to research (15); (16, 17). The increased risk of HIV infection is related to behavioural factors such as sexual encounters with at-risk populations and unprotected sex; and biological factors such as (18). Alcohol consumption leads to risky sexual behaviour, increased unprotected sex, transactional sex and multiple sexual partners (19, 20). Alcohol-serving venues are frequently patronised by individuals who have multiple sex partners and who engage in transactional sex (21, 22). Further, alcohol use has been associated with increased prevalence of sexually transmitted infections related to unprotected sex (23). This is important as HIV infection requires a breach in the vaginal and penile epithelium which is facilitated by sexually transmitted infection (24). Alcohol use increases the incidence of bacterial vaginosis that enhances the risk of acquiring sexually transmitted infection (25). Further, there is increased infectiousness in women who drink due to the accumulation of monocytic phagocytes which are the targets of the HIV virus. Breach in the epithelium and presence of T-cells processes (which are the targets of HIV virus) predominate the valvular area (26, 27).

Unhealthy alcohol use and the HIV treatment cascade

There is evidence that individuals who drink alcohol are less likely to present for HIV testing or delay in HIV testing, and delay in the commencement of antiretroviral therapy (ART)(28). By the time these individuals commence HIV treatment they are at an advanced stage of HIV disease and are likely to have poor treatment outcomes (29). Alcohol, HIV and hepatitis C lead to hepatic failure and thus adversely affect the metabolism of antiretroviral agents (30). Failure to metabolise leads to increased antiretroviral drug toxicity and associated frailties (29).

Alcohol use and adherence

The association between alcohol consumption and poor treatment adherence is well established (11; 31-34). Both the frequency and quantity of drinking result in poor adherence to HIV

treatment (33, 35). AUDs often concur with depression and both of which have been associated with poor adherence to ART (36, 37). Alcohol consumption is associated with cognitive impairment that cause patients to forget to take their antiretroviral drugs or take them out of time (38). Studies have also shown that some PLWH, through inappropriate HIV treatment education, believe that ARVs and alcohol should not be taken together as the combination is poisonous and so they skip medication on drinking days (39, 40). Taking medications 'out of time' on drinking days leads to suboptimal effects of ARVs and lack of viral suppression (40).

Alcohol consumption and viral suppression and CD4

AUDs are often associated with poor viral suppression frequently due to poor adherence to treatment among other factors (41). Adherence of about 95% or more is required to achieve viral suppression. PLWH with drinking problems, especially with dependence, have been shown to have low CD4 (42). However, hazardous use of alcohol and recent commencement on ART do not change the levels of CD4 (43, 44). Virological failure in alcohol drinking PLWH is mainly due to poor adherence to ART (41, 45) but other factors such as concurrent mental health problems and nutrition may be contributory (13).

Safe drinking and the HIV cascade

The National Institutes of Alcohol Abuse and Alcoholism (NIAAA) recommends safe drinking of 14 units per week for females and 21 units per week for males (46). However, safe drinking that applies to HIV negative individuals may not be applicable to PLWH, as studies have shown that PLWH need less alcohol to experience a 'buzz' or to feel intoxicated (35). This is important in screening and brief interventions. The drinking levels need to be reduced in PLWH.

Research has shown that compared with HIV negative individuals, PLWH suffer more physiologic harm from alcohol consumption (47). PLWH who have not achieved viral suppression need less alcohol to get drunk compared with those who have achieved viral suppression (48, 49)

which suggests that the adjustments of daily allowable alcohol need to be different within the PLWH themselves.

In females, binge drinking has been shown in experimental studies (50)to cause changes in the vaginal flora and increased inflammatory activities. As a result, females PLWH with AUDs have also been shown to be more infectious, compared to those who do not drink (26, 51).

Assessment of alcohol use

Currently, multiple ways of assessing alcohol consumption are in use including self-report questionnaire and biological (surrogate) measures. The self-report assessment includes the Alcohol Use Disorders Identification Test (AUDIT) and AUDIT C, (a short version) and the Cut-Annoyed-Guilty-Eye opener (CAGE). While the self-report questionnaires are relatively easy and less expensive to administer, their main drawback is social desirability bias, whether interviewer administered or through electronic medical record (ACASI)(52-54). The surrogate measures include liver enzyme especially the gamma glutamyl transferase (GGT), and the mean corpuscular volume. Other biomarkers include phosphotidylethanol (PE) and ethyl glucuronide (EtG). PE has been found to be robust in assessing alcohol use levels and treatment progress (55, 56). EtG which is found in hair and urine has been found to be especially sensitive and highly specific in assessing recent alcohol consumption (57). GGT and MCV changes can be caused by a variety of conditions and may take longer to correct. PE and EtG are expensive and may be unaffordable in low and middle income countries (58). Yet, screening for alcohol use is an important component of treatment. Screening and Brief Interventions (SBIs) have the most evidence for effectiveness and are recommended by many guidelines for treatment of problematic alcohol use in the general population (59).

Alcohol Interventions in PLWH

Alcohol consumption is recognised as one of the modifiable risk factors for failure to control the HIV pandemic (31) but, despite the availability of many evidence-based alcohol use therapies,

few have proved to be effective in reducing alcohol use in PLWH (60). On a positive note, a recent meta-analysis by Scott-Sheldon found behavioural interventions effective for reducing alcohol use and other behaviours such as risky sex in PLWH (61). Some other explanations for lack of effectiveness are the presence of multiple morbidities in HIV; the extent of alcohol use; the differences in the levels of experience in intervention staff and the number of sessions given (60). As drinking differs in severity, PLWH with alcohol dependence may benefit from stepped-up models of care (62). As such, adjuvant pharmacological interventions may be needed to complement psychotherapeutic and psychosocial modalities (63).

Some commonly used evidence-based treatments for problematic drinking include motivational therapies; cognitive behaviour therapies (CBT); problem solving; risk reduction; and twelve step facilitations (TSF) (60). However, many individual studies have marked heterogeneity in treatment modality to allow for reviews with meta-analysis to find the treatments that have notable treatment effect (60). In order to improve alcohol use treatment outcomes, combinations of these evidence-based therapies are indicated. Some of the treatment combinations are motivational interviewing and CBT such as problem solving and risk reduction (64). Findings on the effectiveness of interventions for hazardous drinking have not been consistent with some only showing effects (60, 65) and it seems that high levels of alcohol consumption may require more intensive interventions (66). The interventions may require a combination of psychological and pharmacological methods in a stepped care design (67). However, again due to the multiple co-morbidities, and a high pill burden, pharmacological treatments for unhealthy alcohol use may encounter similar adherence challenges as with ART.

Task sharing in alcohol use treatment and HIV care

Sub-Saharan Africa (SSA) has high prevalence of HIV infections but also faces severe shortages of health workers, especially in mental health, owing to HIV deaths, brain drain and natural attrition

(68, 69). Further, HIV infection is accompanied by other co-morbid conditions such as depression and anxiety which increase the workload and require specialist care (37, 70). Task-sharing has been identified as a solution, though it may require further training and additional funding to set up (71). Task sharing has been embraced in HIV care settings and has resulted in increased ART coverage, suggesting its' utility in augmenting interventions for alcohol and substance use reduction in PLWH to improve treatment outcomes (72, 73). However mental health care has not fully embraced task sharing, which has a potential to improve coverage and extend to the difficult to reach population.

The HIV/Alcohol use situation in Zimbabwe

Zimbabwe has a high HIV burden and a per capita alcohol consumption of close to 6 litres, according to World Health Organisation (WHO) (74). This is higher than the World Health Organisation Afro-region of 3.2 litres (WHO 2014). PLWH have high prevalence of alcohol use according to research from the United States (9). Therefore, a double burden of HIV and unhealthy alcohol use prevails and HIV elimination as espoused by WHO is a challenge in the context of high alcohol use prevalence. WHO initiated the 'test and treat' policy that stipulates that every person testing positive for HIV be commenced on ART. This has led to more people who may not have been symptomatic receiving HIV treatment (75). This accords with the 90-90-90 targets as set by the UNAIDS, so that by 2020, 90% of people infected with HIV should know their HIV status; 90% be on HIV treatment and 90% achieve viral suppression with a view to eliminating HIV by 2030 (76). As a result, consistent adherence to ART may be a priority requiring novel strategies to retain PLWH in care.

Policies and strategies to improve HIV coverage require attention to such factors as alcohol use treatment within HIV care. However, Zimbabwe – like many countries in the SSA region – has no policies to reduce alcohol consumption among PLWH (77). Calls have been made for implementation interventions for unhealthy alcohol use to improve adherence and achieve significant viral

suppression. The interventions can lead to ART utilisation for an extended life expectancy through reduced risky sexual behaviour and lower rates of new HIV infection (78). However, more research needs to be carried out to establish the most efficacious interventions; the clinical situations enabling intervention delivery; the required intervention doses to effect change; and cost-effective task-sharing models that maintain the quality of interventions. The overall purpose of this study was to identify the possible components, development of treatment protocols and to ascertain treatment efficacy.

Research question

Does a behavioural intervention for unhealthy alcohol consumption in PLWH, as offered by registered general nurses in a resource limited setting, lead to a reduction in alcohol use (as measured by the AUDIT), and an improvement in functional capacity, quality of life and adherence to HAART (as measured by the viral load and CD4)?

Hypothesis

1. An adapted motivational interviewing/cognitive behavioural therapy (MI/CBT) treatment will lead to reduction in unhealthy alcohol use among PLWH.
2. An adapted MI/CBT treatment to reduce unhealthy alcohol use in PLWH compared to WHO mental health GAP Intervention Guide (mh GAP IG) will lead to reduction in alcohol use, adherence to HAART and significantly greater improvement in functional capacity and quality of life.

Specific aims

1. To evaluate the effect of an adapted motivational interviewing and cognitive behavioural therapy (MI/CBT) treatment in people living with AIDS (PLWH) on alcohol use outcomes.
2. To assess whether an adapted MI/CBT treatment for alcohol use in PLWH compared with the WHO mental health GAP Intervention Guide (mh GAP IG) as delivered by Registered General Nurses

(RGN) in a task-sharing model will improve functional ability and quality of life. As nurses are not usually schooled to provide psychological treatments such as motivational interviewing, this treatment trains them to deliver this treatment with the help of a manual. Provision of specialised care by health care workers with a lower scope of training is referred to as task-sharing.

3. To establish whether an adapted MI/CBT intervention for alcohol consumption in PLWH compared with mhGAP IG as delivered by RGN can lead to better treatment adherence in Zimbabwe as measured by viral loads and CD4.

General methods

Full description of the study methodology is included in the accompanying manuscripts.

Ethical considerations

The Health Research Ethics Committee (SI14/10/222) of Stellenbosch University, Cape Town, and the Medical Research Council of Zimbabwe (A/1936), Harare, Zimbabwe approved the study.

To inform the development of the treatment, the scope of review interventions for alcohol use in general and a systematic review of evidence for the psychological evidence-based therapies for unhealthy alcohol use in PLWH in particular was done. Further, a qualitative study to assess the perceptions of drinking in the context of HIV was undertaken among 39 PLWH. In-depth interviews to assess the facilitators and barriers to intervention for unhealthy alcohol use from a program point of view were done with 5 experts in mental health and HIV care. A pilot and feasibility study were conducted at a central Zimbabwean hospital among 40 people living with HIV. Finally, to answer our research questions, a cluster randomised controlled trial involving 16 HIV care clinics was carried out. The accompanying manuscripts show the results of these studies.

Accompanying manuscripts

Systematic review of psychological interventions for alcohol use disorders in PLWH

The systematic review aimed at identifying the appropriate evidence-based treatment and its components for development of a treatment for unhealthy alcohol use for PLWH. In this manuscript we followed PRISMA guidelines to systematically review the literature on interventions designed to test empirically proven psychological interventions for unhealthy alcohol use in PLWH. See methods section of the review manuscript.

Development of the intervention protocol

The aim of this section of the study was to develop a framework including an outline of the treatment arms. We outline the process of developing the MI/CBT intervention arm and mh GAP IG control whilst providing background to the assessment measures.

Qualitative study to understand the effects of drinking in the context of HIV infection

The study aimed to describe and understand the perceptions and impact of alcohol use in a sample of HIV positive individuals. The methods are fully described in the article.

Pilot and feasibility study of an alcohol use disorder intervention

The aim of the study was to assess the feasibility of conducting a cluster randomised controlled trial on the effectiveness of motivational interviewing/cognitive behavioural therapy (MI/CBT) treatment for unhealthy alcohol use compared to the WHO mh GAP IG in PLWH in Zimbabwe. The methods are discussed in the manuscript.

Alcohol use disorders intervention in PLWH in Zimbabwe: a cluster randomised controlled trial (RCT)

The overall aim of the RCT was to compare the effectiveness of an MI/CBT treatment to mh GAP IG on reduction of AUDIT score and HIV treatment outcomes as measured by the viral load and CD4; functional capacity as measured by WHODAS 2.0 tool; and quality of life as measured by

WHOQOL HIV. We also assessed the feasibility of training RGNs and using them to deliver treatment using manuals within the HIV care clinic. The methods used are outlined in the manuscript.

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CHAPTER TWO: SYSTEMATIC REVIEW

Title : Psychological interventions for alcohol use in people living with HIV/AIDS: A Systematic Review

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ABSTRACT

Background

Alcohol use in people living with HIV/AIDS impairs quality of life and is a significant impediment in achieving HIV viral control. As the focus of HIV treatment has moved towards elimination of the disease, alcohol use has been identified as one of the obstacles and treatments for unhealthy alcohol use are therefore essential. Psychological interventions may be effective although a systematic review published in 2013 was inconclusive. The objectives of the review were to identify the literature and synthesize the evidence on the effects of psychological interventions for unhealthy alcohol use in people living with HIV/AIDS.

Methods

A search was conducted through PubMed (1986-2017); Cochrane Central Register of Trials (CENTRAL), MEDLINE (Ovid) (1986-2017; EMBASE (EMBASE.com 1986-2017); PsychInfo (Ovid)(1986-present); and Clinical trials.gov (clinicaltrials.gov) for eligible studies on 10 July 2017. Two reviewers independently screened titles, abstracts, and full texts to select studies that met the inclusion criteria. Two reviewers independently performed data extraction.

Results

Owing to the high degree of heterogeneity in the outcome measures for alcohol use across studies, a meta-analysis was not possible. Fourteen studies met the review inclusion criteria. The majority of studies came from the United States and three from Sub-Saharan Africa. Selection, performance and attrition biases were deemed to be unclear or high in the included studies. In a narrative synthesis, we found beneficial effects for motivational interviewing aided by mobile technology and cognitive behavioural therapy (CBT)in individual studies. Of the studies that assessed secondary outcomes, there were some effects for motivational interviewing on viral loads, other substance use, risky sexual behaviours and adherence to antiretroviral treatment.

Conclusion

As we were unable to perform a meta-analysis, no definitive conclusions can be drawn about the effectiveness of psychological interventions for alcohol use in people living with HIV. There was evidence for the effectiveness of motivational interviewing aided by mobile technology and CBT on its own. Randomised clinical trials of interventions that incorporate technology and which measure alcohol use in a standardised way are needed, especially in low- and middle-income countries.

Key words: Alcohol, HIV, Systematic, Psychological, Motivational, Cognitive, Interventions, Review

Systematic Review PROSPERO Registration CRD42017063856

Background to study

It is estimated that 30-50% of people living with HIV also have alcohol use (Azar, Springer, Meyer, & Altice, 2010; Galvan et al., 2002). This is important, first, because of the general consequences of hazardous alcohol use such as intoxication, accidents, violence, liver disease, and cancers. Secondly, PLWH who drink alcohol are more likely to have delayed HIV treatment initiation, reduced adherence to antiretroviral therapy (ART), more treatment interruptions and a lower chance of achieving viral suppression(Azar et al., 2010). Thirdly, alcohol use is associated with risky sexual behaviour, sexually transmitted infections and hence spread of HIV infections(Morrison, DiClemente, Wingood, & Collins, 1998; Williams et al., 2016). Viral load suppression is a key target in the UNAIDS goals that aim at eliminating HIV by 2030 (Azar et al., 2010). Unhealthy alcohol use is also associated with risky sexual behaviour, non-use of condoms, and reduced uptake of pre-exposure and post-exposure prophylaxis (Van der Elst et al., 2013; van Griensven et al., 2010).

Alcohol use disorders (AUDs) are defined in the American Psychiatric Association's Diagnostic Statistical Manual version 5 (DSM-5) as “a group of disorders that are caused by the consumption of alcohol” (American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders : DSM-5 (5 ed.). Arlington). They include those conditions that were previously referred to individually as alcohol abuse and alcohol dependency (VAPA.). Alcohol abuse refers to persistent consumption of alcohol despite the presence of physical, psychological, and social problems. Alcohol dependence is defined by the presence of tolerance and withdrawal.

Assessment of individuals with alcohol use is usually through clinical evaluation, biological investigations and self-report questionnaires. The biological measures include assessment of blood alcohol concentration, or surrogates such as liver transaminases such as gamma glutaryl transaminase (GGT), mean corpuscular volume (MCV), or markers such as Phosphotidyl ethanol and ethyl glucuronide (EtG) (Eyawo et al., 2018). The self-report assessments include the Cut-Annoyed-

Guilty-Eye-opener which is a 4-question instrument that assesses mainly the presence of dependency, and the Alcohol Use Disorders Identification Test (AUDIT) which is a 10-question instrument developed by the World Health Organisation (WHO) which scores from 0 to 40 (Babor TF, care., & 1989b.).

Interventions for reducing alcohol use are heterogeneous and include brief education, motivational interviewing and longer interventions based on CBT. At the time we began this study there had been two previous systematic reviews in 2010 and 2013 (Azar et al., 2010). Neither of these found conclusive evidence that psychological interventions could improve unhealthy alcohol use in PLWH, or improve viral suppression. New studies have emerged that address alcohol use in the context of HIV treatment (Azar et al., 2010; Hasin et al., 2013; Zule et al., 2014). A systematic review and meta-analysis of behavioural interventions for alcohol use in HIV, with a focus on alcohol quantity, has reported evidence of behavioural therapies on alcohol use quantities, adherence and risky sexual behaviour (Scott-Sheldon, Carey, Johnson, Carey, & Team, 2017). However, this review differs from our review as our study specifically examines alcohol use frequency.

Psychological interventions can be delivered in diverse ways, such as in a group (more than one individual) or individual or both; and in different settings including hospital based, community, primary care settings or emergency services (Brown, DeMartini, Sales, Swartzendruber, & DiClemente, 2013). Improvements in delivery have come through increased use of smartphones and other mobile devices (Aharonovich et al., 2006) and, as technology penetration in high endemic areas increases, this may be preferable as more people can be reached compared to conventional face-to-face methods (Forman et al., 2018). Technology based interventions commonly called mHealth interventions are a promising group of psychological interventions (Aharonovich, Stohl, Cannizzaro, & Hasin, 2017; Murray, Khadjesari, Linke, Hunter, & Freemantle, 2013).

Brief psychological interventions can be offered in emergency care services in an opportunistic way (alcohol use is discussed with patients who are seeking help for other health problems) though

subject to limitations occasioned by the lack of space and time (Strauss, Munoz-Plaza, Tiburcio, & Gwadz, 2012). The services can also be delivered at family/general practice settings that may offer privacy, although many family practitioners avoid discussing alcohol use as they tend to be familiar (they have established a relationship) with patients and, indeed, many may be aware of the drinking patterns of their clients but avoid the subject due to discomfort (Le et al., 2015). Other family practitioners have identified the lack of time and challenging clinical settings that restrict space and personal privacy as barriers to the provision of brief psychological screening interventions (Lee, Olsen, & Sun, 2017).

Given that adherence to ART is the single most important determinant of HIV treatment outcomes, the effects of an AUD-focused psychological intervention may significantly improve HIV treatment outcomes (Gordon et al., 2017). Reviews to date of interventions which targeted adherence only without control of unhealthy alcohol use are inconclusive, leading to calls for interventions that target both adherence and unhealthy alcohol use (Brown et al., 2013; Samet & Walley, 2010). Psychological interventions may be tailored to address comorbid conditions such as depression that are also implicated in poor ART adherence ("<AUD_Depression_Transdiagnostic_WHOSouth-EastAsiaJPublicHealth6150-4198152_113941.pdf>,"; Balhara, Gupta, & Elwadhi, 2017; Etienne, Hossain, Redfield, Stafford, & Amoroso, 2010; Mayston, Kinyanda, Chishinga, Prince, & Patel, 2012; Nakimuli-Mpungu et al., 2012). Psychological interventions may work through providing support; the acquisition of new problem-solving skills to deal with other life problems, and a reduction in time available to drinking through the development of a structured life (usually absent in PLWH dually diagnosed with unhealthy alcohol use within a trans-diagnostic model) (Rodriguez-Seijas, Arfer, Thompson, Hasin, & Eaton, 2017).

Psychosocial interventions may address stigma, depression and anxiety that are faced by PLWH (Chung & Magraw, 1992; Edelman et al., 2017). The collation of evidence for effectiveness of various psychological therapies may help providers select the most suitable therapy to fit individual

patients' circumstances. There are insufficient data on the effectiveness of interventions, the active ingredients of each treatment, the required dosing, and the circumstances under which they work (Brown et al., 2013). Brown et al (2013) called for efficacious interventions to be developed and implemented. This systematic review synthesizes current evidence on the effectiveness of various psychological interventions for unhealthy alcohol use in PLWH.

Objectives

To systematically synthesise evidence on the effectiveness of psychological interventions for unhealthy alcohol use on alcohol consumption and HIV treatment outcomes in people living with HIV/AIDS.

Methods

The protocol of this review was registered with PROSPERO (CRD42017063856). The review is reported using PRISMA guidelines.

Electronic searches

The following keywords were used in the search of the literature:

(((HIV [Title/Abstract] OR AIDS [Title/Abstract] OR "human immunodeficiency virus" [Title/Abstract] OR "acquired immunodeficiency syndrome" [Title/Abstract] OR "retroviral infection" [Title/Abstract])) OR (HIV OR "Acquired Immunodeficiency Syndrome" [MeSH Terms]))) AND (((Alcohol*[Title/Abstract] OR drinking [Title/Abstract])) OR "Alcohol-Induced Disorders" OR "Alcohol-Related Disorders" OR "Alcohol Drinking" [MeSH Terms]))) AND (("Psychological intervention" [Title/Abstract] OR therapy[Title/Abstract] OR psychotherapy [Title/Abstract] OR "motivational interview"[Title/Abstract] OR "motivational interviewing" [Title/Abstract] OR "contingency management" [Title/Abstract] OR "mutual help"[Title/Abstract] OR "twelve step facilitation" [Title/Abstract] OR "twelve steps" [Title/Abstract] OR "twelve step"[Title/Abstract])))

Two reviewers searched, the Cochrane Central Register of Trials (CENTRAL), MEDLINE (Ovid) (1986-2017; EMBASE (EMBASE.com 1986-present); PsychInfo (Ovid)(1986-present), Clinical trials.gov (clinicaltrials.gov/). There were no language restrictions imposed on the search.

Other search sources

A search of the reference list and bibliographic references of the articles selected for inclusion in the review identified additional relevant articles. These were considered for data collection based on their titles and abstracts. Other searches were done through a hand search of authors who have published in the area. Authors whose publications were registered in the trial registers but unavailable in databases were contacted by email.

Criteria for considering studies for this review

Types of studies

The full text of articles of studies that met the inclusion criteria were obtained for data synthesis. Studies included in the review were randomised controlled trials and other designs that used a quasi-random allocation mechanism, such as alternating assignment, next available treatment slot or wait-list controls.

Types of participants

Participants were PLWH aged 16 years and above who had unhealthy alcohol use with or without other substance use and were on antiretroviral therapy at hospitals, in clinics, and in the community.

Types of intervention

The interventions in the review articles included motivational interviewing, motivational enhancement therapy, cognitive behavioural therapy, community contingency therapy, group therapy or any combinations of the above that target unhealthy alcohol use with or without other

substance use. Control conditions included adherence counselling and referral to psychiatric units and usual care.

Types of outcome measures

1. Primary outcomes which were reduction in alcohol use as measured by the reduction in the frequency of alcohol consumption.
2. Secondary outcomes which were other substance use, viral load, CD4 count change, quality of life and adherence to antiretroviral treatment.

Data collection and analysis

Selection of studies

Two reviewers (MM and JJ) independently screened titles, abstracts, and then full texts to select studies that met all inclusion criteria including randomised controlled trials and other designs that used a quasi-random allocation mechanism, such as alternating assignment, next available treatment slot or wait-list controls. The review authors reconciled any differences through discussion at each stage.

Data extraction and management

Two reviewers (MM and AM) extracted data independently using a pre-piloted standardised data extraction form developed and piloted for this review. In the event of disagreements, the reviewers went through the original articles until they reached consensus. For each study included, we extracted the following information: (1) general (e.g. ethics approval, funding and study period); (2) methods (e.g. study design and number of participants randomised per group); (3) participants (e.g. country, setting, age and co-morbidity); interventions (e.g. type and duration of psychological intervention); (4) outcomes (e.g. description and time point collected); (5) results (e.g. numerical results for pre-specified outcomes); (6) comparisons (e.g. motivational interviewing versus treatment

as usual), and (7) risk of bias information (e.g. sequence generation, allocation concealment, and so on).

Assessment of risk of bias in included studies

Two reviewers (MM and AM) independently assessed the risk of bias of the included studies. A Cochrane Risk of Bias tool was used to assess bias in the included studies (Higgins et al., 2011). Domains assessed in the risk of bias assessment included adequacy of sequence generation and allocation concealment with respect to selection bias and blinding of the participants, research staff, and outcome assessors as related to detection bias. The other domains assessed were incomplete/missing outcome data caused by attrition or loss to follow up. Selective reporting was also assessed (i.e. where unfavourable or negative outcomes are not reported), and finally other bias including the influence of funders and other ethical considerations.

Measures of treatment effect

For binary outcomes, we calculated the risk ratio (RR) with its corresponding 95% confidence intervals (CI) where raw data were reported, otherwise we reported the odds ratios (OR) as reported by the study authors. For continuous data, we calculated the mean difference (MD) with its corresponding 95% CI. Both RR and MD were calculated using Review Manager 5.3 software (Review Manager (RevMan) [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre).

Results

Description of studies

Results of the search

A combined total of 7296 studies were identified through the various search methods and, after removing duplicates, screening titles and abstracts, 21 studies were retained. Full texts of the 21 studies were retrieved and 14 studies which met the inclusion criteria were ultimately included in the review. The PRISMA diagram (Figure 1) summarises the results of the search.

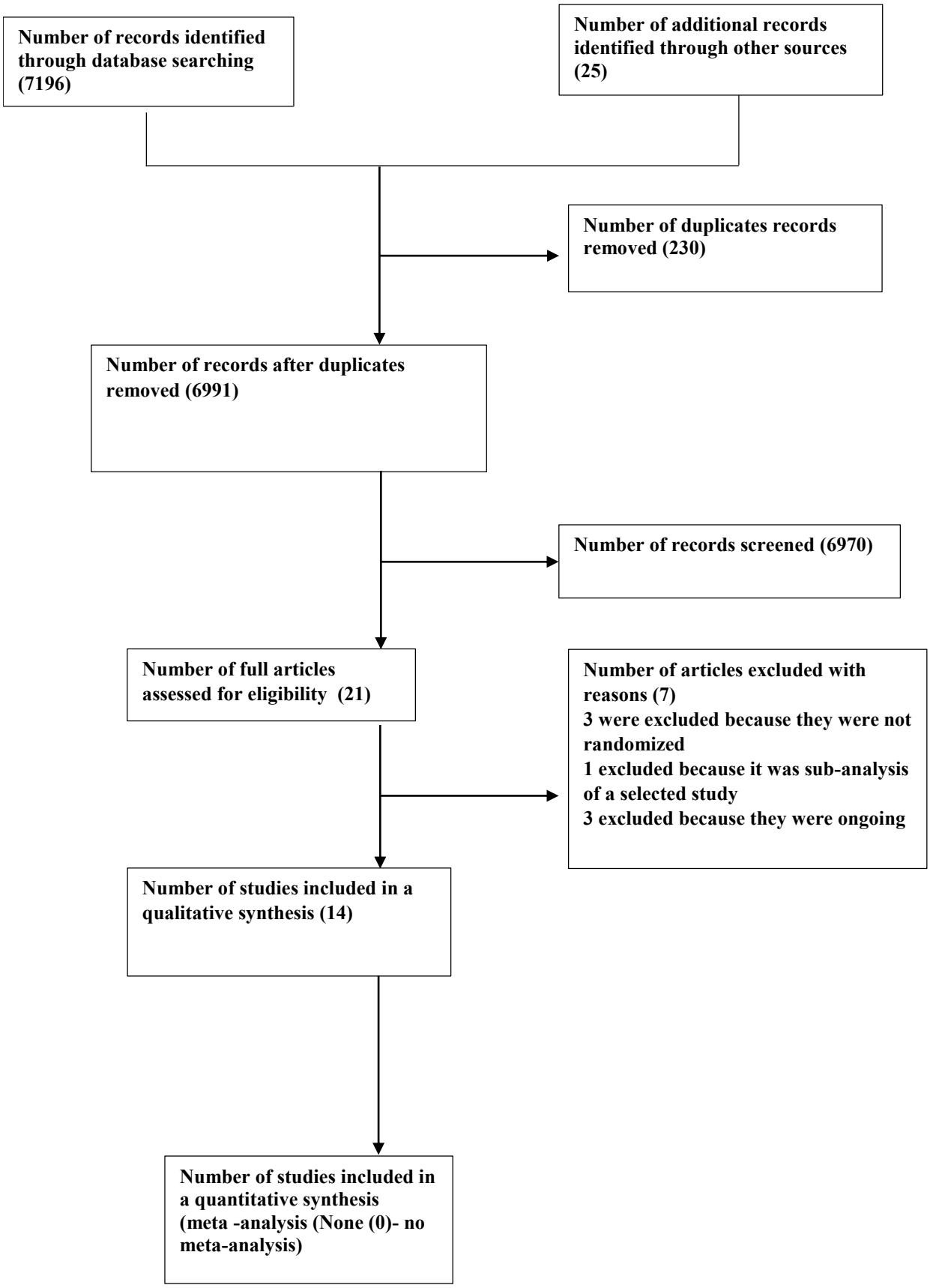

Figure 1: PRISMA Diagram

Characteristics of studies included

The PRISMA diagram (Figure 1) summarises the results of the search. We included 14 studies that assessed alcohol use in PLWH. All 14 studies were randomised controlled trials. Eight studies included both men and women (Gilbert et al., 2008; Hasin et al., 2013; Meade et al., 2010; Papas et al., 2011; Parsons, Golub, Rosof, & Holder, 2007; Samet et al., 2005; Wong et al., 2008), one study included men who have sex with men only (Velasquez et al., 2009) and three studies included women only (Rotheram-Borus et al., 2012; Weiss et al., 2011; Zule et al., 2014). Three studies were from Africa (Papas et al., 2011; Wandera et al., 2017; Zule et al., 2014) while the rest were from the USA (Gilbert et al., 2008; Hasin et al., 2013; Meade et al., 2010; Naar-King et al., 2008; Parsons et al., 2007; Rotheram-Borus et al., 2012; Samet et al., 2005; Velasquez et al., 2009; Weiss et al., 2011; Wong et al., 2008). Six studies employed various forms of motivational interviewing (Gilbert et al., 2008; Hasin et al., 2013; Naar-King et al., 2008; Parsons et al., 2007; Samet et al., 2005; Velasquez et al., 2009) and two used cognitive behavioural therapy (Meade et al., 2010; Papas et al., 2011; Parsons et al., 2007; Weiss et al., 2011). Two studies evaluated motivational therapies with the addition of technology (Gilbert et al., 2008; Hasin et al., 2013). Eight studies (Chander, Hutton, Lau, Xu, & McCaul, 2015; Hasin et al., 2013; Meade et al., 2010; Naar-King et al., 2008; Papas et al., 2011; Parsons et al., 2007; Samet et al., 2005; Wandera et al., 2017; Wong et al., 2008) delivered individual interventions while three delivered group therapies (Rotheram-Borus et al., 2012; Velasquez et al., 2009; Weiss et al., 2011). A wide range of alcohol use measures were administered across the studies, with the majority utilising self-report questionnaires. Table 1 gives a summary of included studies.

Study ID	Country	Age	Sex	Sample size	Design	Intervention	Control	Mode of delivery	Alcohol use measure	Viral load	CD4	Adherence	Risky sexual behavior	Other substance use	Quality of life
Chander 2015	USA	18 Years and above	Females	148	Randomized control end trial, individual non-inferiority	Brief Intervention (SBI)	Brief intervention (BI) versus Treatment as usual (TAU)	Individual delivered	frequency and quantity of alcohol use or >/=4 drinks per occasion	Yes	Yes	Yes	Yes	No	*
Gilbert 2008	USA	18 years and above	Males and Females	476	Parallel groups randomized controlled trial	Motivational interviewing	Computer / Technology versus Treatment as usual (TAU)	Video doctor	Days of illicit alcohol and substance use.	No	No	No	Yes	Yes	No
Hasin 2013	USA	18 years and above	Males and Females	170	Parallel three-arm individually randomized design	Motivational interviewing	Computer / Technology versus Treatment as usual (TAU)	Individual using mobile technology	Frequency and quantity of alcohol use	No	No	No	No	No	No
Meade 2010	USA	18 years and above	Males and female	247	Randomized clinical trial, non-inferiority	Cognitive, stress management	Group versus TAU/Wait list/ Nutritional	Individual	Frequency and quantity of alcohol and clinical syndrome	Yes	Yes	No	No	Yes	No
Naar-King 2008	USA	16-25	Males and females	65	Cognitive, stress management	Motivational enhancement therapy	Motivational Interviewing (MI) versus Control	Individual	Frequency and quantity of alcohol uses	Yes	No	No	Yes	Yes	No
Papas 2011	Kenya	37.2	Males and females	75	Randomized clinical trial comparing CBT usual	Cognitive behavioural therapy	Cognitive Behavioral Therapy	Individual	AUDIT-C	No	No	No	No	No	No

					care (non-inferiority)		versus Control								
Parsons 2007	USA	43.6	Males and females	143	Randomized controlled trial non-inferiority comparison	Motivational interviewing and cognitive behavioural therapy	Motivational Interviewing (MI) versus Control	Individual	AUDIT	Yes	Yes	No	No	No	No
Study ID	Country	Age	Sex	Sample size	Design	Intervention	Control	Mode of delivery	Alcohol use measure	Viral load	CD4	Adherence	Risky sexual behavior	Other substance use	Quality of life
Rotheram-Boras 2011	USA	40.2	Females	310	Randomized controlled non-inferiority	Family based intervention	Group versus TAU/Wait list/ Nutritional	Group	*	Yes	Yes	Yes	Yes	Yes	No
Samet 2007	USA	*	Females	151	Randomized controlled trial non-inferiority comparison	Motivational interviewing	Motivational Interviewing (MI) versus Control	Individual	CAGE	Yes	Yes	Yes	No	Yes	No
Velasquez 2009	USA	31.46	Males and females	253	Randomized controlled compared with TAU	Motivational interviewing	Motivational Interviewing (MI) versus Control	Peer group and individual	AUDIT	yes	No	Yes	Yes	Yes	No
Wandera 2017	Uganda	*	Males and females	1253	Randomized controlled compared with TAU	Brief intervention	Brief intervention (BI) versus Treatment as usual (TAU)	Individual	AUDIT	No		No	No	No	No
Weiss 2011	USA	*	Males and females	900	Randomized trial	Cognitive-Behavioural	Group versus TAU/Wait	Individual and group	Miami alcohol use	Yes	Yes	Yes	Yes	Yes	No

						Therapy Stress Management	list/ Nutritional		questionnaire						
Wong 2008	USA	39.8	Males and females	936	Randomized controlled trial non-inferiority	Case management	Brief intervention (BI) versus Treatment as usual (TAU)	Individual	Self-report	No	Yes	No	Yes	Yes	Yes
Zule 2014	South Africa	*	Males and females	84	Randomized field experiment	HIV counselling and testing	Group versus TAU/Wait list/ Nutritional	Individual	self-reported frequency and quantity of alcohol use,	No	No	Yes	No	Yes	No

Excluded studies

Seven studies out of 21 were excluded from the review. Three were excluded because they were not randomised (Moore et al., 2015; Peltzer, Tabane, Matseke, & Simbayi, 2010); and one excluded because it was a sub-analysis of an included study (Aharonovich et al., 2017). Three (Huis n 't Veld et al 2012, Parry et al 2014 and Madhombiro et al 2017) studies were excluded because they were ongoing studies.

Risk of bias in studies included

The results of the risk of bias assessment are summarized in Figures 2 and 3. Below we briefly report the results.

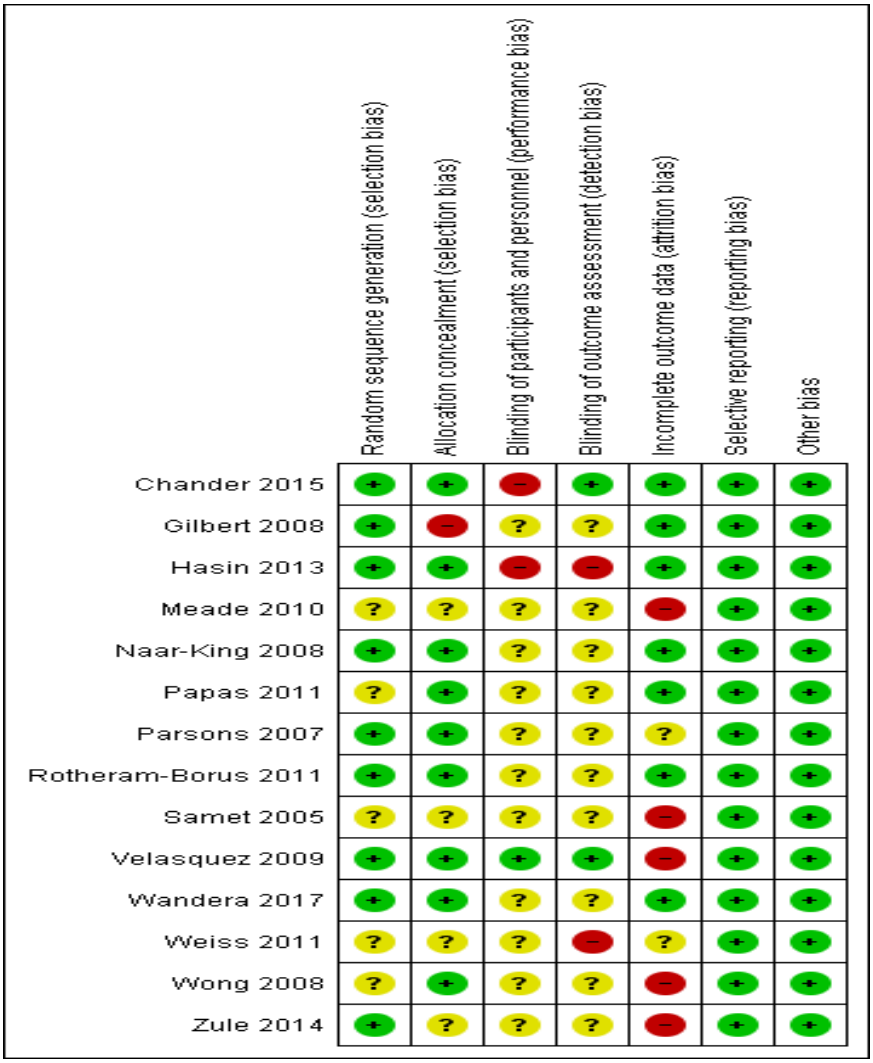

Figure 2: The risk of bias assessment of the 14 studies included in our review. Most studies were at high or unclear risk of performance, detection and attrition biases.

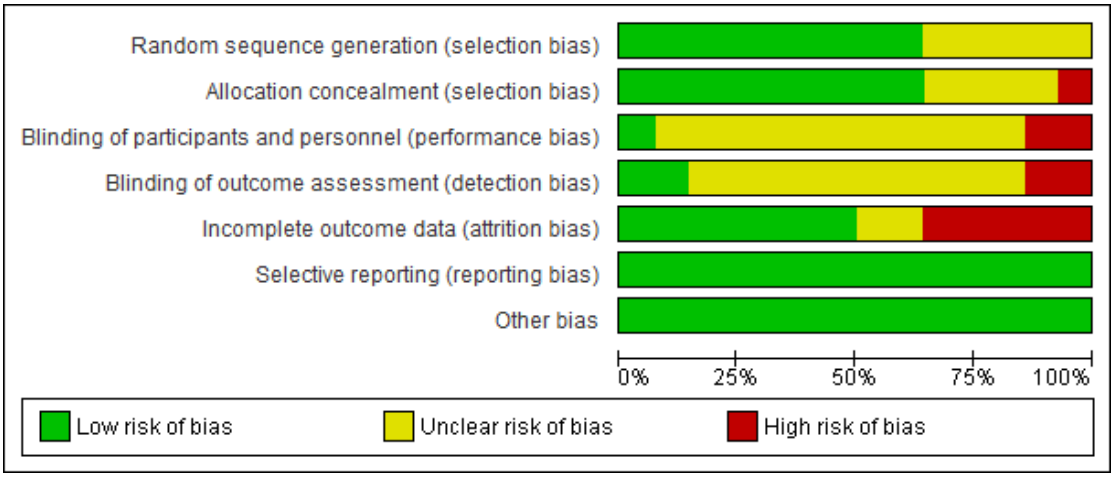

Figure 3: Presentation of assessment of bias findings in the included studies, with most studies being free of selective reporting and other biases.

Allocation (selection bias)

Ten studies (Chander et al., 2015), (Gilbert et al., 2008; Hasin et al., 2013; Naar-King et al., 2008; Parsons et al., 2007; Rotheram-Borus et al., 2012; Velasquez et al., 2009; Wandera et al., 2017; Wong et al., 2008; Zule et al., 2014) were judged to be at low risk of bias for sequence generation as they used computers to assign participants to the allocated treatment arms. Three studies (Gilbert et al., 2008; Wong et al., 2008; Zule et al., 2014) had allocation procedures that were unclear or at high risk of allocation concealment bias either because the participants would have known the arms they were allocated to or the approach to concealment such as use of an opaque envelope was not defined. The Papas et al (2011) study was judged to be at low risk of bias for allocation concealment and an unclear risk of bias for sequence generation.

Blinding (performance bias and detection bias)

Only a single study (Velasquez et al., 2009) was judged to be at low risk of performance detection bias as the assessors were blinded to the intervention. Chander et al (2015) was judged to be at low risk of detection bias, but the presence of performance bias was not clear. All the studies

were either at high or unclear risk of performance bias except Velasquez et al (2009) since they did not report on blinding or they stated that the assessors or participants were not blinded. Apart from Velasquez et al (2009) and Chander et al (2015) all the studies were at high or unclear risk of detection bias as they did not report on how the outcome assessors were blinded.

Incomplete outcome data (attrition bias)

While seven studies (Chander et al., 2015; Gilbert et al., 2008; Hasin et al., 2013; Naar-King et al., 2008; Papas et al., 2011; Rotheram-Borus et al., 2012; Wandera et al., 2017) were judged to be at low risk of attrition bias, five studies (Meade et al., 2010; Samet et al., 2005; Velasquez et al., 2009; Wong et al., 2008; Zule et al., 2014) were at high risk of attrition bias (loss to follow-up) and for two studies (Parsons et al., 2007; Weiss et al., 2011) it was unclear whether there was attrition bias. The studies that were at high risk of incomplete outcome data had high rates of loss to follow-up.

Selective reporting (reporting bias)

All the studies were judged to be at low risk of selective reporting in this review because they all reported on the outcomes they intended to assess.

Other potential sources of bias

None of the studies was judged to be at high risk of other biases as they clearly addressed other issues such as the funding, ethical considerations and they declared authors' interests.

Effects of interventions

The included studies can be classified according to the following five comparisons: (1) Motivational Interviewing (MI) versus Control; (2) Cognitive-Behavioural Therapy (CBT) versus Training as Usual (TAU); (3) Brief Intervention (BI) versus TAU; (4) Computer/ Technology versus TAU; and (5) Group therapy versus TAU/Wait List/Nutritional.

We analysed data separately for each of these comparisons due to the lack of homogeneity.

i. Comparison 1: Motivational Interviewing (MI) versus Control

Five studies assessed this comparison (Hasin et al., 2013; Naar-King et al., 2008; Parsons et al., 2007; Samet et al., 2005; Velasquez et al., 2009).

Primary outcome

Reduction in alcohol use

All five studies measured this outcome. A study involving both females and males with three-parallel groups intervention study (Hasin et al., 2013) measured the number of drinking days over a 60-day period and found no significant difference between the two treatment groups (mean difference [MD] -0.71 days, 95%CI: -1.73 to 0.11, n=170).

A women-only intervention (Naar-King et al., 2008) measured most standard drinks in one week and also found no significant difference in the log-transformed 6-month follow-up change scores between the two treatment groups (MD -0.36, 95%CI: -0.84 to 0.12, n=49).

A predominantly male study (Parsons et al., 2007) measured the number of drinks per drinking day from baseline to 3 months and from baseline to 6 months; however, since the authors did not report the standard deviations, we could not calculate the treatment effect. The authors reported no significant difference between the two treatment groups.

A two-arm study (Samet et al., 2005) measured the number of drinks per day at baseline and short- and long- term follow-up. There were no significant differences between the two treatment groups at both short-term (MD -0.10, 95%CI: -1.48 to 1.68, n=117) and long-term follow-up (MD 0.40, 95%CI: -1.25 to 2.05, n=97).

A men sex with men (MSM) population study (Velasquez et al., 2009) measured the number of drinks per 30-day period. Participants in the control group drank significantly more alcohol

compared to the motivational interviewing group (OR 1.38, 95%CI: 1.02 to 1.86), according to the study authors. However, the study did not report the actual number of participants experiencing the event per treatment group and therefore we could not calculate the risk ratio.

Secondary outcomes

Reduction in viral load

Three studies assessed viral loads. One of the studies (Velasquez et al., 2009) measured the decrease in log viral load from baseline to 6 months and there was no significant difference between motivational interviewing and control groups (MD -1.23, 95%CI: -2.48 to 0.03, n=46).

Another US based study (Samet et al., 2005) measured log viral load at baseline, 3 months, and 6 months. The motivational interviewing group was significantly more likely to reach a 0.5 log viral load reduction (risk ratio [RR] 2.03, 95%CI: 1.11 to 3.70, n=117) and 1.0 log viral load reduction (RR 2.16, 95%CI: 1.02 to 4.58, n=117) at 3 months than the control group. However, there were no significant differences between the two treatment groups at 6 months.

Samet et al (2005) measured log viral load at baseline, short-term and long-term. There were no significant differences between the two treatment groups at both short-term (MD -0.40, 95%CI: -1.03 to 0.23, n=113) and long-term (MD 0.20, 95%CI: -0.49 to 0.89, n=93).

CD4 count

Two studies measured CD4 count (Parsons et al., 2007; Samet et al., 2005). One of the studies (Parsons et al., 2007) measured CD4 count at baseline, 3 months, and 6 months. The motivational interviewing group was significantly more likely to reach a 10% increase in CD4 count (RR 2.60, 95%CI: 1.20 to 5.65, n=117) at 3 months than the control group. However, there were no significant differences between the two treatment groups at 6 months.

The other study (Samet et al., 2005) measured CD4 count at baseline, short term and long-term. CD4 count was significantly higher in the motivational interviewing group compared to the control group at both short-term (MD 105, 95%CI: 10.03 to 199.97, n=113) and long-term (MD 150, 95%CI: 32.89 to 267.11, n=94).

ART adherence

Two studies assessed ART adherence (Parsons et al., 2007; Samet et al., 2005). One of the two studies (Parsons et al., 2007) measured ART adherence in terms of both percent dose adherence and percent day adherence from baseline to 3 months and also from baseline to 6 months. At 3 months, the motivational interviewing group was significantly more likely to adhere in terms of dose adherence than the control group (MD 10.30%, 95%CI: 0.82 to 19.78%, n=121). However, there were no significant differences between the two treatment groups at 6 months (MD 5.30%, 95%CI: -7.41 to 18.01%, n=115). At 3 months, the motivational interviewing group was significantly more likely to adhere in terms of day adherence than the control group (MD 10.70%, 95%CI: 2.58 to 18.82%, n=121). However, there were no significant differences between the two treatment groups at 6 months (MD 8.90%, 95%CI: -3.34 to 21.14%, n=115).

The other study (Samet et al., 2005) measured 30-day adherence at baseline, short-term and long-term. There was no significant difference in adherence between the two treatment groups at both short-term (MD 0.04, 95%CI: -0.05 to 0.13, n=138) and long-term (MD 0.00, 95%CI: -0.06 to 0.06, n=94).

Reduction in HIV risky behaviour

Two studies assessed the comparison to measure HIV risky behaviour. Naar-King et al., (2008) measured the number of unprotected sex acts but there was no significant difference in the log-

transformed 6-month follow-up change scores between the two treatment groups (MD 0.09, 95%CI: -0.54 to 0.72, n=48).

The other study (Velasquez et al., 2009) measured the number of days of unprotected sex per 30-day period. Although there were significant reductions in this outcome over time in each of the treatment groups, there were no significant differences between the two groups, as reported by study authors (p=0.933). We could not calculate the risk ratio since the actual number of participants experiencing the event per intervention group was not given.

Other substance use

One study (Naar-King et al., 2008) assessing this comparison measured the maximum number of times marijuana was used in one week and there was no significant difference in the log-transformed 6-month follow-up change scores between the two treatment groups (p=0.28), as reported by study authors. We could not calculate the treatment effect because the authors erroneously reported the same mean (SD) in both groups.

ii. Comparison 2: Cognitive-Behavioural Therapy (CBT) versus Control

One study (Papas et al., 2011) assessed this comparison.

Primary outcome

Reduction in alcohol use

Papas et al., (2011) measured the percent of drinking days and the number of drinks per drinking day. At 30-days post-treatment, there were significantly larger reductions from baseline in both percent of drinking days (MD -24.93%, 95%CI: -37.44 to -12.42%, n=70) and number of drinks per drinking day (MD -2.88 drinks, 95%CI: -4.58 to -1.18 days, n=70), compared to the control group. Similar results were obtained during the next 30 days (from 30-days to 60-days) in both percent of drinking days (MD -21.87%, 95%CI: -34.97 to -8.77%, n=70) and number of drinks per drinking day

(MD -3.50 drinks, 95%CI: -5.55 to -1.45 days, n=70), compared to the control group. From 60-days to 90-days, the CBT group still experienced significantly greater reductions in both percent of drinking days (MD -16.92%, 95%CI: -30.46 to -3.38%, n=68) and number of drinks per drinking day (MD -2.51 drinks, 95%CI: -4.57 to -0.45 days, n=68), compared to the control group.

Secondary outcomes

The study Papas et al (2011) did not assesses any secondary outcomes.

iii. Comparison 3: Brief intervention (BI) versus Treatment as usual (TAU)

Three studies assessed this comparison.

Reduction in the frequency of alcohol use

All the three studies (Chander et al., 2015; Wandera et al., 2017; Wong et al., 2008) measured the frequency of alcohol use. One study (Chander et al., 2015) measured 90-day drinking frequency, frequency of heavy/binge drinking, and number of standard drinks per drinking day, among HIV positive women. At the 90-day follow-up, the brief intervention significantly reduced the probability of having a drinking day compared to treatment as usual (Odds Ratio [OR] 0.42, 95%CI: 0.23 to 0.75, p=0.0005, n=112). However, the brief intervention failed to reduce 90-day frequency of binge drinking (OR 0.60, 95%CI: 0.24 to 1.54, p=0.293, n=112) significantly and the 90-day number of drinks per drinking day (OR 0.92, 95%CI: 0.68 to 1.24, p=0.586, n=112). There were no raw data reported to calculate treatment effects.

A Ugandan-based study (Wandera et al., 2017) measured alcohol consumption outcomes using the change in Alcohol Use Disorders Identification Tool (AUDIT-C) scores. The brief intervention significantly improved the AUDIT-C score at 3 months (MD 0.80, 95%CI: 0.11 to 1.49, n=291), compared to counselling. However, there was no significant difference in AUDIT-C score at 6 months between brief intervention and counselling groups (MD 0.50, 95%CI: -0.16 to 1.16, n=320).

Wong et al., (2008) measured the number of days using marijuana or alcohol but did not report separate results for alcohol.

Secondary outcomes

Reduction in viral load

Only one study (Chander et al., 2015) measured viral suppression (HIV-1 RNA < 50). They reported no significant effect on viral suppression of a brief intervention compared to counselling in HIV positive women (OR 1.30, 95%CI: 0.65 to 2.61, n=148). We could not confirm the treatment effect because raw data were not reported.

ART adherence

The same study (Chander et al., 2015) measured antiretroviral adherence among HIV positive women but found that brief intervention failed to improve appointment adherence (defined as number of completed visits defined by total scheduled visits) (OR 1.11, 95%CI: 0.85 to 1.45, p=0.43, n=148) significantly, as reported by study authors.

Reduction in HIV risky behaviour

Chander et al., (2015) reported that a brief intervention significantly reduced the likelihood of having unprotected vaginal sex compared to the usual care group (adjusted odds ratio [aOR] 0.39, 95%CI: 0.16 to 0.95, p=0.041, n=148), after adjusting for baseline number of days of unprotected sex, as reported by study authors.

Other substance use

Wong et al., (2008) measured the total number of days using drugs or alcohol. They found a significantly greater reduction over time in the brief intervention group with regards to alcohol/marijuana use (p<0.0001); drugs other than marijuana or alcohol (p<0.0001); and any

substance (p<0.0001), compared to the usual care group They also found a significantly greater reduction in the number of recent days of hard drug use (heroin, cocaine, crack, speedball, MDMA) in the brief intervention group compared to the usual care group (p<0.0001).

iv. Comparison 4: Computer/ Technology versus Treatment as usual (TAU)

Two studies assessed this comparison (Gilbert et al., 2008; Hasin et al., 2013).

Primary outcome

Reduction in alcohol use

Both studies assessing this comparison measured the frequency of alcohol use. One study (Gilbert et al., 2008) compared an interactive patient-tailored computer program, Positive Choice, also referred to as "Video Doctor", with a control group that did not interact with “Video Doctor”. However, there was no significant difference between the two treatment groups in any risky drinking at both 3 months (RR 0.88, 95%CI: 0.63 to 1.22, n=150) and 6 months (RR 0.85, 95%CI: 0.61 to 1.19, n=154). The authors also reported no significant difference in binge drinking episodes and number of drinks per week, both at 3 months and at 6 months (data not shown).

Hasin et al., (2013) compared MI + HealthCall technology versus Attention/Education control and found that the MI + HealthCall technology significantly reduced the number of drinking days during the 60-day period (MD -1.17 days, 95%CI: -1.95 to -0.39, n=172).

Secondary outcomes

Reduction in HIV risky behaviour

Gilbert et al., (2008) found that the “Video Doctor” significantly reduced the number having any unprotected sex compared to the control group at both 3 months (RR 0.75, 95%CI: 0.62 to 0.90, n=218) and 6 months (RR 0.76, 95%CI: 0.63 to 0.93, n=194).

Other substance use

Gilbert et al., (2008) reported that using "Video Doctor" was found to significantly reduce the number with *any drug use* compared to the control group at both 3 months (RR 0.77, 95%CI: 0.61 to 0.97, n=149) and 6 months (RR 0.56, 95%CI: 0.43 to 0.72, n=158).

v. Comparison 5: Group versus TAU/Wait list/ Nutritional

Four studies assessed this comparison (Meade et al., 2010; Rotheram-Borus et al., 2012; Weiss et al., 2011; Zule et al., 2014).

Primary outcome

Reduction in alcohol use

All four studies measured alcohol use. Meade et al., (2010) measured the reduction in the number of drinks per month from baseline to 12 months and found no significant difference between the intervention group compared to the support/ control group (MD 3.50, 95%CI: -1.98 to 8.98, n=247).

A family-based intervention (Rotheram-Borus et al., 2012) assessed mothers living with HIV and their school-going adolescent children using a family-focused cognitive behavioural small group intervention. Among the mothers living with HIV who were using alcohol, those in the intervention unexpectedly drank more than those in the control group ($p<0.01$). Since raw data were not reported, we could not calculate the treatment effect.

In their second study SWP II, Weiss et al., (2011) reported a significant reduction in alcohol use between baseline and 12 months in both treatment groups; however, no comparison between the treatment groups was provided and therefore we cannot make conclusions regarding treatment effect on alcohol use.

A South African study among women (Zule et al., 2014) measured the number who were abstinent from alcohol and compared this outcome between HIV infected women receiving Women's Health Coop (WHC) intervention and a comparison control group. At 12-month follow-up, abstinence from alcohol was significantly higher in the intervention compared to the control group (RR 2.57, 95%CI: 1.20 to 5.50, n=84).

Secondary outcomes

Reduction in viral load

In their second study SWP II, Weiss et al., (2011) reported a significant reduction in viral load in the intervention group ($p<0.01$) and not in the control group over 24 months among HIV positive women with detectable viral loads at baseline. However, no comparison between the treatment groups was given and therefore we cannot make any conclusion regarding treatment effects on viral load.

ART adherence

SWP II study (Weiss et al., 2011) reported that participants in the intervention group had significantly improved ARV adherence compared to the control group ($p<0.05$).

Reduction in HIV risky behaviour

SWP II study (Weiss et al., 2011) reported that the odds of having unprotected sex were significantly reduced in the intervention group compared to the control group ($p<0.038$).

Other substance use

SWP II study (Weiss et al., 2011) reported no change in drug use over time (data not shown).

Quality of life

SWP II study (Weiss et al., 2011) reported significant improvement in mental health quality of life for the intervention group ($p<0.05$) and no increase in the control group. However, no comparisons were performed between the two groups and therefore we cannot make any conclusion regarding treatment effects on quality of life.

Review of results

This systematic review aimed to synthesize studies that have investigated the effectiveness of psychological interventions for problematic alcohol use in PLWH. We identified 14 studies that met our inclusion criteria. Owing to significant differences across studies in terms of the populations studied, the heterogeneity of the interventions, and differences in outcome measures, a meta-analysis could not be performed. We aimed to investigate the effectiveness of psychological interventions for alcohol use in HIV infected populations. We also assessed a number of secondary outcomes (HIV risk reduction, other substance use, CD4, viral load, adherence to ART, and quality of life).

Primary outcome

Motivational Interviewing

For the primary outcome of frequency of alcohol use, five studies of motivational interviewing were used. However, only one study (Velasquez et al., 2009) found a significant difference: the motivational interviewing group significantly reduced the number of drinks per 30-day period compared to the control group. The other four studies (Hasin et al., 2013) (Naar-King et al., 2008; Parsons et al., 2007; Samet et al., 2005) found no significant difference in the frequency of alcohol use. We could not pool results from these five studies in a meta-analysis because outcomes were measured in different ways. Velasquez et al (2009) was judged to be at low risk of bias in all respects except significant loss to follow up. As a result, replication of this study and improvement in retention

is necessary. The other studies that used motivational interviewing had small sample sizes(Naar-King et al., 2008; Parsons et al., 2007; Samet et al., 2005).

Cognitive-Behavioural Therapy (CBT)

Papas et al (2011), a study with small sample size (n=75), assessed the effects of cognitive behavioural therapy on drinking. There were significantly larger reductions in both percent of drinking days and number of drinks per drinking day, compared to the control group, from baseline to 30, 60, and 90 days. Although this study showed a treatment effect it had a small sample.

Brief intervention (BI)

Three studies assessed the effects of brief interventions on frequency of alcohol use.). Two studies (Chander et al., 2015) (Wandera et al., 2017) did not find significant effects on the frequency of alcohol use after 90-days. However, among HIV positive women, Chander et al (2015) found brief intervention significantly reducing the odds of having a drinking day compared to treatment as usual, only up to 90-day follow-up. In the Wandera et al (2017) study, a brief intervention significantly improved the AUDIT-C score at 3 months, compared to alcohol counselling alone. AUDIT-C measures alcohol consumption and not frequency. In the two studies that demonstrated an effect, this effect was seen in women participants. Women have been shown to become more engaged in treatment in other studies and a recent systematic review on adherence treatment showed women to be at lower risk of non-adherence to treatment (Heestermans, Browne, Aitken, Vervoort, & Klipstein-Grobusch, 2016).

Computer/Technology

Hasin et al (2013) found that the combination of MI and HealthCall technology significantly reduced the number of drinking days during a 60-day period. However, Gilbert et al (2008) found that the "Video Doctor" failed to reduce the frequency of alcohol use. This finding in a single study is

important. Mobile penetration has significantly improved world-wide including countries in Sub-Saharan Africa which have a high burden of HIV with nearly half a billion persons with mobile connectivity (www.gsmaintelligence.com). Use of these platforms can help these countries improve HIV treatment adherence as delivery of these interventions may be cost effective (Forman et al., 2018). Brown et al (2013) in their review and critique suggested the use of booster sessions to improve outcomes of psychosocial interventions, and the use of mobile technologies may be a solution.

Group intervention

Zule et al (2014), in a study among women in South Africa, found that abstinence from alcohol was significantly higher in the intervention group compared to the control group at 12-months follow-up. Meade et al (2010) measured the reduction in the number of drinks per month from baseline to 12 months and found no significant difference between the intervention and support/control groups. Rotheram-Borus et al (2011) found that among mothers living with HIV who were using alcohol, those in the intervention unexpectedly drank more than those in the control group. Zule at el (2014) was judged to be at significant high risk of bias or unclear results, while Rotheram-Borus (2011) was at low or unclear risk of bias. This suggests more work in development of this intervention which is deemed low cost.

Secondary outcomes

Reduction in viral load

Out of the three studies that used motivational interviewing and measured viral load, one study Parsons et al (2007) found a significant group difference: the motivational interviewing group was significantly more likely to reach 0.5 and 1.0 log viral load reductions at 3 months, although there

was no significant group difference at 6 months. Chander et al (2015) who used a brief intervention did not show an improvement in viral load.

CD4

The two studies using motivational interviewing that reported on CD4 count found significant differences in favour of the motivational interviewing group. Meade et al (2010) using cognitive stress management found a greater odd of attaining a 10% increase in CD4 count at 3 months, compared to the control group. Samet et al (2005) found a significantly higher CD4 count in the motivational interviewing group compared to the control group, both in the short- and long- term. Although CD4 has been replaced by viral load as the key measure for initiating HIV treatment and assessing treatment progress, it is still considered valuable in assessing all-cause mortality in HIV care (Ford, Meintjes, Vitoria, Greene, & Chiller, 2017).

ART adherence

Motivational interviewing was used in two studies that reported on ART adherence (Parsons et al., 2007; Samet et al., 2005). Parsons et al (2007) found that the motivational interviewing group was significantly more likely to adhere in terms of both percent dose adherence and percent day adherence from baseline to 3 months, compared to the control group. However, there were no significant differences in both outcomes from baseline to 6 months. Samet et al (2005) measured 30-day adherence at baseline, short term and long-term; however, there was no significant difference in adherence between the two treatment groups at both short- and long-term follow-up.

Weiss et al (2011) reported that the intervention significantly improved ARV (antiretroviral) adherence compared to the control group. However, they reported no change in drug use.

Reduction in HIV risky behaviour

Two studies used motivational interviewing measured HIV risky behaviour. Naar-King et al (2008) found no significant difference in the number of unprotected sex acts between the two treatment groups Velasquez et al (2009) also found no significant difference in the number of days of unprotected sex per 30-day period. However, Gilbert et al (2008) found that the "Video Doctor" significantly reduced the number having any unprotected sex compared to the control group at both 3 and 6 months. Reduction in new infections has become the latest target in the control of HIV. Use of Pre-Exposure Prophylaxis (PrEP) reduces the risk of infections, but in populations where this is not available, behavioural interventions that target risky behaviours and sexually transmitted infections control are essential.

Other substance abuse

Wong et al (2008) found that a brief intervention significantly reduced alcohol/ marijuana use and other drug use including hard drugs (heroin, cocaine, crack, and speedball, MDMA), compared to the usual care group. Gilbert et al (2008) also found that the "Video Doctor" significantly reduced the number with any drug use compared to the number in the control group at both 3 and 6 months. Despite the advent of harm reduction strategies such as needle exchange in injection drug users (Nishijima et al., 2013), HIV infections are still high in populations that engage in these practices (Young et al., 2017). HIV interventions therefore, need to include strategies to reduce substance abuse.

Quality of life

Only one study, (Weiss et al., 2011), assessed quality of life improvement. They found a group intervention effective in improving quality of life in PLWH. Quality of life should be a key outcome in HIV treatment programs as it directly relates to treatment engagement (Jong, Carrico, Cooper, Thompson, & Portillo, 2017; Logie, Kennedy, Tharao, Ahmed, & Loutfy, 2017).

Overview of results

The studies that we identified in this review were diverse, included two or more active arms, and largely focused on motivational interviewing and cognitive behavioural therapies with boosters delivered through technological aids. The fact that only four studies had a significant effect and ten had no significant effect on alcohol use, calls for more research into developing interventions that are methodologically sound, easy to deliver, acceptable, time-saving and culturally appropriate. There are ongoing efforts to deliver interventions using technology platforms such as smartphone and computers (Gilbert et al., 2008; Hasin et al., 2013). These interventions, however, may require more capital outlay in the rollout but, once that is achieved, longer-term benefits may be realized.

Another important challenge with interventions included in this review was the diversity of assessment tools used to assess alcohol use outcomes. While some studies measured the quantity of alcohol consumed, other studies assessed drinking frequency, and yet others used tools such as the AUDIT to measure a number of drinking parameters. Although in their narrative review, Brown et al (2013) (Brown et al., 2013) called for studies that directly target alcohol use, they also called for the inclusion of an assessment that directly measures alcohol use.

This review sought to assess the effectiveness of psychological interventions on other behaviours that impact on HIV treatment. Some studies (Parsons et al., 2007) and (Weiss et al., 2011) assessed risky sexual behaviour while other studies (Samet et al., 2005) and (Parsons et al., 2007) assessed CD4 count, both which showed positive change over three months. This is important, as most studies demonstrated no effect on alcohol use frequency which is important as it has a direct effect on adherence to ART, STIs and HIV transmission (Morrison et al., 1998). Two studies demonstrated improvement in adherence (Parsons et al., 2007; Weiss et al., 2011). In light of these findings, it is important that more research be undertaken to develop interventions that improve these outcomes.

A number of limitations deserve mention. Most important is the lack of standardised measures of alcohol use outcomes, whether frequency or quantity. Biochemical measures of alcohol use, such as the phosphotidyl ethanol and ethyl glucuronide, are recommended, in addition to self-report instruments. Given that the effects of alcohol on PLWH are not only related to effects on adherence, sexual risk, use of other substances and virological control, but are also associated with immunosuppressant and deleterious effects on the liver, these outcomes need to be included as treatment targets. Further, the studies in this review included participants with different levels of alcohol use which may dilute the effects of an intervention. More severe users, including those with dependence, may require different doses of an intervention and perhaps adjunctive pharmacological therapies.

Potential biases in the review processes

The search was comprehensive and encompassed electronic searches of key databases and a search of reference lists of included studies and relevant reviews for additional studies. It is unlikely that any studies were missed. To reduce the potential for bias, two review authors independently undertook the selection of studies, extraction of data, and assessment for the risk of bias. If we had chosen different comparisons, we may have potentially ended up with different conclusions; however, our choice of comparisons was based on sound theoretical knowledge. Furthermore, we could have obtained more data if we had contacted authors and requested additional data but it was not possible owing to time constraints. Finally, using GRADEpro to assess the quality of evidence would have given more robust results; however, the heterogeneity in outcomes made it difficult to tease out outcomes for inclusion in GRADEpro (https://gradepro.org/).

To our knowledge, this is the fourth systematic review to assess the evidence for psychological interventions for problematic alcohol use in PLWH. Brown et al (2013) had similar concerns in a review pertaining to outcome measures and the variation in study methodologies. A review by Samet

et al (2010) found limited evidence for the effectiveness of behavioural interventions, a finding replicated in this review. However, a recent review by Scott-Sheldon et al (2017) found behavioural interventions to be effective in reducing alcohol consumption, risky sexual behaviour and viral loads in PLWH. However, the interventions reviewed had no effects on alcohol use frequency as we also found in our systematic review.

Conclusions

Our review of psychological interventions for problematic alcohol use in PLWH finds some evidence for the effectiveness of motivational interviewing, cognitive behavioural therapy and brief intervention in reducing alcohol use in people living with HIV. Use of mobile health technology modestly improved motivational interviewing effects on alcohol use outcomes. For the studies that assessed secondary outcomes, there were some effects of motivational interviewing on viral loads, use of other substances, risky sexual behaviours and adherence to ART. No quantitative synthesis was possible because of the heterogeneity in outcomes. In sum, there was an overall lack of evidence for the effectiveness of the psychological interventions on alcohol use. In terms of practice, there is insufficient evidence to recommend any particular treatment modality.

It is important that well designed, adequately-powered, pragmatic randomised controlled trials in high burden communities that focus specifically on alcohol use in PLWH be conducted. These studies need to incorporate standardised measures of alcohol use to allow for comparability between studies.

Abbreviations

ART	Antiretroviral Treatment
ARV	Antiretroviral
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test-Consumption
AUDs	Alcohol Use Disorders
BI	Brief Intervention
CBT	Cognitive Behavioural Therapy
HIV	Human Immunodeficiency Virus
MI	Motivational Interviewing
PLWH	People Living with HIV/AIDS
TAU	Treatment as Usual
STI	Sexually Transmitted Infections

Declarations

Ethics approval and consent to participate

This is a systematic review and has no contact with human and other materials.

Consent for publication

All the authors have read and consent to the publication of this manuscript.

Availability of data and material

Additional materials to this manuscript are available

Competing interests

MM – has no interest to declare

JJ-has no interest to declare

AM- has no interest to declare

AC- has no interest to declare

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Authors' contributions

MM and SS conceived the idea and developed the initial protocol. AC and MA refined the topic and revised the protocol. MM and JJ carried out the electronic searches, screened the titles and searched for studies in reviews and other sources. MM and AM developed data extraction form, extracted the data and carried out the risk of bias assessments. AM performed all the data analyses, reported the results. MM and SS summarised the results in the discussion section. All the authors revised the draft manuscript and provided essential revisions to the draft.

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CHAPTER THREE:

Perceptions of alcohol use in the context of HIV treatment: a qualitative study

HIV/AIDS - Research and Palliative Care

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ORIGINAL RESEARCH

Perceptions of alcohol use in the context of HIV treatment: a qualitative study

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Background: Alcohol use is associated with poor HIV treatment outcomes. This study aimed to understand patients' perceptions of the impact of alcohol use in the context of HIV care.

Methods: The study design was a descriptive qualitative study of HIV positive individuals receiving antiretroviral treatment. The study involved four focus group discussions with male and female participants at a tertiary center, city clinic, and rural church. We employed convenience sampling and invited patients coming for their routine visits and medication refills to participate.

Results: Participants had an awareness of both the direct and indirect effects of alcohol use. The direct effects related to the incompatibility of HIV medication and alcohol. The indirect effects related to the negative impact of alcohol on treatment adherence. Participants proffered reasons why HIV infected individuals on HIV treatment drink and felt that patients had to make a deliberate choice to stop drinking. Participants displayed some knowledge of interventions for drinking cessation and highlighted the use of pharmacological interventions to stop drinking. Participants indicated that they preferred HIV counselors to provide counseling services in view of the existing relationships that patients had with counselors.

Conclusion: People living with HIV have adequate knowledge of the effects of alcohol use in the context of HIV treatment. Stigma and the time taken to engage in an alcohol use intervention appeared to be the main impediments to uptake. The current model of HIV treatment, based on trust with the HIV care team, and maintenance of this trust, could bolster the uptake of an intervention. Involvement of HIV patients in their treatment is necessary to improve treatment outcomes in the context of alcohol use.

Keywords: alcohol use, HIV, impact, perceptions, Zimbabwe

Introduction

The advent of antiretroviral therapies has transformed HIV treatment and control, and HIV has become a chronic illness.[1,2] The rate of new HIV infections in Zimbabwe is on the decline and mirrors a promising global picture with respect to longevity for HIV infected individuals.[3,4] Behavioral change and advocacy have also proven to be key in HIV and AIDS care and control.[5] However, alcohol use disorders (AUDs) are of major concern in the context of HIV and AIDS care.[6,7] Evidence indicates that HIV infected individuals have a higher prevalence of AUDs than HIV negative individuals.[8] Alcohol use is also associated with erratic treatment adherence.[9,10] In addition, HIV positive people suffer more physiologic harm from alcohol consumption, with increased cases of liver damage, in comparison to HIV negative individuals.[11,12]

Due to immunosuppression, patients with HIV who also have an AUD may suffer from concurrent medical conditions, such as TB, and consequently be on a variety of medications with a high pill burden,[13] contributing to decreased adherence and resistance.[14] In addition, pharmacological interventions may be unaffordable, particularly in low-income settings, with the only available treatments being psychosocial in nature. However, psychosocial interventions are sensitive to the "who, where, and what questions," and, as such, require an understanding of the lived experiences of the affected.[15,16]

Patients who receive HIV treatment are assessed and counseled for alcohol use as part of the pre-treatment work up in Zimbabwe.[17] Patients who drink are defined as not operationally ready for antiretroviral treatment (ART) commencement[17] and policy stipulates that HIV treatment cannot be commenced when there is evidence of alcohol use.[17] A qualitative understanding of patient experiences and subjective expectations of treatment is important to inform the success of HIV and AUD programs.[18] To this end, our study aimed to describe and understand the perceptions and impact of alcohol use in a sample of HIV positive individuals. The study was nested within an on-going, cluster randomized controlled trial of an AUD intervention.[19]

Methods

This study used a descriptive qualitative design to understand HIV infected individuals' perceptions ("who, why, and how") about alcohol use.[20] Patients recruited into the study were already on ART after receipt of counseling and testing. Almost a third of the participants (30%) had an AUD as defined by the Alcohol Use Disorders Identification Test (with a cutoff of 6 for females and 7 for males).[21] In addition, we included participants who denied alcohol use to obtain their perspectives. In addition, data were collected through focus group discussions (FGDs) with people living with HIV/AIDS (PLWHA) in order to obtain their perspectives on the status of care of HIV-infected individuals.

Context and setting

We obtained approval to undertake the study from the Medical Research Council of Zimbabwe (A/1936), Stellenbosch University Health Research Ethics Committee (SI14/10/222), the hospital ethics committees, and the Ministry of Health Permanent Secretary of Zimbabwe. The FGDs were held at an HIV clinic at a rural church-run hospital (n = 2), at a central hospital (n = 1), and at a city polyclinic (n = 1).

Sampling strategy

Convenience sampling was used. HIV infected patients, who had received a health education talk on adherence (as is standard practice and required for all) were informed of the study, and individually approached for consent. The health education talk consists of information on adherence to medication, the use of protection when engaging in sexual activity, signs and symptoms of opportunistic infections, abstention from alcohol and drug abuse, and good nutritional practices. Patients who agreed and gave written consent were assigned identifier numbers, which denoted their identities in the FGDs. Participants received $3 (USD) as compensation.

Data collection

Data were collected between May and August 2015. A questionnaire was specifically developed for the FGDs. The FGDs were conducted in the local vernacular (Shona), audio recorded, and translated for analysis. The first two FGDs were of mixed gender (Table 1).

Trained facilitators who were conversant with the study moderated the FGDs. The training involved setting up the group, managing the group (such as dealing with dominating participants), administration of the questionnaire, understanding the content and context of the study, diary entries, and an approach to follow-up questions. Facilitators used questionnaires with initial prompts but then took their lead from participants. Data were derived from transcripts and analyzed using Atlas.ti.[22]

Table 1 Description of FGDs

	FGD1	FGD2	FGD3	FGD4
Venue	Central hospital	City clinic	Church-linked hospital	Church-linked hospital
Participants				
N	13	13	7	6
Gender	Mixed	Mixed	Male	Female
Facilitators				
n	3	3	2	2
Gender	(2 females, 1 male)	(2 females, 1 male)	(1 male, 1 female)	Female

Abbreviations: FGD, focus group discussion.

Data analysis

Transcripts were read and coded by two independent reviewers and conflicts were resolved through discussion. Data from the transcripts were sorted and coded according to broad themes. Outputs from the transcripts were generated as a list of codes and quotations. Trained personnel identified, developed, and grouped emerging themes.

Techniques to enhance reliability

Triangulation, reflexivity, dependability, and conformability, as Guba's constructs, were adopted as tools to enhance reliability of the data obtained.[23] Interviewers were from various fields, including nursing (BM-D, MK-U), psychiatry (MD, MM), and linguistics (AP). In order to contain the subjective opinions of the interviewers, they worked in groups of three in each FGD.

Results

Participants

Thirty-nine patients participated in the FDGs. Their baseline demographic information is summarized in Table 2.

The major themes identified in the study included: 1) perceptions of the impact of alcohol use on HIV treatment; 2) participants' perceptions of HIV infected patients who drink alcohol; 3) fear and stigma; and 4) help and support. Table 3 summarizes the major themes and thematic areas.

Perceptions of the impact of alcohol use on HIV treatment

Participants perceived alcohol use to have both direct and indirect influences on HIV treatment.

Alcohol use has a direct influence

Participants perceived alcohol use to have a direct influence on HIV treatment, stating that "[…] drinking beer is not good because alcohol and medication are not compatible." [Participant 17, FGD2, M, 42y] and "drinking alcohol weakens the white blood cells. There will be competition between alcohol and medication." [Participant 24, FGD2, F, 48y] One participant also noted that on the "container of alcohol is written harmful. So alcohol is a drug on its own so drinking it would have meant that we are mixing various incompatible drugs." [Participant 7, FGD1, M, 35y] Thus, participants indicated awareness of the negative influence of alcohol, in and of itself, as well as alcohol's incompatibility with HIV medication. However, some participants perceived that: "It depends with the type of alcohol one has taken. Some will have drank kachasu [illicit brew], and other types are better." [Participant 6, FGD1, M, 36y] Another also mentioned the "[…] alcohol that is brewed in the villages in different types and several different things are added into the mixture." [Participant 4, FGD3, F, 43y] which is more intoxicating.

Table 2 Participants' sociodemographic data

Sociodemographic data	N (%)
Gender	
Male	23 (59)
Female	16 (41)
Marital status	
Married	27 (69)
Widowed	9 (23)
Single	2 (5)
Alcohol use[illegible]er	13 (30)
	Mean (SD)
Age (years)	40 (16.0)
Education (years in school)	10.65 (3.68)

Alcohol use has an indirect influence

In addition to the direct negative effects of alcohol use on HIV treatment, participants also perceived that alcohol had indirect effects. Specifically, "[…] you can forget to take your medication when you are drunk." [Participant 10, FGD3, F, 39y] Similarly, "[…] you drink alcohol and get drunk, the first thing to happen is to forget the time to take your tablet." [Participant 5, FGD1, F, 44y]

Besides forgetting to drink your medication, or not drinking it at the correct time; when you: "[…] drink alcohol you end up forgetting to eat your sadza or eating food and you end up going to the beer hall." [Participant 28, FGD4, M, 47y] Thus, after "[…] drinking beer, the following morning one will have a hangover which causes one to lose appetite. Without eating food one cannot take the medication." [Participant 16, FGD2, F, 38y]

Lastly, drinking "[…] beer gives one confidence to indulge in bad things." [Participant 21, FGD2, M, 51y] More specifically, one "[…] can engage in sexual activities without any protection because they cannot think properly because of being drunk." [Participant 1, FGD1, M, 45y] It should be noted, however, that "unprotected sex" was only mentioned as a risk in the mixed FGD. In the men-only FGD "unprotected sex" was not mentioned as a risk per se; instead, participants mentioned "[…] he would drink alcohol and end up taking prostitutes from the beer hall." [Participant 34, FGD4, M, 41y] Thus, the risk was considered to be associated more with "prostitutes" than with "unprotected sex". In contrast, in the women-only FGD group no reference was made to either "unprotected sex" or "prostitutes".

Table 3 Major themes and thematic areas

Major themes	Thematic area	Quote
Perceptions of alcohol use in terms of HIV treatment	Alcohol use has a direct influence	"Drinking beer is not good because alcohol and medication are not compatible"
		"Drinking alcohol weakens the body, there will be competition between alcohol and medication"
	Alcohol has an indirect influence	"You can forget to take your medication"
		"[…] drink alcohol you end up forgetting to eat your sadza [corn meal] or eating food and you end up going to the beer hall"
Participant perceptions of HIV infected patients who drink alcohol	Some patients understood the difficulty	"[…] you feel sorry for them, so I feel this program should be done […] so that people can stop taking alcohol"
		"HIV infected patients who drink alcohol must be: "[…] asked why they continue to drink […] [it] may be stress about the home and families […] If they require any help this can be forthcoming in order to relieve stress and stop falling in the trap of drinking alcohol"
	They cannot be helped	"You [person drinking alcohol] are a difficult person who cannot be helped"
		"[…] you don't listen and you are stubborn"
		"[…] nurses should strongly threaten them [people drinking alcohol] with death"
	Other participants acknowledged taking responsibility	"[…] to make a choice to either continue drinking beer or smoking and risk ending your life […] it is all up to the patient"
		"[…] you are told what is required and what is not required it's you[r] chance to choose what you want, alcohol or tablets"
Fear and stigma		"If the [health] workers are not free or approachable this creates barriers. If they are free and friendly people can be helped. If they are not, people can be afraid to look for help"
		"You can hide the tablets from your friends thinking that they will laugh at you when in actual fact taking tablets is important and you should tell your friends so that they can remind you to take your tablets"
Help and support is there	Participants saw something good in the AUD intervention	"[…] it is appropriate for people to be asked about the quantity of alcohol they drink"
	Pills to stop drinking	"There are pills to aid one in stopping drinking beer, let them be approved […] some people are no longer able on their own to stop drinking"
		"As government institutions are generally lacking in terms of facilities, for example I heard that at [hospital] there is a doctor who has a drug to completely stop someone from drinking alcohol. So, sometimes such facilities are not yet there at government hospitals"
	Counselors are trusted	"[…] but before that I should make use of the counselor information before I overload the doctor with unnecessary work"
		"[…] this is the work of counselors. Looking for help allover the place will cause risks of misinformation and this is dangerous. It is important just to go to those who are skilled to do the job"
	Provide health education	"[…] continuous health education from counselors […] Health education should be an on-going process so that everyone [is] equipped with knowledge"
		"I think counselors are more appropriate because they were skilled in approaching and educating patients"

Abbreviations: AUD, alcohol use disorder.

Participants' perceptions of HIV infected patients who drink alcohol

Participants differed in their perceptions of HIV infected patients who drink alcohol whilst on HIV treatment.

Understanding the difficulty

Some participants appeared to have an understanding of the reasons for drinking and/or how difficult it was to stop drinking. Participant 41 said: "[…] you feel sorry for them, so I feel this program should be done […] so that people can stop taking alcohol." [FGD3, F, 38y] Another stated that HIV infected patients who drink alcohol must be: "[…] asked why they continue to drink […] [it] may be stress about the home and families […] If they require any help this can be forthcoming in order to relieve stress and stop falling in the trap of drinking alcohol." [Participant 8, FGD1, F, 42y]

They must take responsibility

Others noted that it is the responsibility of the patient: "[…] to make a choice to either continue drinking beer or smoking

and risk ending your life [...] it is all up to the patient." [Participant 8, FGD1, M, 43y] Similarly, Participant 36 said: "[...] you are told what is required and what is not required it's you[r] chance to choose what you want, alcohol or tablets." [FGD3, F, 37y] Others described how they: "[...] just accepted my status and chose to leave beer drinking." [Participant 22, FGD3, F, 37y]

They cannot be helped

Some participants, however, had a negative perception of those who drink alcohol whilst on treatment stating: "You [person drinking alcohol] are a difficult person who cannot be helped." [Participant 26, FGD2, F, 35y] Such a person can: "[...] get advice but it falls on deaf ears." [Participant 23, FGD2, F, 39y] "[...] you don't listen and you are stubborn." [Participant 42, FGD4, F, 41y] It was also stated that: "[...] drinking is a habit and not a disease." [Participant 11, FGD1, M, 43y] implying that a person has no excuse for not being able to stop drinking. One participant suggested: "[...] nurses should strongly threaten them [people drinking alcohol] with death." [Participant 19, FGD2, M, 39y]

Fear and stigma

From the data, it was evident that fear was prevalent among participants. Fear may lead to non-disclosure: "One can be afraid to say that they are drinking alcohol." [Participant 38, FGD3, F, 47y] Similarly, Participant 8 said: "If the [health] workers are not free or approachable this creates barriers. If they are free and friendly people can be helped. If they are not, people can be afraid to look for help." [FGD1, F. 49y] Participants also said that there was a lot of stigma associated with HIV which made disclosure to drinking partners difficult: "You can hide the tablets from your friends thinking that they will laugh at you when in actual fact taking tablets is important and you should tell your friends so that they can remind you to take your tablets." [Participant 28, FGD4, M, 36y]

There is help and support

In general, participants perceived an AUD intervention program, and screening patients for alcohol use, to be good. Participants mentioned: "[...] it is appropriate for people to be asked about the quantity of alcohol they drink." [Participant 8, FGD1, M, 43y] They also mentioned strategies that they perceived would be helpful for patients who needed them.

Pills to stop drinking

One participant mentioned that if "[...] there are pills to aid one in stopping drinking beer, let them be approved [...] some people are no longer able on their own to stop drinking." [Participant 25, FGD2, M, 44y] Similarly, another stated:

> As government institutions are generally lacking in terms of facilities, for example I heard that at [hospital] there is a doctor who has a drug to completely stop someone from drinking alcohol. So, sometimes such facilities are not yet there at government hospitals. [Participant 9, FGD1, F 37y]

Counselors are trusted

Participants thought that counselors could be trusted and should be approached first for help: "But before that I should make use of the counselor information before I overload the doctor with unnecessary work." [Participant 11, FGD1, M 31y] Participant 9 responded that he was in agreement: "[...] this is the work of counselors. Looking for help all over the place will cause risks of misinformation and this is dangerous. It is important just to go to those who are skilled to do the job." [FGD1, M, 39y]

Additionally, it appeared as if fear of health workers assisted some of the participants to stop drinking alcohol: "Some don't drink the beer because they fear for their health and the health workers." [Participant 20, FGD2, M, 37y]

Provide health education

Another form of help identified included "[...] continuous health education from counselors [...] Health education should be an on-going process so that everyone [is] equipped with knowledge." [Participant 17, FGD2, F, 41y] Counselors were especially trusted to provide this education: "I think counselors are more appropriate because they were skilled in approaching and educating patients." [Participant 3, FGD1, M, 35y]

Discussion

This study aimed to understand patients' perceptions of the impact of alcohol use in the context of HIV care. Participants perceived alcohol use to have both direct and indirect effects on HIV treatment. Stigma and fear about their ability to access treatment in the event that they disclose their HIV status were some of the barriers to receiving care for AUDs. However, participants were receptive to the offer of treatment for AUDs. Interventions for AUDs in the context of HIV should, therefore, be developed.

Perceptions of AUDs in the context of HIV treatment

Participants understood that alcohol use is a challenge in the context of HIV infection and treatment. They were aware of

the direct and indirect effects of alcohol use on HIV treatment. A direct effect described was the incompatibility of alcohol use with HIV treatment. An indirect effect was non-adherence to medication when using alcohol. The belief that alcohol use was not compatible with ART has been described in research in Sub-Saharan Africa.[24] Kalichman et al documented planned omission of ART if patients were going to drink, fearing toxicity of mixing alcohol and HIV treatment.[25]

Participants' perceptions of HIV infected patients who drink alcohol

The participants were of the opinion that they could not take medication while drinking beer. This implied that they perceived that alcohol would either interact negatively with medication, or the staff would not dispense medication as long as they were known to drink. As the health education session is given before the commencement of ART, this to many patients means that ART and HIV are incompatible and can lead to death. HIV and AUDs health education messages need to be clear to avoid wrong interpretations by patients. The Kalichman et al study indicated deliberate skipping of medication by patients with AUDs due to beliefs of incompatibility of alcohol and HIV treatment.[26] This highlights the need to train counseling staff on the impact of, and treatment for, co-occurring HIV and AUDs.

Fear and stigma

Stigma related to mental and AUDs is a major impediment and several studies have found it to be a particularly challenging barrier to seeking treatment or adhering to treatment.[27,28] Stigma has to be addressed at individual, community, and programmatic levels. Improving disclosure could translate into better adherence and improved support for HIV infected individuals with problematic alcohol use.[29]

Participants noted that both HIV treatment and alcohol use are stigmatized. This prevented them from disclosing both their HIV status and drinking. Hospital and clinic staff often delay antiretroviral treatment initiation once they discover that patients have an alcohol use problem, as required by the Zimbabwe National Operational Guide.[17] This may underlie the negativity displayed by participants in the study as the messages passed on by staff are also supported by national guidelines. This is despite the fact that the same guidelines used for commencing HIV treatment do not include treatment for AUDs. This is underscored by another study which indicated that fear of being discriminated against (due to drinking habits) by HIV counselors and nursing staff was a barrier to seeking help.[30]

There is help and support

In terms of the management of alcohol related problems, participants appeared to prefer pharmacological approaches. With respect to psychosocial interventions, participants favored primary care counselors as the agents of change, citing existing relationships with the counselors. Participants welcomed the use of health education to deal with alcohol use problems in the context of HIV treatment. For patients who have alcohol dependency, there may be a need for referral to specialist care that may include pharmacological interventions. In patients where there is high non-adherence to treatment and increased pill burden, monthly depot naltrexone may be a preferred treatment.[31,32]

The level of knowledge displayed by participants of the link between HIV treatment and alcohol use was high. This knowledge can be exploited to address alcohol use in the context of HIV treatment. It is notable that while nurses and primary care counselors have invested in educating patients on the impediments to optimum HIV care, educational information is presented in a negative way that may dissuade participants from opening up about their problems, including alcohol use. Thus, similar to observations made by previous studies, there is a need to train staff in counseling skills through refresher courses.[33]

AUD interventions

This study shows the challenges that HIV care staff face in dealing with dual diagnosis patients in Zimbabwe. If patients are not commenced on ART as a result of an alcohol use history, delays will inevitably lead to poorer outcomes. Studies have shown that brief interventions can be effective in reducing AUDs. Appropriate health education on the assessment and treatment of HIV and AUDs is imperative in HIV treatment settings. Lack of trained personnel, lack of time, and an unmotivated work force may be barriers. However, task sharing using nurses, general medical staff, and peer or lay-counselors may cover that gap. Use of manuals may be used to improve fidelity to treatment.

Zimbabwe has no separate nor embedded AUD treatment program for HIV infected individuals. Further, due to the prevailing economic situation, the cost of pharmacological agents for AUDs have been beyond the reach of the HIV infected individuals. However, from the study, it appears that there was limited use of pharmacological agents. This may need to be scaled up.

However, in the development of the interventions, given the seeming power of health staff over patients, resources need to be invested in developing the motivational skills of

staff so they appreciate the collaborative and integrated treatment approach that is required. This needs to be coupled with helping patients understand that the receipt of treatment is a right. Human rights training needs to be embedded in the training of health workers as well.

Systematic reviews have shown that Screening and Referral Interventions(SBRITs) are helpful in reducing [illegible] in the general population without HIV infection despite requiring specific adjustments to suit patients, the professionals, and the characteristics of the organization.[34] Brown et al showed in a narrative review that the interventions were able to reduce alcohol use in HIV infected individuals, but called for studies that isolate the effective components of the interventions.[35] Although HIV infected patients are already on many treatments, some with alcohol dependency may require pharmacological interventions to improve both HIV and AUD outcomes.[36] A number of trials to integrate AUDs in HIV care settings are on-going.[37] Some of the findings in this study can inform the design of future trials, for example taking gender into account as single-gender groups in this setting may help to optimize participation in behavioral interventions.

The need for SBRITs is highlighted in this study with participants calling for both behavioral and pharmacological interventions. The preferred staff to offer this intervention are the primary care counselors and nurses. This has been shown to be feasible in the management of other conditions, including TB and HIV.[38] Lay health workers have been successfully recruited to offer community-based treatment for common mental disorders in Zimbabwe.[39] The content should include motivational "talk" delivered in an empathetic manner, with a non-judgmental attitude and stigma reduction. There is also a need to obtain buy-in from policy makers for the integration of HIV and AUD treatments.

Limitations

These findings should be interpreted with a number of limitations in mind. First, as the FGDs were used to gather information, contributory effects of "group think" and "group polarization" may have influenced responses to questions.[40]

Second, alcohol use in HIV is a sensitive area of enquiry, especially given that patients may be disallowed HIV treatment initiation unless they discontinue drinking. This may have fed into the negative views that participants had of drinking whilst on ART.

Third, the presence of the nurse who gave a health education talk to the group before the FDG may have prompted some participants to respond more favorably than they would otherwise have done. This FGD was in a church related hospital where morality issues are important. The view in this community is that women should not drink and HIV is transmitted due to "bad morals". This may have influenced participants' responses. The women, therefore, shied away from talking about prostitution and unprotected sex. Most of the participants were married women who might have acquired HIV from a partner and/or through unwanted sex. It is recommended that future researchers are cognizant of the fact that the venue where FDGs are conducted may have an influence on participants' responses.

Finally, it became evident that participants were not able to express themselves freely owing to the mixed gender status of the FGDs, as in Zimbabwe it is viewed as culturally inappropriate for women to drink and drinking among women is associated with commercial sex work. Consequently, one "female only", and one "male only" FGDs were conducted.

Acknowledgments

The principal researcher is a clinical psychiatrist (MM) pursuing doctoral studies. Whilst he did not know the participants prior to the FGD, he is involved in the care of PLWHA. ASJ vd W is a psychiatric researcher with an MA in psychology by thesis qualification. BM is a psychiatric nurse practitioner and lecturer with an MPhil, who is not involved in the care of PLWHA. However, the study participants may have been receiving care from nurses and do share with them confidential information. MD is a psychiatrist trained in the World Health Organization Mental Health Cap Action Programme (WHO mhGAP) intervention guide and participates in the care of PLWHA, albeit not this particular group. MKU is a nurse with a Masters Level qualification. AP is a researcher who specializes in adult education and has no contact with these participants or any similar group other than the informal contact. DC is a researcher/psychiatrist with a PhD who has contact with patients similar to this study population. SR is a professor in public health and has no contact with this group of patients. SS is a distinguished professor of psychiatry and senior researcher on the project which interacts with patients similar to this sample, but has no contact with this study sample.

Author contributions

MM is the principal researcher. MM and SS were involved in the conception and development of the study protocol. SR, SS and DC were involved in developing the methodology. AP, MD, BM, MKU, and MM were involved in focus groups. SS, SR, DS and DC had no contact with participants. MM and ASJ vd W drafted the first version of the manuscript. All authors

contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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CHAPTER FOUR

PILOT AND FEASIBILITY STUDY

Title: Intervention for alcohol use disorders at an HIV care clinic in Harare: a pilot and feasibility study

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Abstract

Alcohol use in HIV infected patients is associated with risky sexual behaviour, poor adherence to Highly Active Antiretroviral Therapy (HAART), treatment failure and increased physiologic harm. An intervention for HIV infected patients with problematic alcohol use, developed through adaptation of existing evidence based psychological treatments, was assessed for its feasibility at a tertiary HIV care clinic in Zimbabwe. Registered general nurses, using a manualised protocol, delivered the intervention. Forty patients were recruited and randomised to receive either an MI/CBT intervention or the WHO mhGAP Intervention Guide for AUDs (n=20 patients per group).

Women who scored 6 or more on the Alcohol Use Disorders Identification Test (AUDIT) and men who scored 7 or more on the AUDIT were eligible. Dementia and other mental disorders, age less than 18 years, and inability to commit to follow-up for 3 months were disqualifications. Patients who were on treatment for drug related problems were also ineligible.

The objectives of the study were to pilot the outcome assessments to be used in the trial proper, assess the feasibility of delivery of a brief MI/CBT intervention compared to an WHO mhGAP intervention for problematic alcohol use in PLWH in Zimbabwe, and pilot the effectiveness (on alcohol use, functionality and CD4 count) of these interventions at 3 months in a randomised controlled trial design.

Out of 40 participants enrolled, 31 were successfully followed up for three months with a loss to follow-up rate of 23%. There was a statistically significant decrease in AUDIT score over time in

both groups (p <0.00), however no statistically significant group difference with a mean difference of 0.80, standard error of 2.07 and p value of 0.70. For the CD4 count, the median and interquartile ranges at baseline for MI/CBT and WHO mhGAP IG groups were 218(274) and 484(211.50), respectively. At follow-up, median and interquartile ranges for the CD4 count for MI/CBT and WHO mhGAP IG groups were 390(280) and 567(378), respectively, indicative of improvement in immunological parameters in both arms. Although the rate of loss to follow-up was 23%, this pilot study suggests that a brief MI/CBT delivered by Registered General Nurses for problematic alcohol use is feasible in this population but will require the implementation of additional measures to improve retention.

Key words: Alcohol; HIV; MI/CBT Intervention; Psychological; Task sharing; Zimbabwe

Trial registration: Pan African Clinical Trial Registry, current PACTR201509001211149.

Introduction

Alcohol and illicit drug use can interfere with the success of HIV treatment programs and should be specifically targeted at patients in HIV care settings(Teixeira, Dourado Mde, Santos, & Brites, 2013). A US study found that alcohol use in HIV positive individuals was associated with higher rates of medical complications and poorer HIV treatment outcomes, including reduced viral load suppression (Braithwaite & Bryant, 2010). Studies have shown that people living with HIV (PLWH) drink twice as much as the general population, with increased mortality and physiological injury occurring at relatively low levels of alcohol use(Galvan et al., 2002). Studies from Nigeria, Brazil and Ethiopia have documented prevalence rates of problematic alcohol use in PLWH in the range of 14% to 32%(da Silva, Mendoza-Sassi, da Mota, Nader, & de Martinez, 2017; Egbe et al., 2017; Soboka, Tesfaye, Feyissa, & Hanlon, 2014). There is no data on problematic alcohol use in HIV infected persons in Zimbabwe Although the burden of disease is high with 1.6 million Zimbabweans living with HIV and 800 000 on antiretroviral treatment (Council, 2016). With this burden of HIV and with high levels of alcohol intake, a significant proportion of the population may have problematic alcohol use requiring intervention that is culturally acceptable.

A systematic review for determinants of adherence to HAART found alcohol use to be an obstacle to adherence(Heestermans, Browne, Aitken, Vervoort, & Klipstein-Grobusch, 2016). Alcohol use is associated with Hepatitis B and C co-infection and in PLWH liver malfunction may affect the metabolism of antiretroviral drugs(Puoti, Moioli, Travi, & Rossotti, 2012). Aside from the problems of non-adherence in PLWH, poor treatment outcomes may result from the physiological effects of alcohol. There is evidence that interventions for alcohol use can lead to the reduction in alcohol consumption in the general population(R. S. Braithwaite & Bryant, 2010). Studies have also shown that psychological interventions in PLWH can improve medication adherence even when these interventions have no effect on alcohol use (Samet et al., 2005; Wandera et al., 2017). Motivational

interviewing, cognitive behaviour therapy, problem solving techniques, contingency management and twelve-step facilitation are some of the psychological interventions that have evidence of effectiveness(Brown, DeMartini, Sales, Swartzendruber, & DiClemente, 2013).

In developed countries where, highly trained specialists usually deliver psychological therapies, it has been shown that they can lead to a change in drinking behaviour. There have only been a few studies in low resource settings (Patel et al., 2007). A Kenyan study by Papas et al. (2011), using an adapted cognitive behavioural therapy intervention, showed improvement in alcohol use outcomes in HIV infected individuals(Papas et al., 2011). Another study from Uganda found that counselling and motivational interviewing, had more beneficial effects in women than in men with hazardous alcohol use(Wandera et al., 2017). Another study undertaken in South Africa that utilised group therapy also documented a reduction in the amount of alcohol consumed by drinking participants (Zule et al., 2014). A qualitative study to explore the acceptability of an alcohol use intervention by Morojele et al. (2014) found that participants were willing to engage in an alcohol-focused motivational interviewing treatment (Kekwaletswe & Morojele, 2014).

Although motivational interviewing is effective in motivating individuals to reduce alcohol consumption, its effects have been shown to fade over time and booster sessions have been recommended (Parsons, Golub, Rosof, & Holder, 2007). Further, some studies have combined motivational interviewing with cognitive behavioural therapy in participants with comorbidities, such as depression and anxiety(Riper et al., 2014). Zimbabwe has commenced rollout of the WHO mh-GAP IG for mental health interventions (https://www.msf.org.za/system/.../newsletter_msf_zimbabwe_issue1_2017.pdf?...) This has followed a call by the WHO for wide dissemination of the WHO mh GAP IG in an endeavour to close the treatment gap for mental, neurological and substance use disorders. Moreover, Counselling for Alcohol Problems (CAP), a large study in India used WHO mh-GAP IG as a comparison in their

mental health trials(Nadkarni, Weiss, et al., 2017). Use of the WHO mh-GAP IG in PLWH with problematic alcohol use, if shown to be effective, can further reduce the treatment gap for mental disorder comorbidities in this vulnerable population.

While these studies have demonstrated benefits, larger sample studies are required (Papas et al., 2011; Wandera et al., 2017). Further, variation in selection criteria and in the type of interventions across studies makes comparability challenging (Edelman et al., 2016). For example, patients with more depence may require a larger dose of an intervention and may also benefit from stepped up care, yet most studies focus on a single intervention (Edelman et al., 2017). To this end, there are studies being conducted to assess the effectiveness of psychological therapies in HIV in addressing mental health and drinking problems (Madhombiro et al., 2017; Parry et al., 2014). Limited access to skilled staff may impede the successful implementation of interventions for the management of HIV and comorbid alcohol use (Perngparn, Assanangkornchai, Pilley, & Aramrattana, 2008)and there have been calls to use task sharing as a way to address the staff and skills shortage (Collins, Musisi, Frehywot, & Patel, 2015; Lund et al., 2014; Patel et al., 2007). Given that highly skilled personnel have traditionally delivered psychological therapies it is essential to find innovative ways of bridging this gap. HIV care providers, such as nurses, could be trained in the safe and effective delivery of treatments for problematic alcohopl use in PLWH and in so doing improve medication adherence and HIV outcomes (Bernstein et al., 2007).

Feasibility studies are necessary to assess (i) contextual factors that may need to be incorporated into treatment protocols, (ii) barriers and facilitators to the provision of interventions, (iii) service-related factors and (iv) the availability of resources to deliver the interventions as this can potentially influence outcomes (Bernal, 2006). This study sought to obtain baseline data on problematic alcohol use using the AUDIT in a nurse driven HIV care setting. In addition, we sought to

assess the utility of the AUDIT and obtain pilot data on the effectiveness of an intervention for problematic alcohol use, as delivered by registered general nurses.

Ethics

The Health Research Ethics Committee of the Stellenbosch University (SI14/10/222), the Medical Research Council of Zimbabwe (A/1936) and the Harare Hospital Ethics Committee approved this study.

Aim

To pilot the outcome assessments to be used in the trial proper, assess the feasibility of delivery of a brief MI/CBT intervention compared to an WHO mhGAP intervention for problematic alcohol use in PLWH in Zimbabwe, and pilot the effectiveness (on alcohol use, functionality and CD4 count) of these interventions at 3 months in a randomised controlled trial design functional capacity

Methods

Recruitment

Recruitment of participants took place from the 8th to the 28th January 2016. The final assessment of outcomes was completed on the 30th of April 2016. The study setting was a tertiary HIV clinic run by nurses and medical doctors. Research assistants recruited participants during their routine clinic attendance. Informed consent was obtained from willing participants. Baseline data were collected on all participants and the interventions were delivered in February and March 2016. A computer-generated randomization schedule was used to assign participants to the two interventions. As a retention strategy, we noted the contact details of participants and their significant others and reminded participants of their appointments on the day prior to their study visits.

Setting

Harare Central Hospital HIV care clinic which is a tertiary level clinic. Patients were referred from acute medical wards and primary care clinics in the city of Harare and Zimbabwe as a whole.

Inclusion and exclusion criteria

Participants were adults aged 18 years and older. In order to be included, female participants had to score at least 6 and male participants at least 7 (Perula-de Torres et al., 2005), respectively, on the Alcohol Use Disorders Identification Test (AUDIT), scores that are indicative of problematic drinking (www.who.int/substance_abuse/publications/audit/en). There is evidence that low alcohol consumption in HIV positive individuals is associated with increased harm than in HIV negative adults(R. Scott Braithwaite et al., 2008). Participants were screened for cognitive impairment with the International HIV Dementia Scale (IHDS) with those by scoring 10 or less excluded. A score of 11 and below indicated cognitive impairment. Mental illness was assessed with the Substance Abuse Mental Illness Symptom Screener (SAMISS)(Whetten et al., 2005). Positive responses to questions 8-16 are suggestive of mental illness while questions 1-7 are suggestive of alcohol and other substance use problems. The Drug Use Disorders Identification Test (DUDIT) assesses other substance use with positive cut-points of 2 or more for females and 6 or more for males (Berman, Bergman, Palmstierna, & Schlyter, 2005). Participants had to be in receipt of HIV treatment at the clinic and receiving followed-up care for at least three months.

Nurse training

Ten registered general nurses were invited to participate. Training included the use of PowerPoint presentations, role-play, quizzes and assignments. Training was provided both in a classroom setting and on-site. Both interventions were manualised and 5 nurses each were trained in these interventions. The trainers included two psychiatrists, a nurse practitioner and a clinical psychologist. The training was conducted over two days with the first day covering Good Clinical

Practice and ethical principles for both groups of nurses. However, groups were separated on Day 2 of the training with each group receiving training in either MI/CBT or the WHO mh-GAP IG.

Quality assurance

Consent was obtained from the nurses to audio-record the training and this formed the basis of supervision whereby the recordings were collectively reviewed and feedback provided in order to facilitate the acquisition of a similar level of skill among the nurses. Ten percent of the sessions that were administered and audiotaped were reviewed with the nurses and feedback was provided during supervision visits. The 7 sessions that were audio taped were reviewed at the 4 supervision sessions that were held during the study. The supervision visits were held on days and times when the clinic was closed to patients for medication collection. Where inconsistencies were noted, further training was provided, both in individual and group supervision format. Client evaluation and satisfaction cards were reviewed with each nurse, and where concerns were identified, they were discussed and resolved.

MI/CBT Intervention

The MI/CBT intervention comprised a combination of motivational enhancement and cognitive-behavioural techniques and was an adaptation of these evidence-based therapies for problematic alcohol use (Sobell, Breslin, & Sobell, 1998).("Matching alcoholism treatments to client heterogeneity: treatment main effects and matching effects on drinking during treatment. Project MATCH Research Group," 1998) Motivational interviewing is a therapy developed by William Miller and Stephen Rollnick to treat patients with problematic alcohol use(Miller WR). It can also be used for other problematic behaviours. Patients with unhealthy alcohol use can change their drinking patterns when sufficiently motivated through counselling that emphasizes empathic listening, avoiding arguments, rolling with resistance, and self-efficacy. Cognitive behavioural therapy (CBT) is a treatment based on the premise that certain behaviours are the result of faulty thinking. Drinking

behaviour is associated with certain thinking patterns that result in cravings that can be addressed by CBT. Drinking can also be avoided if the patient has certain drink refusal skills that can be developed through CBT.

The intervention comprised 4 sessions, with each session delivered in two parts as shown in Table 1. The duration of these sessions ranged from 30 minutes to one hour. Table 1 shows the content (Miller WR)and duration of sessions. The motivational enhancement therapy themes included providing personal feedback on alcohol use, 'change talk' themes, and readiness to change the 'ruler'. The cognitive therapy elements encompassed setting goals, dealing with cravings and cues, faulty thinking patterns, dealing with stresses, and developing 'drink refusal' skills. Problem solving skills were also included in the intervention. All of the intervention sessions were audiotaped and reviewed with the intervention staff to facilitate uniformity in the delivery of the intervention.

Session 1a, 30 minutes	General life personal goal setting Alcohol goals General life personal goal setting How alcohol use interfere with goals
Session 1b, 30 minutes	Possible reasons why people drink Establish you clients' reasons for drink: Providing personal feedback moving the client towards change Explaining the implications of drinking on treatment as indicated on CD4 and viral load Meaning of improvement and the value of a functional life and quality of life. Drinking problems warning signs
Session 2a, 30 mins	Use MI to build rapport and develop readiness to change Assess readiness to change (using readiness ruler) Assess pros and cons of change (Decision-balance exercise) Use MI to try and shift participant Elicit a commitment to change
Session 2b, 30 minutes	Brief explanation and principles of CBT Explanation on what triggers, urges and cues are and how they lead to drinking Discussion on how triggers arise and how they lead to use and effects. Managing thoughts about drink
Session 3a, 30 minutes	Triggers External Internal Drink refusals skills

	Managing situations were drinking are unavoidable
Session 3a, 30 minutes	Dealing with specific treatment issues like: Receiving viral load and CD4 results, treatment problems, Losing a spouse, Employment threatened by illness, New illness related to the viral infection Running out of medication
Session 4, 30 minutes	Planning future direction Life is back to normal: Do I drink? Dealing with anger and criticism Dealing with failure Self-referral Conclusion and planning the future

Table 1: Summary of session content and objectives

WHO mh-GAP IG The World Health Organisation Mental Health Action Programme Intervention Guide (WHO mh-GAP IG) was the comparator(Organisation, 2010). The WHO mhGAP IG is designed for screening and management of common mental disorders, including problematic alcohol use, in primary care settings. It has been used as a control in other studies in low and middle-income countries (Nadkarni, Weobong, et al., 2017). The WHO mhGAP comprised an assessment of alcohol use on history, brief advice on harmful alcohol use, and referral for probable alcohol dependence. This intervention was administered in a single session of one hour by trained RGNs.

Assessment measures

At baseline `and follow-up, the AUDIT, CD4 count, WHODAS 2.0 and the WHOQoL were administered. Follow-up assessments were conducted for both group at three months.

WHO AUDIT

The WHO AUDIT was used to screen participants and was also the primary outcome measure. The AUDIT is a 10-item tool with a score range of 0 to 40(Bohn, Babor, & Kranzler, 1995; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). In this study, scores of 6 and 7 for females and males, respectively, were applied as cut-offs to identify patients with problematic drinking based on psychometric performance of the AUDIT in previous studies (Perula-de Torres et al., 2005). Some

studies have shown that HIV infected individuals require much less alcohol to get intoxicated and suffer physiologic harm(Justice et al., 2016; McGinnis et al., 2016). Although the AUDIT has not been validated in Zimbabwe or among people living with HIV, it has been used in diverse population groups in Southern Africa and in Zimbabwe(Chandiwana et al., 1999; Chinyadza et al., 1993). The AUDIT has good psychometric properties with a Cronbach alpha of 0.93 [95% CI (0.921-0.941)], specificity of 89.6% (95% CI, 76.11-96.02 and sensitivity of 95.07% (95% CI, 92.18-96.97) against gold standard DSM-IV criteria, at a cut point of 6 (Perula-de Torres et al., 2005). The Cronbach alpha for the AUDIT in this study was 0.72.

Viral load and CD4

Trained general nurses collected blood for baseline viral loads and CD4 count. These assays were done at the hospital laboratory. As a result of budgetary constraints, viral loads were not done at the 3-month assessment.

World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0)

The WHODAS 2.0 is a tool developed by the WHO to assess the degree of disability and has been validated for a variety of health conditions(Garin et al., 2010; www.who.int/icidh/whodas/; www.who.int/mental_health/media/en/613.pdf). Although the WHODAS 2.0 has not been validated in Zimbabwe, it has been used in rural Ethiopia and was found to have good psychometric properties with an internal consistency ranging from very good to excellent (Crobach's alpha 0.82 to 0.98)(Habtamu et al., 2017). The WHODAS 2.0 has been validated for chronic diseases, such as HIV, and had good psychometric features(Garin et al., 2010). The Cronbach alpha for the WHODAS 2.0 in this study was 0.91.

World Health Organisation Quality of Life HIV (WHOQoL HIV)

Quality of life was assessed using the WHO Quality of Life HIV (WHOQoL HIV) that has been validated for HIV elsewhere but not in Zimbabwe(Group, 2004; Hsiung et al., 2011; www.who.int/mental_health/media/en/613.pdf). The WHOQoL HIV has been validated in South Africa and Zambia and has good internal consistency with Cronbach alphas ranging from 0.889 to 0.933 in the Zambian study(Mweemba, Zeller, Ludwick, Gosnell, & Michelo, 2011; Van Biljon, Nel, & Roos, 2015). The Cronbach alpha for the WHOQoL HIV in this study was for 0.9 D for domain I, 0.59 for domain II, 0.92for domain III,.and 0.49 for domain IV.

Data analysis

Data were analysed using Stata version 14(StataCorp. 2015. Stata Statistical Software: Release 14. College Station). Intention to treat was the approach to analysis. The standardized mean difference of the AUDIT score was the measure of treatment effect. We summarized continuous variables using means (standard deviation) or medians (interquartile range) depending on the distribution, and categorical variables using counts (percentages). We used t-tests or Mann-Whitney U tests to compare means or medians between the two intervention groups. We used chi-square tests or Fisher's exact tests to test the association between study groups and other categorical variables. Alpha was set at = 0.05 and all tests were two sided.

Results

Recruitment, randomisation and retention

One hundred and two (102) patients were invited to participate in the study. At screening, 33 scored less than 6 on the AUDIT and 69 had scores at or above the cut-off. Eleven participants failed to meet the eligibility criteria and 18 declined to participate for reasons including moving away from Harare, work commitments and other reasons. Forty participants were randomised to each group with no baseline differences between the groups, as shown in Table 3. At follow up, 4 participants were lost in the MI/CBT group and 5 in the mhGAP IG group. Three participants in the MI/CBT group

and 4 in the mhGAP IG group relocated from Harare, while 1 participant in the MI/CBT group and 1 in the WHO mhGAP IG group were unable to secure time off from work (see Fig. 1).

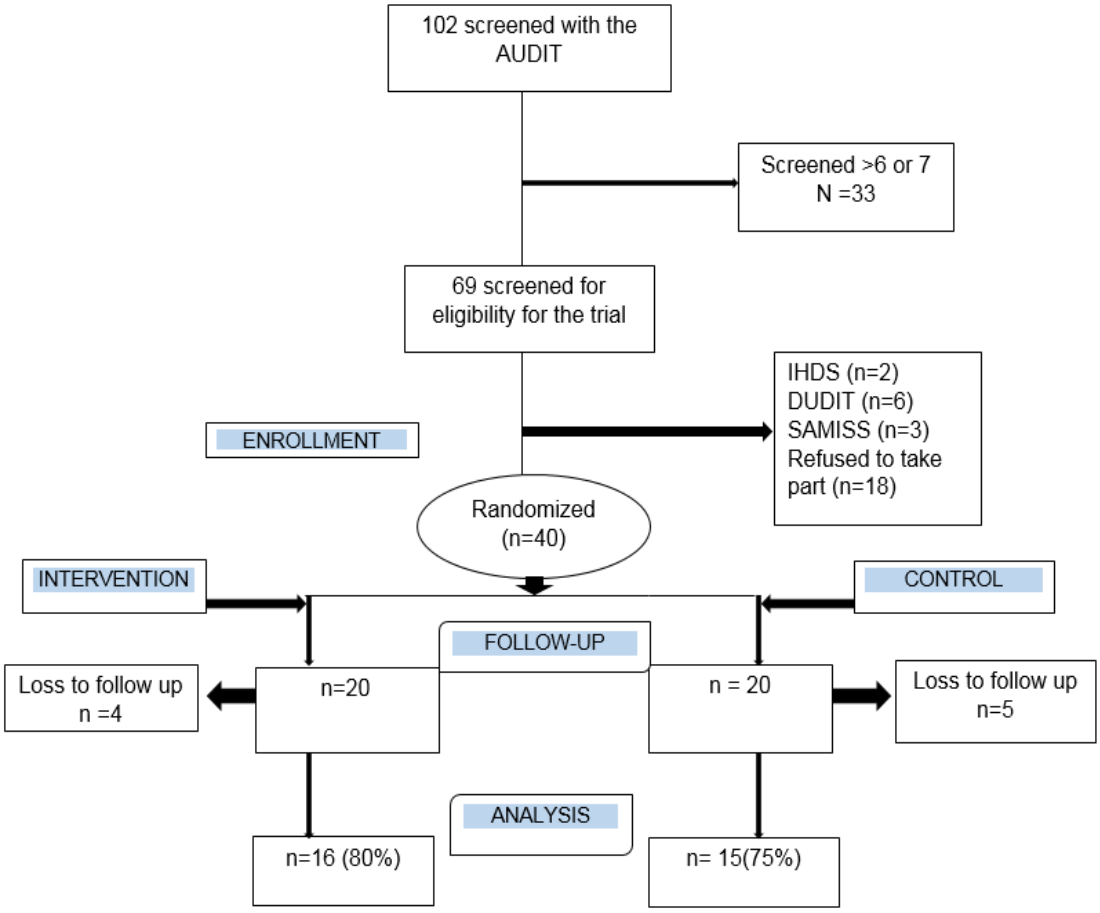

Figure 1 shows the study flow from screening to analysis.

Comparisons Cell {#1}-{#2}	LSD test; variable AUDIT (Spreadsheet8 in PILOT DATA SET FINAL.stw) Simultaneous confidence intervals Effect: group*time 1st Mean	2nd Mean	Mean Differ.	Standard Error	p
{1}-{2}	control*pre	control*post	8.05	1.95	0.00
{1}-{3}	control*pre	intervention*pre	1.20	2.07	0.57
{1}-{4}	control*pre	intervention*post	8.85	2.07	0.00
{2}-{3}	control*post	intervention*pre	-6.85	2.07	0.00
{2}-{4}	control*post	intervention*post	0.80	2.07	0.70
{3}-{4}	intervention*pre	intervention*post	7.65	1.95	0.00

KEY: means Control*pre; means Control*post; means Intervention*pre; means Intervention*post
Table 3 is showing AUDIT SCORES between MI/CBT and mhGAP

Baseline characteristics

There were 17 female and 23 male participants in the study. The combined mean age was 39.5 years (SD=9.59), with a mean age of 41.7 years (SD=9.61) in eth MI/CBT group and a mean age of 37.3 years (SD=9.29) in the mhGAP IG group. Table 2 shows the socio-demographic characteristics of the sample. At study entry, 6(15%) participants were on second line HAART and 34(85%) had achieved viral suppression. Participants had been on HAART for 3.5(SD1.2) years. The MI/CBT group had a significantly lower median CD4 count 201.5 (range of 85 to 367) than the mhGAP group 390(range of 200 to 400) (p=0.03). Table 2 Shows the sociodemographic features of the study population. The participants were predominantly male and more than 50% were married.

	Frequency	Mean	Standard deviation
Age		39.5	9.59
Females (%)	17 (42.50)		
Males (%)	23 (57.50)		
Marital status			
Single (%)	7 (17.50)		
Married (%)	21 (52.50)		
Divorced (%)	6 (15)		
Widowed (%)	6 (15)		
Education -years in school			3.10

Interventions

A total of 74 interventions sessions were administered with a median of 3.7(1 to 4 sessions) sessions per participant and 14.8 sessions per nurse. The duration of sessions ranged from 30-55 minutes. In the mhGAP group, each nurse conducted a single session of the mhGAP at the first contact. A total of 20 sessions were administered to this group.

Outcomes

Alcohol use outcomes

There was no statistically significant difference in the AUDIT score at baseline (p=0.57) between the groups as shown in Table 2. There was a statistically significant change in alcohol use in both groups over time (p <0.0) as shown on Table 2. There was no difference in the magnitude of

change between the groups as shown the 95% confidence intervals in Fig 2. In the MI/CBT group, there was a change in mean AUDIT score from 14.85(7.78) to 7.20(5.07) and for the mhGAP IG group, the mean AUDIT score changed from 16.05(7.20) to 8.00(5.79) over time as shown in Table 4.

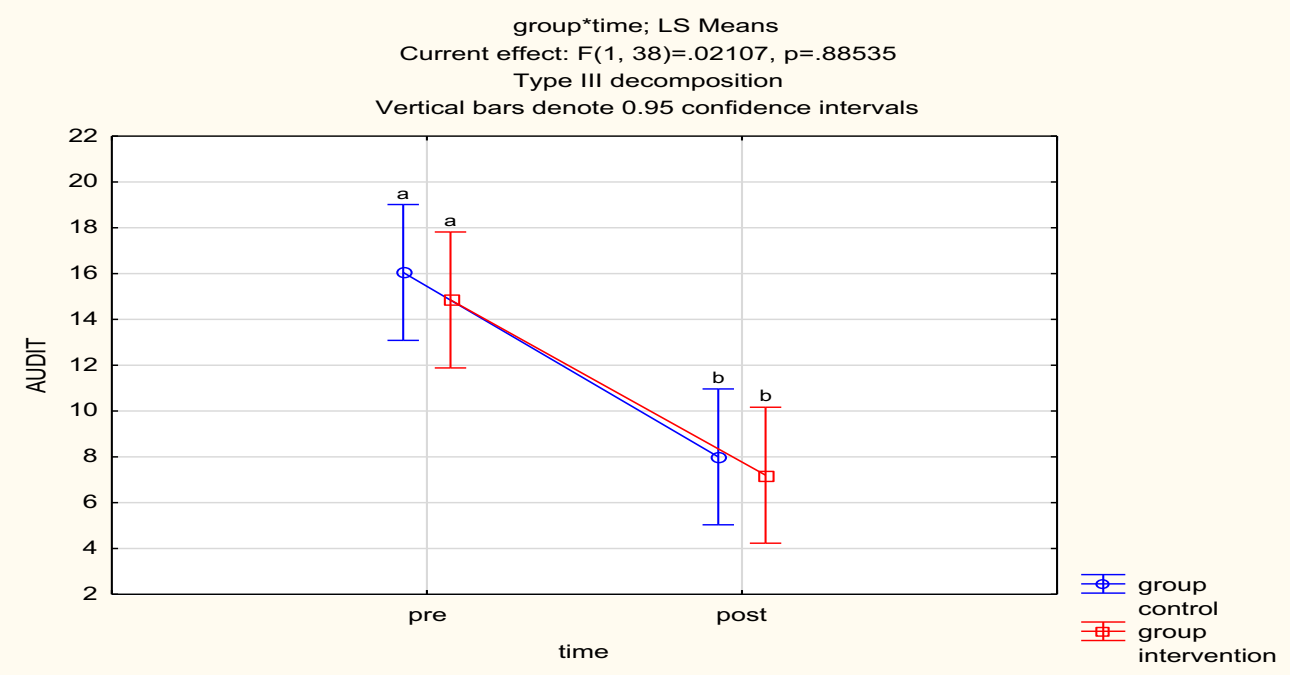

Figure 2 is showing the AUDIT for both arms. Both arms recorded significant falls in their AUDIT Score.

Effect	Descriptive Statistics (Spreadsheet8 in PILOT DATA SE				
	Level of Factor	Level of Factor	N	AUDIT Mean	AUDIT Std.Dev.
Total			80	11.53	7.56
group	control		40	12.02	7.63
group	intervention		40	11.03	7.55
time	pre		40	15.45	7.43
time	post		40	7.60	5.39
group*time	control	pre	20	16.05	7.21
group*time	control	post	20	8.00	5.79
group*time	intervention	pre	20	14.85	7.78
group*time	intervention	post	20	7.20	5.07

Table 4 Descriptive Statistics is showing comparisons between Audit scores between both arms

CD4

Due to the skewness in the data, we report medians and interquartile ranges. At follow-up, the median and interquartile ranges for the MI/CBT and mhGAP IG groups were 390(280) and

567(378), respectively, indicative of improvement in immunological parameters although groups differences were not statistically significant as shown in Table 5 and Fig 3

Source	MI/CBT Median	MI/CBT IQR	MH GAP IG Median	MH GAP IQR
CD4 Count Baseline	218	274	484	211.5
CD4 Counts Follow-up	390	280	567	378

Table 5 shows comparisons between baseline CD4 count and follow-up CD4 count

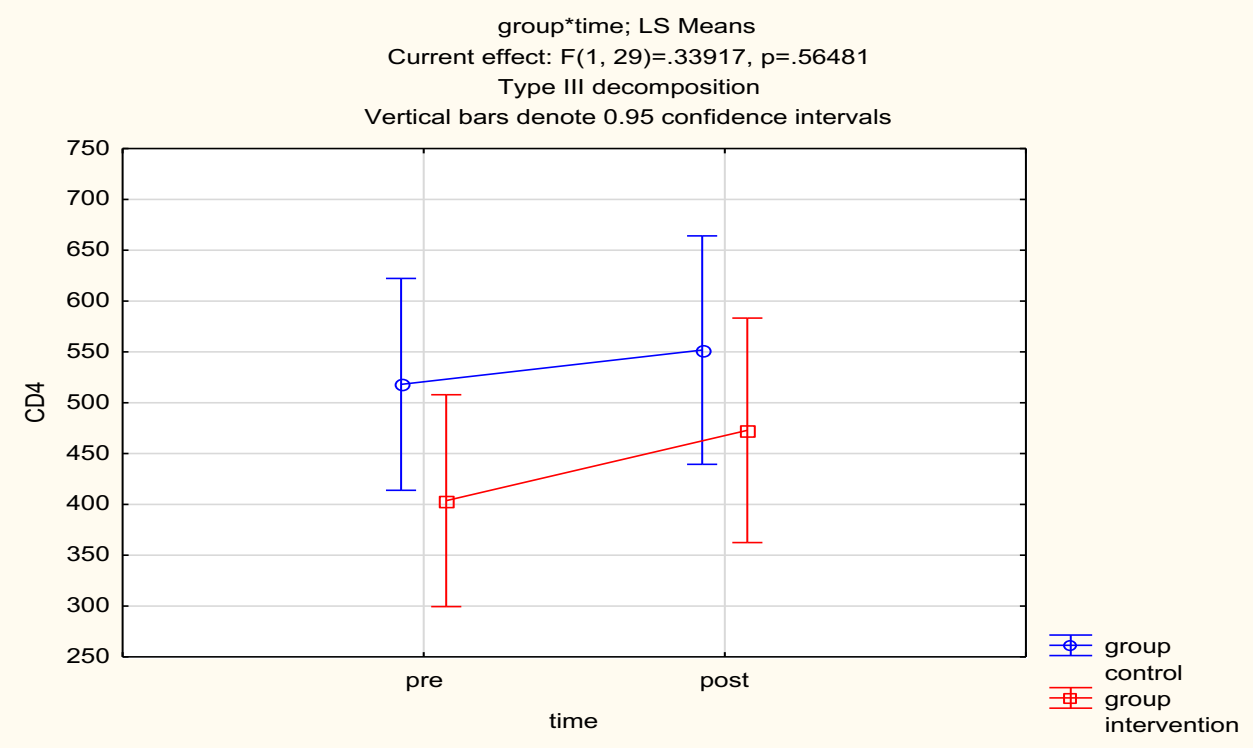

Figure 3 is showing the CD4 Count for both arms. Group control represents the mh GAP IG arm and group intervention represents the MI/CBT arm.

Functioning and quality of life

Functioning and quality of life, as measured on the WHODAS 2.0 and the WHOQoL HIV, showed no change over time.

WHODAS	MEAN	STAND ERROR	STD DEV	95% C I	
Baseline					
MI/CBT	13.7	1.54	6.88	10.48	16.92
mhGAP	15.5	1.45	6.48	12.47	18.53
3 months					
MI/CBT	13.44	.95	3.80	11.42	15.46
mhGAP	13.27	1.12	4.35	10.86	15.68

Table 6 is showing the disability for baseline and 3 months

WHOQOL	MEAN	STAND ERROR	STD DEV	95% C I	
Baseline					
MI/CBT	23.65	.69	3.07	22.22	25.05
mhGAP	22.63	.86	3.73	20.83	24.43
3 months					
MI/CBT	22.33	.80	3.11	20.61	23.84
mhGAP	22.94	.42	1.70	22.06	24.06

Table 7 is showing the quality of life for baseline and 3 months

Discussion

The aim of this study was to pilot the outcome assessments to be used in an adequately powered trial, assess the feasibility of delivery of a brief MI/CBT intervention compared to an WHO mhGAP intervention for problematic alcohol use in PLWH in Zimbabwe, and assess their preliminary effectiveness using a task-sharing model in a low resource setting with a huge HIV burden. This sample of 40 HIV infected patients was drawn from an HIV care setting at a tertiary institution where participants received either blended motivational interviewing/CBT or the WHO MH GAP IG. The

retention rate was 77% at 3 months with no statistically significant group difference. In both groups, drinking behaviour as assessed by AUDIT score and CD4 count improved after treatment.

Improvement in alcohol use in this population supports previous findings that participation in screening and exposure to alcohol counselling, and receipt of pamphlets or presentations can lead to reduction in alcohol use(Brown et al., 2013). Studies have shown that in participants with early and low levels of alcohol use, low intensity interventions can lead to change in the level of alcohol use(Babor, Ritson, & Hodgson, 1986). However, studies have also shown that patients who are dependent on alcohol do not change their drinking behaviour even with longer exposure to interventions (Moyer, Finney, Swearingen, & Vergun, 2002). Although we hypothesized that MI/CBT would result in a greater reduction in drinking than the mhGAP IG, this was not the case. Both interventions could be considered as 'active' treatments. There has been a call to adapt and test treatments such as the WHO MH GAP IG, that are scalable in low- and middle- income countries(Baingana, al'Absi, Becker, & Pringle, 2015).

Although there was change in the CD4 count in both groups, this was not statistically significant. Some studies have found no relationship between alcohol use and CD4 count(Azar, Springer, Meyer, & Altice, 2010). Functional capacity and quality of life did not show any change over time in the trial. The small sample size may have contributed to the lack of detection of a significant effect

The loss to follow up was 23% despite retention efforts such as confirming appointments. Follow up assessments did not always coincide with scheduled clinic visits. Participants at the clinic at which recruitment took place (a tertiary institution) are poorly adherent, have late stage disease and high rates of treatment failure. These are some of the characteristics of loss to follow up that were documented in a study in Ethiopia(Megerso et al., 2016).

The study provides preliminary evidence that registered general nurses can be trained to offer a psychological intervention for dually diagnosed adults with HIV and unhealthy alcohol use. In Zimbabwe, nurses are at the forefront of provision of both curative and preventive interventions in Zimbabwe. While task sharing an intervention for unhealthy alcoholuse to nurses may be novel, nurses have been at the forefront of provision of HIV treatment with results that are comparable to those achieved by doctors(Fairall et al., 2012).

This pilot study has a number of limitations. It is characterized by a small sample and, as such, not adequately powered to demonstrate true treatment differences and hence prone to Type I error. Further, the alcohol screening used the AUDIT, which is a self-report tool. As a result, has social desirability bias(Davis, Thake, & Vilhena, 2010). The study was undertaken at a tertiary institution which serves as a referral centre for patients and not in primary or district care settings, thus morbidity present in the sample may not be reflective of HIV patients receiving care in the latter settings.

Conclusion

This study demonstrates the feasibility of administering the assessment tools employed here and delivering a brief MI/CBT intervention in HIV care clinics. The interventions led to change in alcohol use. Further large samples studies that are adequately powered are needed. Strategies to retain participants need to be carefully considered when integrating interventions for alcohol use treatment into usual care.

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CHAPTER FIVE: PROTOCOL

Title: A cluster randomised controlled trial protocol of an adapted intervention for alcohol use disorders in people living with HIV and AIDS: impact on alcohol use, general functional ability, quality of life and adherence to HAART

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STUDY PROTOCOL Open Access

A cluster randomised controlled trial protocol of an adapted intervention for alcohol use disorders in people living with HIV and AIDS: impact on alcohol use, general functional ability, quality of life and adherence to HAART

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Abstract

Background: Interventions for alcohol use disorders (AUDs) in HIV infected individuals have been primarily targeted at HIV risk reduction and improved antiretroviral treatment adherence. However, reduction in alcohol use is an important goal. Alcohol use affects other key factors that may influence treatment course and outcome. In this study the authors aim to administer an adapted intervention for AUDs to reduce alcohol use in people living with HIV/AIDS (PLWHA).

Methods: This study is a cluster randomised controlled trial at 16 HIV care clinics. A motivational interviewing and cognitive behavioural therapy based intervention for AUDs, developed through adaptation and piloted in Zimbabwe, will be administered to PLWHA with AUDs recruited at HIV clinics. The intervention will be administered over 16 sessions at 8 HIV clinics. This intervention will be compared with an equal attention control in the form of the World Health Organization Mental Health Gap Action Programme (WHO mhGAP) guide, adapted for the Zimbabwean context. General function, quality of life, and adherence to highly active antiretroviral treatment (HAART) will be secondary outcomes. Booster sessions will be administered to both groups at 3 and 6 months respectively.

The primary outcome measure will be the Alcohol Use Disorder Identification Test (AUDIT) score. The World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0), World Health Organisation Quality of Life (WHOQoL) HIV, viral load, and CD4 counts will be secondary outcome measures. Outcome assessments will be administered at baseline, 3, 6, and 12 months. Moderating factors such as perceived social support, how people cope with difficult situations and post-traumatic exposure and experience will be assessed at baseline. Trained research assistants will recruit participants. The outcome assessors who will be trained in administering the outcome and moderating tools will be blinded to the treatment arms allocated to the participants. However, the principal investigator, participants and intervention staff will be unblinded.

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Data will be analysed using STATA Version 14. Primary and secondary outcomes will be measured at four time points that is; at baseline, 3, 6, and 12 months respectively. All participants will be included in the analysis of primary and secondary outcome measures. The mean AUDIT scores will be compared between groups using student t-tests. Multilevel logistic regression analysis will be performed for binominal variables and multilevel linear regression for continuous variables. Descriptive statistics will be computed for baseline and follow-up assessments.

Discussion: The study will be the first to address problematic alcohol use in PLWHA in Zimbabwe. It seeks to use local resources in delivering a modified, brief, evidence-based, and culturally contextualised intervention. The study results will determine the effectiveness of adapting psychological interventions for AUDs in HIV infected adults using a task-sharing framework.

Trial registration: Pan African Clinical Trial Registry, PACTR201509001211149. Registered 22 July 2015.

Keywords: Alcohol use disorders, Motivational interviewing, Cognitive behavioural therapy, Intervention, Zimbabwe

Background

According to the World Health Organization (WHO), alcohol abuse is one of the top three causes of health related problems apart from child underweight and unsafe sex [1]. In low and middle income countries, AUDs cause 19.5 million Disability Adjusted Life Years (DALYS) [2]. Harmful alcohol use results in 3.3 million deaths per year globally. In 2012, according to WHO alcohol use contributed 5.1% to the global burden of diseases or 139 million net DALYS. Zimbabwe is a country with one of the highest per capita alcohol consumption rates in the WHO Afro-Region at 5.7 l per capita per year in 2010 [3].

Alcohol consumption is high among people living with HIV/AIDS (PLWHA) especially hazardous alcohol consumption and this is associated with decreased survival [4]. Studies have also shown that alcohol consumption is linked to HIV infection, adherence to the highly effective antiretroviral therapy (HAART), HIV prevention, delayed testing and treatment, and general poor outcome in HIV care and treatment [5, 6]. PLWHA are at increased risk of physiologic injury such as liver disease from alcohol [7].

Heavy episodic drinking is common in sub-Saharan Africa, the epicentre of the HIV pandemic [8]. The quantity of alcohol consumed is more closely related to HIV infection than the frequency although some studies have indicated that the drinking context is as important [9]. In addition to alcohol and other drug abuse, depression, anxiety and psychosis, are linked to non-adherence to HAART and to treatment interruptions [10–12]. In order to achieve adequate viral suppression and improve adherence to HAART, AUDs and other psychiatric disorders need to be appropriately treated. Wu et al., after controlling for adherence, showed that daily consumption of alcohol was associated with a viral load increase, while reduction of alcohol intake to once weekly intake was associated with a reduction in viral load [13].

There is evidence that alcohol affects the functioning of the human immune system negatively [14]. Alcohol has been shown to increase the concentration of HIV RNA in semen and the vagina [15]. There is also some evidence that vaginal shedding of viral RNA is increased by alcohol which is associated with increased infectiousness [16].

AUDs and low adherence to HAART are associated with poor health outcomes and quality of life [17, 18], while simplification of HAART has been associated with improved adherence and quality life [19, 20]. Alcohol consumption has implications for HIV treatment through direct toxic effects on the liver and the interactions with HAART [21, 22].

Despite the high prevalence of alcohol use disorders among people living with HIV/AIDS (PLWHA) and the potential for adverse health consequences, there is not enough contextual evidence for behavioural interventions for AUDs in African settings. Motivational interviewing (MI), cognitive behavioural therapy (CBT), problem solving, and risk reduction are some of the evidence-based treatments that have been used to treat alcohol use disorders [23]. MI and CBT have been used both in combination and separately [24].

Sub-Saharan Africa suffers from the world's most pronounced crisis in terms of human resources for health [25]. A streamlined and rationalized chain of care that relieves pressure on individual workers is needed. However this chain of care for patients, while increasing access to and uptake of interventions, must be quality assured [26]. Up skilling various cadres of staff to provide services that are normally delivered by highly skilled workers is recommended [27]. Task sharing has been proposed as an approach to provide services that are normally provided by highly skilled staff by the lesser skilled through training and provision of treatment manuals. For task-sharing to work, attention needs to be paid to the selection of staff, their current workload, the adequacy of training, and the availability of manualised interventions [28]. Supervision and support visits are essential for quality control and maintaining fidelity [29]. Task-sharing has the potential to build capacity and integrate HIV care, thereby also addressing the

gap that results from health worker attrition due to immigration and HIV [30].

Most studies on HIV in Zimbabwe have focused on behavioural change with particular emphasis on risk reduction and adherence to HAART. There have been no studies of the management of AUDs among PLWHA in Zimbabwe. This is to our knowledge, the first intervention study that specifically targets AUDs in PLWHA. This intervention for AUDs intervention will be compared with the mhGAP intervention guide alcohol use management module which is a part of the WHO Mental Health Gap Action Programme (WHO mhGAP) [31]. The mhGAP intervention guide was developed for primary care settings and has been used in developing countries for the identification and management of various mental and neurological and substance use disorders (MNS).

Methods/Design

Preparatory-work

In the development of the intervention for the proposed study, a literature review was undertaken to evaluate the available scientific evidence on the magnitude of the AUDs in PLWHA across Low and Medium Income Countries (LMIC). The review of literature for efficacy and effectiveness studies was focused on relevant socio-demographic variables (including gender), methods used, HIV disease progression and alcohol outcomes. This evidence was then presented to experts and HIV specialists to bring their attention to the problem and get them on board to expand on the work and bring in local context. The study flow is shown in Fig. 1.

Focus in the development of this intervention was on integration and adaptation of MI and CBT, which were the main intervention theoretical frameworks and brought in the local contextual framework. Development of treatment manuals, and exploratory work with a small number of patients then followed. The intervention development and design included meetings and workshops that were qualitative in nature. This involved experts such as provincial medical officers, district medical officers, nurses, and stakeholders from community leadership and provincial government, NGOs and alcohol service organizations such as the alcoholics anonymous and PLWHA. Interactions and formal meetings with the Ministry of Health, College of Health Sciences (Departments of Medicine, Psychiatry and Community Medicine) were done to gather their views. The National AIDS Council, which is the statutory body mandated with planning, coordinating, and evaluation of HIV/AIDS activities in Zimbabwe participated in the development of the intervention.

Focus group discussions, which were conducted with PLWHA, were around the language of alcohol and knowledge gaps concerning alcohol use. Barriers and facilitators of AUDs treatment were explored. Issues around

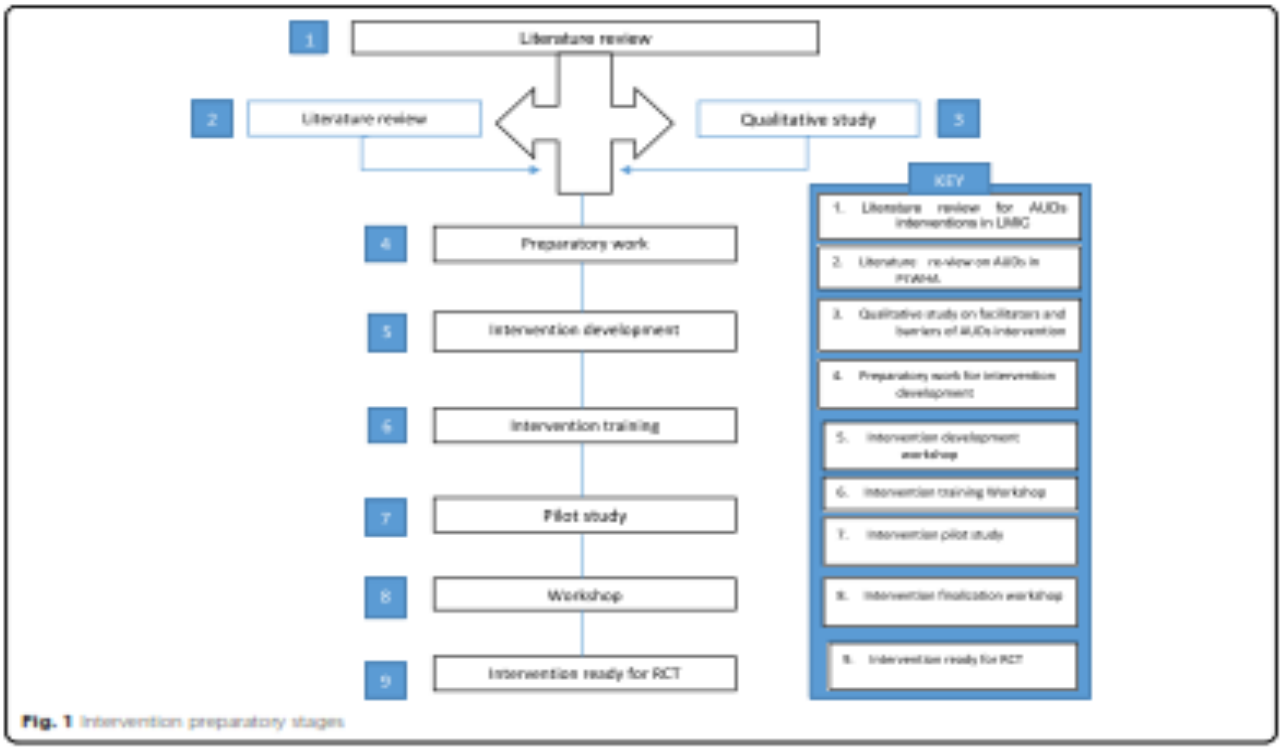

Fig. 1 Intervention preparatory stages

'messaging' in the intervention and patient information leaflet were discussed as well.

The current HIV clinic setup, existing staff skills in counselling and established counsellor-patient relationships was identified as the main facilitators to intervention. Stigma, lack of skills among health professionals, absence of brief culturally appropriate screening tools, and patient and provider attitudes toward their own alcohol use were identified as the main barriers. The pilot study showed that the RGNs could deliver the intervention. The recruitment and retention of participants was feasible and adjustments to the study instruments needed to be done to allow smooth flow of the study.

Aims

1. To evaluate the effectiveness through a cluster randomized controlled trial of an adapted MI/CBT AUDs intervention in PLWHA.
2. To assess the impact of the AUDs intervention on adherence to HAART as measured by viral load and CD4 count, functional capacity as measured by the WHODAS 2.0, and quality of life as measured by the WHOQoL HIV.
3. To identify the moderators between alcohol and HIV treatment using the Cope-13, *Multidimensional Scale of Perceived Social Support (MSPSS* and the Davison Trauma Scale (DTS).

Design

Two-arm cluster randomised controlled trial at 16 HIV clinics in Zimbabwe, with the unit of randomization HIV clinics, comparing Motivational Enhancement Therapy and Cognitive Behavioural Therapy from Project MATCH adaptation based treatment, with the WHO mhGAP intervention guide, adapted for the local context. This design has been selected to increase administrative efficiency and decrease the risk of experimental contamination at clinic level. The registered general nurses (RGNs) will be trained to administer the intervention and control using manuals.

Study setting

The study will be conducted in HIV clinics in Zimbabwe, a sub-Saharan African country with an estimated 1,6 million PLWHA whose HIV care is decentralised. RGNs run the HIV care clinics and physicians provide supervision. RGNs provide HIV testing, adherence counseling and monitor treatment progress. The patients are reviewed, largely for reboarding of their medication. There is an electronic database of all the patients at every clinic.

Participants

Participants are treatment-seeking adults who are HIV positive and who screen positive for AUD as per the inclusion criteria.

Study materials

Socio-demographic data

Socio-demographic data such as gender, age, marital status, employment and years of education will be collected.

Clinical data

Clinical data such as the date of HIV testing, duration on HIV treatment, treatment regimen, CD4 count and viral load will be collected.

Primary outcome tools

The primary outcome measures will be the change in alcohol use as measured by AUDIT score change from the baseline. Although alcohol use biomarkers would have been ideal, due to resource constraints a self-report tool will be used in this study.

Alcohol Use Disorder Identification Test (AUDIT) [32]

The AUDIT has not been validated in Zimbabwe, however several studies have utilized the AUDIT as an instrument to assess alcohol use in various communities including Zimbabwe [33]. In a study by Bush et al. [34] the AUDIT was found to have a sensitivity of 89% and a specificity of 67%. The unit of alcohol as defined in the AUDIT is 10 g. The legislation requires that the percentage of alcohol in alcoholic beverages be specified and follow the regional norm. The alcohol quantity in grams is however more informative. A traditional brew in the rural areas of Zimbabwe, which has 40 g of alcohol in 1.5 l, is estimated to have 4 units of alcohol and will be used to assess the quantity of units consumed according to local norms.

Secondary outcome tools

The secondary outcomes will be the functional capacity, the quality of life and adherence to HAART.

World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0) [35]

The WHODAS 2.0 will be a secondary outcome measure and will be administered at baseline, 3, 6, and 12 months respectively to assess functional capacity. The WHODAS 2.0 contains 6 domains, which are cognition, mobility, self-care, getting along, life activities and participation. It is fairly short and simple and takes about 5–20 min to administer. Although the WHODAS 2.0 has not been validated in Zimbabwe, it has been used in HIV patients in South Africa [36].

World Health Organization Quality of Life (WHOQoL HIV) [37]
The WHOQoL HIV is a tool that assesses the quality of life of persons with HIV. The WHOQoL HIV has six domains that include physical, psychological, level of independence, social relationships, environment, and spirituality domains (http://www.who.int/msa/qol/). In a study to assess the overall health-related quality of life in a sample of HIV infected South Africans, results showed that quality of life, as measured by WHOQoL, was poor, with further analysis showing that the WHOQoL domains predicted overall quality of life in PLWHA [38]. Although the WHOQoL has not been validated in Zimbabwe, the Department of Psychiatry, University of Zimbabwe was involved in its development and the tool has been used in the region [39].

Tools for confirming eligibility

The tools to confirm eligibility will assess the presence of other drug use and exclusion of participants with dementia and other psychiatric conditions.

Drug Use Disorders Identification Test (DUDIT) [40]
The DUDIT screens for the presence of substances of abuse other than alcohol [41]. The DUDIT has validity in determining the severity of dependency although caution needs to be exercised in deciding on cut- off points [42]. In a study in the USA the assessment of its psychometric properties, the DUDIT had a sensitivity and specificity of 90% and 80%, respectively, with an optimal cut-off of 8 [43]. The DUDIT has not been validated in Zimbabwe.

Substance Abuse Mental Illness Symptom Screener (SAMISS) [44]
The SAMISS identifies individuals with substance abuse and mental illness. It can be simply scored and assists in the identification of patients with probable mental illness. The SAMISS has been validated in South Africa and has been identified as a tool that can be used in primary care settings for PLWHA [45]. The SAMISS was found to have a sensitivity of 94% and a specificity of 58% and was better at identifying alcohol use (sensitivity 94% and specificity 85%) and mental illness (sensitivity 97% and specificity 60%) [45]. However, it has not been validated in Zimbabwe.

M.I.N.I (MINI International Neuropsychiatric Interview 7.0 [46]
The M.I.N.I for the DSM-5 is the gold standard diagnostic interview in this study and will be administered by a clinician [47]. The clinician-administered M.I.N.I. will be used to assess for common psychiatric disorders. The M.I.N.I has been recognised as a short diagnostic interview that can be easily incorporated into routine clinical assessment [48].

International HIV Dementia Scale (IHDS) [49]
Patients with dementia will be excluded and referred for specialist care, as they may not be able to cognitively engage with the requirements of the intervention. The IHDS has not been validated in Zimbabwe, but has been used in sub-Saharan Africa samples. In cohorts in USA and Uganda, the sensitivity and specificity using cut-off of 10 or less were 80 and 57% in the USA and 80 to 55% in Uganda [50].

Additional assessments/ moderators

These tools assess the factors that may be related to alcohol use and HIV treatment such as history of trauma, social support and coping with stress.

Davidson Trauma Scale (DTS) [51]
The DTS will be used to determine the presence of traumatic event exposure and possible posttraumatic stress symptoms. HIV is associated with traumatic experiences and features of post-traumatic stress disorder (PTSD). The Davidson Trauma Scale was developed as a self-rating tool which has been shown to be useful in diagnosing and measuring symptom severity and treatment outcome in PTSD [52].

COPE-13 [53]
This instrument assesses how people respond to difficult or stressful events in their lives. The COPE-13 was developed to assess situational and dispositional coping styles and has been used in different samples in communities affected by natural disasters in caregivers and patients [54].

Multidimensional Scale of Perceived Social Support (MSPSS) [55]
The MSPSS aims to assess the social support available to the patient from significant others, family and friends. Social support can act as a buffer for psychological distress whilst the lack of it can lead to adverse outcomes such as relapse into depression and emotional distress in physical illness [56]. The MSPSS has been shown to be reliable and valid in some populations (e.g. in the Thai population) but has not been validated in Zimbabwe.

Procedures

Intervention

The intervention will be blended motivational interviewing (MI) and cognitive behaviour therapy (CBT). The four key principles of MI which are to (a) express empathy, (b) develop discrepancy, (c) roll with resistance, and (d) support self-efficacy will be employed in this intervention. MI topics will help in building client motivation and emphasize responsibility for change. The provider gives guidance and support with no specific

assumptions regarding the course of treatment. Cognitive behavioural therapy will include (a) identifying intrapersonal and interpersonal triggers for relapse, (b) coping-skills training, (c) alcohol refusal skills training, (d) functional analysis of alcohol use, and (e) increasing non-drinking related activities.

The intervention will have 16 sessions. Eight sessions will be given at baseline and 4 each at 3 and 6 months.

Sessions 1, 4, 6 and 7 will be repeated at 3 and 6 months. Additional sessions, with content dependent on individual problems identified, will be administered. The content of the intervention is shown in Fig. 2.

Control

An adapted version of the mhGAP intervention guide (the alcohol section) will be administered to participants at 8 clinics. The session will also focus on providing feedback on the AUDIT score, the CD4 count, viral load, and on functioning and quality of life. This intervention is expected to last one hour (based on our experience in the pilot study). At 3 and 6 months, the control intervention will be re-administered and outcomes assessed with the final assessment done at 12 months.

Training

The principal investigator will be the chief trainer on the MI/CBT AUDs intervention while a co-investigator trained in the mhGAP intervention guide will train the control arm interventionists.

RGNs will be trained in the use of the intervention (MI/CBT) and control (mhGAP) manuals. Sixty-four nurses working at 16 HIV Care clinics will be trained.

Session 1, 45 minutes	**Goal setting** General life personal goal setting Alcohol goals How alcohol interferes with goals
Session 2, 1 hour	**HIV and drinking** Possible reasons why people drink Establish client's reasons for drinking Provide personal feedback moving the client towards change Examine the impact of drinking on HIV treatment, CD4 count and viral load Meaning of improvement and the value of a functional life and quality of life. Drinking problems and warning signs
Session 3, 1 hour	**Motivational interviewing and the intervention** Use MI to build rapport and develop readiness to change Assess readiness to change (using readiness ruler) Assess pros and cons of change (decision-balance exercise) Use MI to try and shift participant Elicit a commitment to change
Session 4, 30 minutes	**Cognitive behavioural therapy and intervention** Brief explanation and principles of CBT Explanation on the triggers, urges and cues are and how they lead to drinking Discussion of how triggers arise and how they lead to alcohol use and its effects Managing thoughts about drinking
Session 5, 45 minutes	**Triggers and relapse** External Internal Drink refusal skills Managing situations where drinking is unavoidable
Session 6, 30 minutes	**Dealing with specific treatment issues like:** Viral load and CD4 count results, treatment problems Losing a spouse Employment compromised by illness Illness complications related to HIV infection Running out of medication
Session 7, 1 hour	**Planning future direction** Life is back to normal: Do I drink? Dealing with anger and criticism Dealing with failure Self-referral
Session 8, 1 hour	**Conclusion and planning the future**

Fig. 2 Intervention sessions, expected time and goals

Material covered in the training manual will include evidence-based interventions for co-occurring HIV and AUDs, administration of the AUDIT and other data gathering tools, the theoretical basis of the intervention, counselling skills and supervision. Further, RGNs will receive training in good clinical practice, covering research ethics, the importance of maintaining confidentiality, reporting adverse events, the intervention protocol, and the process of referring patients for specialized care. Practical exercises will include self-administered quizzes, small group discussions, and case study exercises.

Training materials developed during the preparatory phase of the study will be used in the intervention and control training. RGNs who were identified and trained for the pilot study will be recruited for the training. Staff trained in the feasibility study, who are RGNs by profession, will do supervisory visits. Supervisors will use supervision protocols developed for the study. Supervisory visits will be undertaken at 3, 6 and 12 months. The ability to follow essential elements of the intervention manual as judged in a meeting of supervisors through the review of audio and videotaping will be the standard of practice. Further, trained intervention staff will be required to take a written test covering the content of the intervention and control manual and attain a pass mark of 50%.

Participants

Recruitment

The selected 16 HIV clinics will be requested to provide patient registration numbers, which will then be entered into a remote computer to randomly select participants for screening for study eligibility. Consenting patients will be screened with the AUDIT for eligibility. A cut-off of 6 for females and 7 for males will be used [57]. The recruitment procedure and study flow are shown in Fig. 3.

Inclusion criteria

Study participants, aged 18 years and older, will be drawn from PLWHA on HAART receiving services from HIV care clinics in Zimbabwe. To be eligible, participants need to have been on HAART for at least three months and must be regular clinic attenders to reduce loss to follow up.

Exclusion criteria

Participants who are on treatment for alcohol dependency, other primary drug use disorder, and those with primary psychiatric disorder or dementia will also be excluded and referred to the psychiatrist for further assessment and care.

Outcome measures

The primary outcome measure will be the AUDIT score. This will measure the effect of the intervention on drinking. Secondary outcome measures will comprise scores on the WHODAS 2.0, WHOQoL HIV, CD4 count and viral load. Research assistants who are graduates in health and social sciences will be trained to administer the outcome assessments. The training will include the scoring of the AUDIT, the WHODAS and the WHOQoL HIV.

Fidelity

Fidelity has four defined components: design of the intervention, training in the intervention, monitoring the delivery of the intervention and monitoring its receipt. As it is essential to maintain fidelity, the treatment will be manualised and intervention staff will be appropriately trained to adhere to the treatment guides. Training in the intervention includes role-playing, which facilitates competence in the delivery of the intervention. As part of the training, an intervention training manual has been developed that will be used in the intervention and controls. Delivery of the intervention will be monitored through patient cards and video and audio recordings of patient session. Supervision will also be used to maintain fidelity. The standard operating procedures will contain supervision protocols. The receipt of the intervention will be monitored through patient record cards and interviews. Overall fidelity will be assessed with a comprehensive intervention fidelity guide (CIFG) [58].

Randomization

A computer generated block randomization will be used to assign clinics to either intervention or control arm (as shown in Fig. 4).

Allocation concealment

A statistician on the study based in South Africa will maintain concealment of allocation.

Blinding

Participants will not be blind to treatment. Research assistants who administer the outcome measures will be blinded to the assignment of clinics to intervention and control. Blinding will be achieved by retaining the same assessors at a site from the baseline, the 3,6 and 12 months assessments. In order to minimise assessment bias, assessors will not have access to the data collected at previous assessments. The Principal Investigator will be not be blinded to clinic status as he will be a trainer on the interventions.

Visits

At the baseline visit, the AUDIT, DUDIT, SAMISS, IHDS, WHOQoL HIV and WHODAS 2 will be administered. The AUDIT, WHOQoL HIV, and WHODAS will be administered at 3, 6, and 12 months. The CD4 count and viral load will be measured at baseline, 3, 6 and 12 months

1 **Cluster identification**
This involves randomly selecting 16 OI clinics with the following distribution: 2 provincial, 5 district 6 Mission, 3 City Health clinics from 7 Provincial, 37 District, 41 Mission hospitals, 24 City Health clinics.

2 **Cluster recruitment**
Recruitment of clusters involves engaging health authorities to obtain access to the health facilities and informing randomly selected sites of the study.

3 **Randomization of participants**
The Principal Investigator will obtain access to the ART database at the selected OI clinics. ART patient numbers will then be used to randomize (using a remote computer) potential participants.

4 **Randomization of Clusters**
The selected 16 OI clinics will be randomized into the 2 treatment arm (8 per treatment arm). Randomization will be done by a remote computer and all research staff will be blinded with the exception of the Principal Investigator.

5 **Training of the Research teams**
Training of interventionists and research assistants will be undertaken. Interventionists (RGNs at selected sites) will be trained on how to use treatment manuals and research assistants will be trained on questionnaire administration and the use of tablets. GCP (good clinical practice) will also form part of this training.

6 **Recruitment of Participants**
Research assistants will screen randomly selected patents and those meeting the inclusion criteria will be recruited into the study.

7 **Baseline Assessment**
Recruited participants will be assessed on alcohol use, severity of dependency on alcohol and drugs, quality of life, common psychiatric disorders, dementia, the presence of traumatic event exposure, posttraumatic stress symptoms, stressful events, social support, CD4 count and viral load.

8 **Follow-up Visits**
Primary and secondary outcomes will be assessed at 3, 6 and 12 months.

9 **Outcome-Assessment**
Final Assessment and analysis of results

Fig. 3 Identification of clusters and recruitment of participants

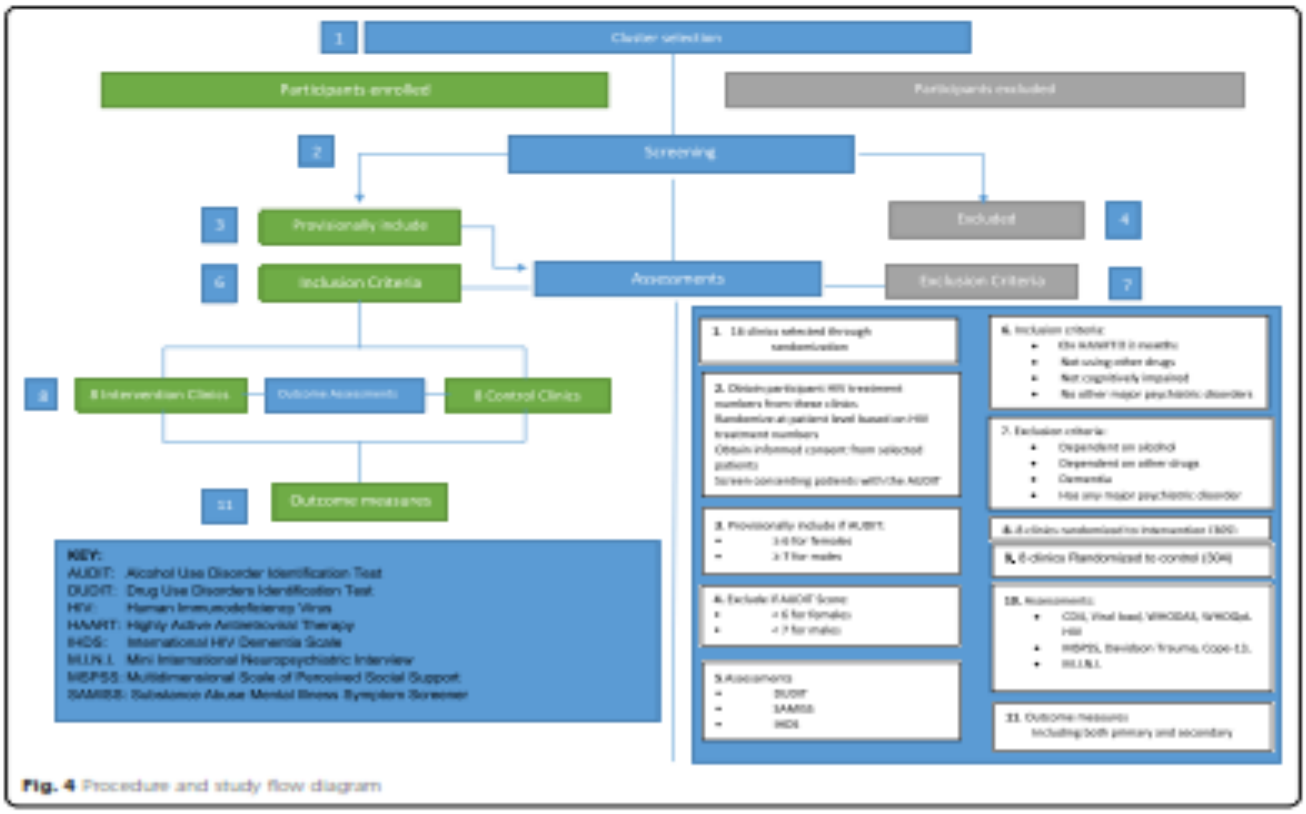

Fig. 4 Procedure and study flow diagram

to assess adherence. The MSPSS, COPE-13, and the Davison Trauma Scale will assess social support, coping and resilience at baseline and 12 months, and included as moderator variables in the analysis

Statistical analysis

Sample size

A meta-analysis suggested that a clinically significant difference in negative status on the AUDIT between brief intervention and control of 13% [59]. Shersten et al. [60] describe intra-cluster correlation coefficient in human subjects to be between 0.01 and 0.02 and assumed the intra-cluster correlation in this study to be 0.02. A total of 16 clusters (8 clusters per group) to achieve 80% power to detect a mean difference of 2.5 (with precision of ± 0.45) between the treatment condition means when the standard deviation within a cluster is 4 and the intra-cluster correlation are 0.02 and a significance level of 0.05.

An estimated sample size of 180 patients (90 in the intervention group and 90 in the control group) will be required to detect a difference of 13% between intervention and control groups taking into account the design effect of 1.56. Assuming an attrition rate of 30% (as identified in the pilot study), a total sample size of 240 will be required. Fifteen participants will be randomly selected (with equal probability) at each clinic from a patient number list.

Analysis of covariance (ANCOVAs) and mixed effects linear regression models will be performed for all continuous variables. Generalised linear mixed effects logistic regression model will be performed for binary outcomes. All analyses will allow for within-clinic clustering.

Management of missing data

Intention to treat will be the principle of statistical analysis.

Clinic level

All clinics randomized at cluster level will be analysed by the treatment arm allocated at randomization.

Participant level

All participants in the study will be included in the analysis of primary and secondary outcomes.

Analysis approach

Data will be analysed using STATA Version14 [59]. Primary and secondary outcomes will be measured at four time points: baseline, 3, 6, and 12 months. To account for the stratified cluster trial design, the repeated binary

and linear nature of the primary and secondary outcomes, as well as missing data at follow-up, a Generalized Estimation Equations (GEE) approach will be used. Descriptive statistics will be computed for baseline and follow-up assessments. The mean AUDIT scores will be compared using student t-tests. Multilevel logistic regression will be performed for binominal and multilevel linear regression for continuous variables.

Ethics

In order to promote quality control and quality assurance of the study, research staff and the principal investigator will receive training in research ethics and good clinical practise. A data research coordinator will ensure accurate data collection and the secure transfer and storage of electronic data. Weekly feedback meetings will be held with study personnel, the data manager, and the project coordinator to address problems and study-related queries.

Confidentiality

Participants will be assured of the confidential nature of the study. Anonymity will be maintained by de-identifying collected data and participants will be identifiable by unique identifier codes. Patient-level data will be stored securely on a computer encrypted and password protected for the study team. Files will be stored in a locked cabinet at the University of Zimbabwe College of Health Sciences, Department of Psychiatry for five years.

Risks and discomfort

Although no adverse effects are anticipated, participants who experience discomfort or who wish to withdraw for any other reason will be free to do so. Participants who become distressed and uncomfortable with answering the assessment questions which address sensitive topics such as alcohol use and non-adherence and when providing blood samples for CD4 counts and viral loads will be referred to a psychiatrist for further care. Participants will be free to leave the study at any point without prejudice.

Interim analysis

Interim statistical analysis will be carried out at 3 and 6 months. A Data and Safety Monitoring Board (DSMB) comprising of experts in HIV/AUDS, an independent statistician and a bioethicist, and the MRCZ will review study-related concerns (e.g. adverse events) that arise. They will review study protocols and procedures (e.g. data collection and storage), as they deem necessary during the data collection phase. Safeguards will be implemented throughout the project to protect participant confidentiality, as described and required by the monitoring board, and to minimize the risk of potential physical and psychological harms.

Costs and compensation

Participants will be reimbursed for transport costs and refreshments (US$3) for each visit.

Benefits

Participants may directly benefit from the interventions. Any individual identified as alcohol dependent will be referred for alcohol treatment services. Individuals assigned to the MI/CBT intervention may reduce their alcohol consumption, in turn improving HAART adherence and HIV disease outcomes. Clinic staff will benefit as they will be trained in delivering the intervention aimed at reducing harmful/hazardous alcohol consumption. Finally, substantial public health knowledge will likely be gained from this search.

Discussion

In this study it is hypothesized that an adapted MI/CBT intervention will lead to a significant reduction in alcohol use in PLWHA. It is further hypothesized that reduction in alcohol use will lead to improved function as measured by the WHODAS 2.0, improved quality of life as measured by the WHOQoL HIV, and improved adherence to HAART as measured by the CD4 and viral load. This study further seeks to establish whether registered general nurses in primary health care facilities in Zimbabwe will be effective in providing the MI/CBT intervention to reduce alcohol use and improve patient engagement with treatment.

We will test the effectiveness of an MI/CBT intervention that can be used by RGNs for alcohol reduction in PLWHA. If successful, the intervention will be implemented in HIV clinics in Zimbabwe and other settings where general nurses oversee HIV treatment. We hypothesize that patients may view their ability to return to work as important and this may motivate them to adhere to the treatment. Improved quality of life has been shown to improve adherence in other studies.

Given that most behavioural interventions for alcohol use have been developed within a Western framework, the use of an adapted intervention in this study will inform us about its effectiveness in reducing alcohol use in PLWHA in a resource limited setting. In resource rich environments, inpatient and outpatient services for addictions are usually widely available. However, in Zimbabwe, as in many other resource-limited settings, inpatient management of AUDs may be unaffordable for the majority. Outpatient care, if available, is the rule rather than the exception.

To the authors' knowledge, no published study from Zimbabwe has examined functioning and quality of life in PLWHA with AUDs. Improvement in functioning and quality of life are key aspects to address in this population. Quality of life has been shown to improve

upon initiation of HAART (http://www.stata.com) and studies in other countries have documented an improvement in adherence with an improvement in quality of life [61]. Over a quarter of 15–49 year olds in sub-Saharan Africa are living with AIDS [62]. Given that this is the most productive age group in the community, improving functioning will likely have positive socio-economic impacts on the community.

There are few limitations that warrant mention. Firstly, we will use a self-report screening measure of drinking. Self-report may not accurately reveal drinking quantity and behaviour. That said, the AUDIT has excellent sensitivity and specificity and cross-cultural applicability and can be used in remote areas where sampling for alcohol biomarkers may be challenging. Secondly, brief interventions have been shown to be more useful when provided at community level although the lack training often hampers provision at community level. Thirdly, viral suppression may not correlate well with adherence; even in resource rich settings viral suppression can be low despite an adherence of 80–95%. In this study viral load will be a proxy measure of adherence. CD4 count in addition to the viral load will be used as a measure of adherence.

This is a task-sharing intervention study. It is hoped that, upon successful completion of this study, RGNs from district hospitals and municipal health facilities will be trained in recognising and managing AUDs in HIV infected patients.

Abbreviations

AIDS: Acquired immunodeficiency syndrome; ANCOVA: Analysis of covariance; AUDIT: Alcohol use disorder identification test; CBT: Cognitive behavioural therapy; CIPG: Comprehensive Intervention fidelity guide; DSMB: Data monitoring and safety board; DTS: Davidson trauma scale; DUDIT: Drug use disorders identification test; FGD: Focus Group Discussion; GEE: Generalized estimation equations; HAART: Highly active antiretrovital therapy; HIV: Human immunodeficiency virus; IHDS: International HIV dementia scale; MINI: Mini International neuropsychiatric interview; mhGAP: Mental health gap action programme; MI/CBT: Motivational interviewing/cognitive behavioural therapy; MSPSS: Multidimensional scale of perceived social support; PLWHA: People living with HIV/AIDS; PTSD: Post-traumatic stress disorder; RCT: Randomised controlled trial; RGN: Registered general nurses; SAMISS: Substance abuse mental illness symptom screener; WHO: World Health Organisation; WHODAS: World Health Organisation Disability Assessment Schedule; WHOQoL: World Health Organisation Quality of Life

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Availability of data and materials

Not available.

Authors' contributions

MM and SS conceived and developed the study. DS provided critical input on the intervention. MZ provided input on the statistical plan. RS critically reviewed statistical plan. DC provided input on the methods and revised the entire manuscript. MD and BMD helped with development of the intervention and controls and revised the manuscript. All authors critically revised the article for important intellectual content and all authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study has received relevant institutional approvals from the Medical Research Council of Zimbabwe, Stellenbosch University Human Research Ethics Committee, and the Harare Hospital Ethics Committee. The Ministry of Health Permanent Secretary of Zimbabwe has also approved the study.

Informed consent will be sought and obtained from participants. Participants will be in- formed that their decision to participate in the study is voluntary and will not affect current or future care. They will also be informed that they may terminate participation at any time without penalty. Research staff who are not clinic employees or linked to participants' medical care will obtain informed consent. Through the informed consent process, prospective participants will be informed of all foreseeable risks involved in the study. Individuals with low or no literacy will have the consent form read to them by a person of their choosing, and verbal consent will be obtained, witnessed by an independent person.

The consent forms will be translated and back-translated and adapted for cultural appropriateness and readability into Shona and Ndebele, the main local languages in Zimbabwe. Research personnel who have contact with participants will be asked to sign a confidentiality agreement, and receive on-going training and supervision on ethical conduct and confidentiality protection. To minimise the possibility of a breach of confidentiality by participants during the focus group discussions, participants will be asked to not disclose the identity or content of commentary of any fellow focus group discussion members to anyone outside of the focus group.

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CHAPTER SIX

THE EFFECTIVENESS OF INTERVENTION FOR PROBLEMATIC ALCOHOL USE IN PLWH

Title: The effectiveness of problematic alcohol use intervention in reducing alcohol use and improving adherence to ART, functional capacity and quality of life of people living with HIV in Zimbabwe: results from a cluster randomized controlled trial.

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Abstract

Background Alcohol use disrupts effectiveness of HIV management throughout the HIV care cascade. There is paucity of data on effectiveness of interventions for problematic alcohol use in the context of HIV infection, diagnosis and treatment especially in Low- and Medium-Income Countries (LMIC). Due to shortage of health care workers especially psychosocial specialists to deliver the interventions for alcohol disorders, task-sharing models of care are essential. We conducted a

cluster randomised controlled trial to assess the effectives of an intervention for problematic alcohol use and on alcohol use reduction, viral load reduction, CD4 improvement, functionality improvement and change in quality of life among people living with HIV/AIDS(PLWH) in HIV care clinics in Zimbabwe.

Methods We conducted a cluster randomised controlled trial involving 16 HIV care clinics that were randomly selected from a total of 109 clinics in Zimbabwe. Clinics were randomly assigned (1;1) to a motivational interviewing/Cognitive behavioural therapy (MI/CBT) intervention or a World Health Organisation Mental Health Gap Action Program Intervention Guide (mh GAP IG) control. The treatments were both manualized and delivered by trained registered general nurses (RGNs). The primary outcome was a reduction in alcohol use as measured by the alcohol use disorders identification test (AUDIT) score (Mean Difference). The secondary outcomes were change in viral loads, CD4 count, functionality and quality of life. Participants were not blinded to treatment, however, research assistants who assessed outcomes were blinded. The trial was registered with Pan African Clinical Trial Registry, PACTR201509001211149. Registered 22 July 2015.

Findings 234 PLWH with problematic alcohol use were recruited from 16 HIV care clinics in Zimbabwe between December 2016 to September 2017.

Eight clinics each were assigned to MI/CBT and mh GAP IG, with 25 RGNs in each arm. The MI/CBT arm recorded a statistically significant reduction in AUDIT score 3.33(1.88;4.78) p <0.001 at 3 months and a further reduction 2.41(0.99;3.83) p <0.001 at 6 months. The mh GAP IG recorded a statistically significant reduction in alcohol use only up to 3 months 2.53(1.25;3.81) p < 0.001. There were statistically significant differences (p=0.05) between MI/CBT and mh GAP IG in favour of the MI/CBT. There was a statistically significant change in the viral load from baseline to 6 months for MI/CBT 0.77(0.41;1.13) p-value <0.001 and mh GAP IG 0.40(-0.51;0.84) p=0.0408. There were no statistically significant group differences on viral loads between the MI/CBT and mh GAP IG (p=0.46). The

functional capacity improved between 3 and 6 months ((MD0.95 95% CI (0.10; 1.80) p =0.029) and mh GAP IG (MD 1.25 95%CI (0.39;2.52) p= 0.008). There was significant improvement in quality of life in both groups between 3 to 6 months ((MI/CBT MD-13.63 95%CI (-17.05; -10.21, p <0.001; mh GAP IG MD -12.21 95% CI (-14.71; -9.72) p<0.001).

Interpretation Interventions for problematic alcohol use delivered by RGNs in PLWH lead to reduction alcohol use. An adapted MI/CBT resulted in sustained improvement compared to an mh GAP IG. Further, viral load, functional capacity and quality of life improved in PLWH who are exposed to an intervention of problematic alcohol use. Substantial improvements in HIV treatment outcomes can be achieved by incorporating interventions for problematic alcohol use in PLWH in low resource and high HIV burden settings like Zimbabwe. The findings from this study may be incorporated in ongoing interventions for common mental disorders, depression and other HIV interventions in Zimbabwe.

Background

HIV remains a global priority for the following reasons; 0.8% of adults 15-49 years of age living with HIV worldwide, it has caused 37 million death, close to 2 million new infections occur in a single year and 1 in 25 adults infected with HIV in Sub-Saharan Africa(1). In response, Joint United Nations Program on HIV/AIDS (UNAIDS) has come up with the 90-90-90 targets. The targets are that 90% of HIV infected people should know their status; 90% should be accessing antiretrovirals; 90% should achieve viral suppression by 2020(2). The goal is to have an HIV/AIDS-free world by 2030(3). In order to achieve these targets, the HIV testing must be intensified; more people have to be put on treatment through increased resource mobilization and allocation; adherence has to be optimal so as to achieve adequate viral suppression. Alcohol use has been implicated in increased vulnerability

to HIV infection, delay in HIV testing, inadequate adherence to ART leading to failure to achieve viral suppression(4-6).

Studies have documented a high prevalence of problematic alcohol use in PLWH, with studies from the USA showing that they may be twice as common in PLWH as in non-infected individuals(7). Systematic reviews indicate that alcohol contributes to increased rates of infection as it is associated with risky sexual practice(8, 9). PLWH are less likely to get tested early for HIV, are more likely to be lost to care early, are unlikely to achieve the required levels of adherence to treatment, have heightened disease progression and in general have poor outcomes to treatment (10, 11). In PLWH, alcohol is also a potent immunosuppressant and has effects on the liver that may affect the metabolism of ARVs and potentially result in ARV toxicity(12). Further, it has also been shown that PLWH need less alcohol consumption to feel drunk and suffer more physiologic harms with lower alcohol consumption(13). It is therefore necessary to come up with different drinking guidelines for PLWH considering the effects of alcohol on their health achieve good treatment outcomes.

Alcohol has also been associated with the acquisition of HIV infection through non-use of preventive measures such as condoms, pre- and post- exposure prophylaxis (PrEP and PEP, respectively) and engagement in risky sexual behaviours(14). Research has also shown that alcohol increases infectiousness in HIV positive, as there is an increase in viral reservoirs due to the damage of the natural protective vaginal mucosa(15). Alcohol causes cognitive impairment especially memory loss leading to inconsistent adherence to treatment, and taking medication out-of-time thereby contributing to poor adherence(16). A systematic review on the relationship between alcohol and HIV in Sub-Saharan Africa (SSA) showed that alcohol use was associated with HIV transmission(8, 17). The effects of alcohol in increasing risky sexual behaviour have also been documented in another systematic review in SSA(18). Empirical data from SSA also found that the risk of unprotected sex increased with the quantity of alcohol consumed rather than with the frequency of drinking(19-21).

It thus suggests that the effects of problematic alcohol use on HIV are multipronged and may need diverse approaches targeting new infections preventive approaches, medication adherence promotion and viral loads assessments that are linked to alcohol consumption strategies.

Although, some studies have shown that psychological interventions are able to reduce drinking in settings outside HIV infection, the same outcomes have not been demonstrated in addressing alcohol use in PLWH(22) (23). A systematic review of HIV risk-alcohol reduction and adherence improvement through alcohol use control and drinking reduction did not show any marked effect(24). Another systematic review assessing the effectiveness of psychological interventions on adherence was negative(25).

Few interventional studies that have been undertaken in SSA, show some benefits in reducing alcohol use along HIV treatment cascade however(26-28). Zule et al (2014) in a study conducted in South Africa (Cape Town) showed that group intervention was effective in imparting skills to reduce risky sex in the context of alcohol consumption, sexual negotiation and condom use mastery and exploration of relationships and communication reduced alcohol consumption in females(27). In a study with a small sample size, in Kenya, Papas et al (2011) showed that CBT can reduce alcohol consumption in PLWH (26). Wandera et al (2017) in Uganda found that a brief intervention reduced alcohol consumption in females, although there were no effects in males(28). Qualitative studies suggest that PLWH are aware of the effects of alcohol on ART have and are willing to engage in behavioural interventions for AUDs (29, 30). A study from Uganda showed an increase in abstinence from alcohol, in individuals who had commenced ART suggesting that once tested for HIV and on treatment there is an effort to abstain(31).

According to the World Health Organisation (WHO) there are an estimated 22.5 mental healthcare workers for every 100000 population reflecting a 79% gap(32). Yet the need for the populations and the populations are increasing. In order to meet this need and close the treatment

gap, there is therefore need to adapt interventions for problematic alcohol use and adopt task sharing in health care in general and in alcohol use reduction treatment in particular. The treatments can be delivered by less trained cadres, as recommended by the World Health Organisation WHO(33). Studies in HIV care delivery have shown that the quality and outcomes of treatment delivered within a task-sharing model are similar to that delivered by physicians(34). In Zimbabwe, Chibanda et al (2016) showed that lay health workers can effectively deliver a cognitive behavioural therapy for depression(35).

Interventions for problematic alcohol use must target alcohol use, non-adherence to treatment and risky sexual behaviour that have all been shown to negatively affect adherence.

Objectives

1. To evaluate the effect of an adapted Motivational Interviewing and Cognitive Behavioural Therapy (MI/CBT) intervention in people living with AIDS (PLWH) on alcohol use outcomes using the Alcohol Use Disorders Identification Test (AUDIT) score.
2. To assess whether an adapted MI/CBT intervention for problematic alcohol use in PLWH compared with the World Health Organisation mental health GAP Intervention Guide (mh GAP IG) as delivered by Registered General Nurses (RGN) improves their functional ability and quality of life.
3. To establish whether an adapted MI-CBT intervention for alcohol use in PLWH compared with mhGAP IG as delivered by RGN can lead to better treatment adherence in Zimbabwe as measured by viral loads and CD4.

Methods

The study was a 2-arm cluster randomised controlled trial. The clinics were stratified by level of care, into provincial (tertiary care), district (secondary care), church related (secondary care but funded by churches) and city health polyclinics (primary care). The intervention arm was an adapted

motivational interviewing and cognitive behavioural therapy based on Project MATCH manuals (36). The developed intervention was piloted at an HIV care clinic in Harare. The pilot helped assess the duration of the intervention and was adjusted accordingly. The comparator was a section of the World Health Organisation Mental Health Gap Action Program Intervention Guide(mh GAP IG) that deals with the management of alcohol use, developed for primary care settings but used in research in other countries(37).

Clinic recruitment

The HIV care clinics in the study were randomly selected as follows; provincial clinics (n=2), district hospitals (n=7), church related clinics (n=4) and city health clinics (n=3). A study investigator used a computer-generated algorithm that assigned clinics on a 1;1 to the MI/CBT and mh GAP arms (8 clinics per arm). We randomly selected 450 patients per HIV care clinic. We obtained their contact numbers and locations and reached out to them requesting their participation in the study.

Allocation concealment

The trial statistician generated the randomisation schedule and provided this to the research team for the recruitment of participants.

Participant recruitment

Participants were HIV positive individuals recruited from HIV electronic database kept at the HIV care clinic. This is a database that is hospital based and linked to the Zimbabwean national HIV/AIDS program. The database was screened to exclude those who did not meet our initial eligibility criteria, namely patients less than 18 years of age, or not followed up at the clinic in the previous 3 months. From the remaining patients in the database, 450 were randomly selected and contacted, with the aim of recruiting 15 participants. Research assistants, used the contact information in the database to locate potential participants. The research assistants then explained the study to the

potential participants. To the participants who gave initial consent, the AUDIT was administered on them. Females were required to score 6 or more on the AUDIT or greater and males needed a score of 7 or greater to be included. The decision to use the cut-off of lower for females was based on the recognition that females get more harm with lower alcohol consumption(38). The score with good specificity and sensitivity is 8, however, in this study we used a lower cut-off of 6/7 as the AUDIT has not been validated and there are high levels of unrecorded alcohol consumption in the areas that were under study(39).

Other exclusion criteria included patients who were on treatment for alcohol and any other substance use, had florid mental illness. Two hundred and ninety-six patients were excluded as they did not meet the inclusion criteria, while 109 declined to participate. Figure 1 (CONSORT diagram) shows the flow of the study.

The International HIV Dementia Scale (IHDS) was used to screen for the presence of dementia with a cut off of 10 applied (40). The Drug Use Disorders Identification Test (DUDIT) and the Substance Abuse Mental Illness Symptom Screener were used to screen for presence of other substance abuse(41). Participants with severe other substance use as assessed by the DUDIT were excluded. The M.I.N.I (Mini International Neuropsychiatric Interview) was the gold standard psychiatric diagnostic interviews(42).

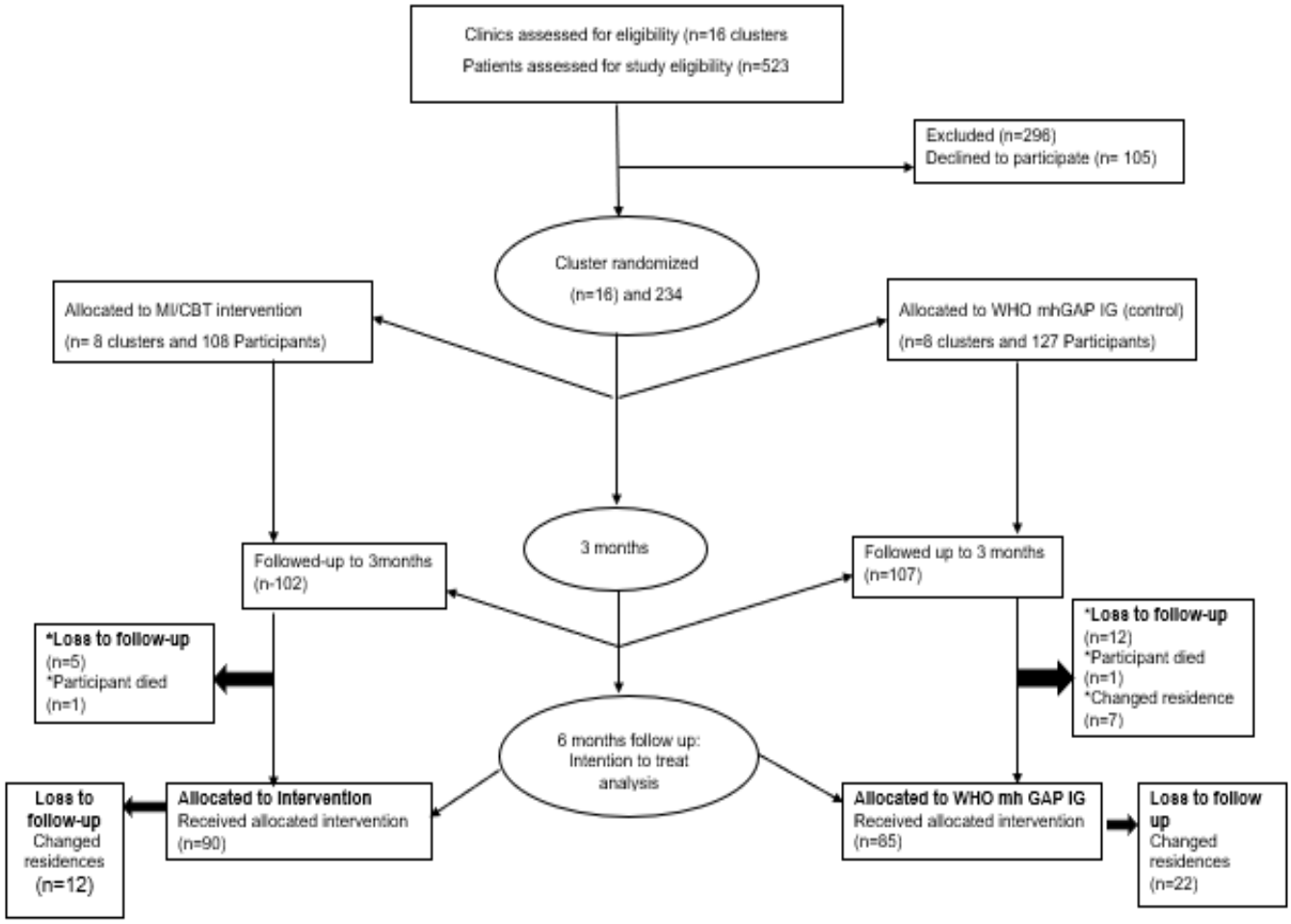

Figure 1; Consort diagram showing recruitment and flow of the participants in the study.

Interventions

MI/CBT Intervention

The intervention was a blended motivational interviewing and cognitive behavioural therapy (MI/CBT). The intervention was made into a manual and consisted of 8 sessions delivered by RGNs. The intervention was based on themes covered in Project MATCH Motivational Enhancement Therapy(MET) and Cognitive Behavioural Therapy (CBT) manuals(43). Other aspects covered included feedback to participants on the risks associated with drinking whilst on HIV treatment. Emphasis was on the link between HIV and alcohol use, feedback on AUDIT scores, the viral load and CD4.

The participants had to be booked and allocated to a specific nurse who had to complete the full treatment. The booking system was adopted to avoid disrupt normal clinic's activities. The sessions were audio-recorded with consent to do so having been received. The recording was done for use in feedback for RGNs, for checking and improving fidelity. The MI/CBT training team was made up of (MM, BD and TM). The mh GAP IG was made up of (MD and WM). The two teams provided two supervision sessions to each clinic at 3 months. The supervision consisted of review of sessions conducted, review of audio-records of 10% of the records and participants record cards. Table 1 provides the MI/CBT content.

Table 1 describes the content of the MI/CBT intervention.

Session 1, 45 minutes	Goal setting General life personal goal setting Alcohol goals How alcohol interferes with goals
Session 2, I hour	HIV and drinking Possible reasons why people drink Establish client's reasons for drinking Provide personal feedback Moving the client towards change Examine the impact of drinking on HIV treatment, CD4 count and viral load Meaning of improvement and the value of functional life and quality of life Drinking problems and warning signs
Session 3, 1-hour	Motivational interviewing and the intervention Use MI to build rapport and develop readiness to change Assess readiness to change (using readiness ruler) Assess pros and cons of change (decision-balance exercise) Use MI to try and shift participant Elicit a commitment to change
Session 4, 30 minutes	Cognitive behavioural therapy and intervention Brief explanation and principles of CBT Explanation on the triggers, urges and cues are and how they lead to drinking Discussion of how triggers arise and how they lead to alcohol use and its effects Managing thoughts about drinking
Session 5, 45 minutes	Triggers and relapse External Internal Drinking refusal skills Managing situations where drinking is unavoidable
Session 6, 30 minutes	Dealing with specific treatment issues like: Viral load and CD4 count results, treatment problems Loosing spouse Employment compromised by illness Illness complications related to HIV infection Running out of medication
Session 7, 1 Hour	Planning future direction Life is back to normal: Do I drink? Dealing with anger and criticism Dealing with failure Self-referral
Session 8, 1-hour	Conclusion and planning the future

Mh GAP IG

RGNs administered the mh GAP IG alcohol use section using manuals. Besides counselling on alcohol use, participants received feedback on their AUDIT score, CD4 count and viral load.

Training

Two teams trained the RGNs, one team exclusively undertaking training in the MI/CBT intervention and the other team training on the mh GAP IG. The training involved PowerPoint presentations, quizzes and role-plays. The training took place at the clinics requiring no more resources such as transport and allowing the RGNs to provide their usual care. The training for MI/CBT lasted 6 hours, while mh GAP IG training lasted 3 hours. Refreshments and a per diem allowance were provided to the trained RGNs.

VARIABLES	***MI/CBT***	***mh GAP IG***	***Total***
Number of Sites	8	8	16
Number of Participants	108	126	234
Number of Active Nurses	25	25	50
Number of Sessions	1 032	528	1 560
Mean number of sessions per site	129	66	97.5
Mean number of sessions per participant	9.56	4.19	6.67
Mean number of participants per nurse	4.32	5.04	4.68

Table 2: Details of training of intervention staff in MI/CBT and mh GAP IG.

Intervention delivery

Of the 104 RGNs in that were trained, 25 actives in each arm during the trial (54 were not able to participate as they were assigned to other clinic duties). One thousand and thirty-two sessions were delivered in the MI/CBT intervention and 528 in the mh GAP IG control (129 sessions per clinic in the MI/CBT and 66 sessions per clinic in the mh GAP IG arm). The participants in the MI/CBT were seen once every 2 weeks for twelve weeks and once a month for 12 weeks those in the mh GAP IG were seen once every month for at baseline, followed by 1 session, at three months and at 6 months where the outcome measures were taken. Participants in MI/CBT intervention and mh GAP IG received a mean (SD) of 9.56(3.52) and 4.19(2.33) sessions, respectively.

Fidelity

Both the MI/CBT and mh GAP IG were manualised. This was done to improve fidelity. Further, the trainings were conducted by the same team on each arm. Further all the sessions were audio-taped, with 10% of the in MI/CBT and mh GAP IG were audio-tapes reviewed. Participants record of intervention experience were also reviewed. The deviations from the protocol were corrected through additional training of the sites that showed deviations from the protocol. The nurses also kept a record of the sessions, with information such as the duration of the session, difficulties experience in the session. 10% of these records were reviewed and used to improve on the intervention delivery. Uniformity in training, assessment of the participants records, nurse records and audio-tapes ensured maximum fidelity to the protocol.

Outcomes

Primary outcomes

The primary outcome was the Alcohol Use Disorders Identification Test (AUDIT) score at 3 and 6-months follow-up. The AUDIT was developed to screen for alcohol use in primary care settings and has not been validated in Zimbabwe. It has been validated in HIV populations in South Africa(44, 45).

Secondary outcomes

The secondary outcome measures were the functionality measured by World Health Organisation Disability Assessment Schedule 2.0(WHODAS 2.0)(46), quality of life measured by the World Health Organisation Quality of Life HIV (WHOQoL HIV)(47), viral load and CD4 count.

The WHODAS 2.0 is a 12-item tool that measures functional capacity in 6 domains that include mobility, life activity, cognition, participation, self-care and getting along(48). The WHODAS 2.0 has been validated in other HIV populations but has not been validated in Zimbabwe HIV population. The WHOQoL HIV assesses the quality of life in the context of HIV(47). The WHOQoL HIV has 6 domains,

which include physical health, psychological health, level of independence, social relationships, environmental health and spiritual health(49). The WHOQoL HIV has however been validated in Ethiopia and Zambia (50, 51). The WHOQoL has not been validated in Zimbabwe.

Moderator assessments

The moderator tools were The Multidimensional Scale of Perceived Social Support (MSPSS), Davidson Trauma Scale (DTS) and The COPE 13. The MSPSS assesses for perceived social support from Family, friends and Significant Others(52, 53). The scale has 12 items each with 4 items each subscale. The DTS is a 17-item self-report questionnaire that assess the impact of trauma that is based on the DSM IV(54). DTS assessed for traumatic experience. The COPE 13 is a tool developed to assess how people cope with various situations(55). It has been included in this study to assess how PLWH cope with their lives in the light of HIV infection.

Eligibility tools

Sample size

The calculated sample size required to show statistically significant differences between the intervention and control of 13% with intra-cluster correlation of 0.02 was 180, with 90 for each arm. The pilot estimated loss to follow-up at 30% making the estimated sample size of 240. The RCT was able to enroll 234 participants with 108 for MI/CBT arm and the mh GAP IG enrolling 126.

Blinding

Participants were not blinded to treatment allocation. In addition, the Principal Investigator (MM) was a trainer on the interventions was not blinded. Research assistants who administered the outcome measures were blinded to the assignment of clinics. Blinding of research assistants was achieved by retaining the same outcome assessors at a site from the baseline, the 3- and 6-months

assessments. In order to minimise assessment bias, assessors did not have access to the data collected at previous assessments.

Outcome assessment visits

At the baseline visit, the AUDIT, SAMISS, WHOQoL HIV and WHODAS 2 were administered. The AUDIT, WHOQoL HIV, and WHODAS were administered at 3 and 6 months. The CD4 count and viral load were measured at baseline and at 6 months.

Statistical methods

Management of missing data

All participants were analysed in the arm that they were allocated to at recruitment.

Clinic level

All clinics randomized at cluster level were analysed by the treatment arm allocated at randomization.

Participant level

All participants were included in the analysis of primary and secondary outcomes.

Analysis approach

Data were analysed using SPSS. A mixed model ANOVA was used in data analysis. Primary and some secondary outcomes were measured at three time points: baseline, 3 and 6 months. To account for the stratified cluster trial design, the repeated binary and linear nature of primary and secondary outcomes a Generalised Estimation Equations (GEE) approach was used. Descriptive statistics were computed for baseline and follow-up assessments. Mean AUDIT scores were compared between groups using student t-tests. Multilevel logistic regression was performed for binominal and multilevel linear regression for continuous variables.

Analysis of covariance (ANCOVAs) and mixed effects linear regression models were performed for all continuous variables. Generalised linear mixed effects logistic regression model was performed for binary outcomes. All analyses allowed for within-clinic clustering.

Ethical considerations

This study received approvals from the Stellenbosch Health Research Ethics Committee (HREC) (SI/10/14/222) and the Medical Research Council of Zimbabwe (MRCZ) (A/1936). In order to promote quality control and quality assurance of the study, research staff and the Principal Investigator received training in research ethics and Good Clinical Practice. A data research coordinator ensured accurate data collection and the secure transfer and storage of electronic data. Weekly feedback meetings were held with study personnel, the data manager, and the project coordinator to address problems and study-related queries.

Confidentiality

Participants were assured of the confidential nature of the study. Anonymity was maintained by de-identifying collected data and participants were identifiable by unique identifier codes. Patient-level data was stored securely on a computer encrypted and password protected for the study. Files will be stored in a locked cabinet at the University of Zimbabwe College of Health Sciences, Department of Psychiatry for five years.

Costs and compensation

Participants were reimbursed for transport costs and refreshments (US$3) for each visit. RGNs were compensated for their time at ($5) per session.

Results

Two hundred and thirty-four participants were recruited from 529 PLWH who were screened. There were 108(46%) and 126(54%) participants in the MI/CBT and mh GAP IG arms, respectively. There were more males than females in both MI/CBT 91(84.3% and mh GAP IG 93(73.8%) groups. The majority of the participants were married (MI/CBT 71(65.7%) and mh GAP 75 (59.5%). The level of education was (MI/CBT 10.2(SD 4.2) and mh GAP IG 10.8(SD 3.8). The majority of participants were in informal employment/self-employed (MI/CBT 60(47.62 *%*) and mh GAP IG 66(61.11 *%*). There no statistically significant differences between the arms in all sociodemographic data assessed at baseline.

At baseline, the mean AUDIT scores (SD) for MI/CBT and mh GAP IG groups were 14.9(6.3) and 14.7(6.2), respectively and there were no statistically significant differences(p=0.44). The MI/CBT arm had a higher log10 viral load 1.86(1.12) than the mh GAP IG arm 1.48(1.41) at baseline which were not statistically significant(p=0.13). The baseline CD4 were similar with MI/CBT at 338.7(234.6) and the mh GAP IG at 338.7(234.6) and there no statistically significant variations(p=0.37). There were however no between-group baseline differences on WHODAS 2.0 and WHOQOL. Table 3 gives the summary of the sociodemographic and baseline characteristics.

At baseline, a third of participants screened positive for (71(30%)) other substances use other than alcohol, 50% (117) screened positive for depression, 54% (126) for anxiety, while a third 32% (75) screened positive for PTSD. There were no significant differences on these measures between the groups. Table 4 gives the prevalence of selected mental disorders.

Variable	MI/CBT Intervention n=108 (46%)	Mh GAP IG Control n=126 (54%)
Age	43.6(SD 9.4)	43.0(SD 9.3)
Gender		
Female (%)	17(15.7%)	33(26.2%)
Male (%)	91(84.3%)	93(73.8%)
Marital status		
Married (%)	71(65.7%)	75(59.5%)
Divorced (%)	11(6.5%)	12(9.5%)
Single (%)	10(9.3%)	24(19.1%)
Widow (%) (%)	7(6.5%)	8(6.4%)
Co-habit (%)	9(8.3%)	7(5.6%)
Mean number of years in school	10.77(SD 3.2)	10.19(SD 2.9)
Main work status (%)		
Paid work (%)	38 (30.16 %)	27(25 %)
Self-employed (%)	60(47.62 %)	66(61.11 %)
Non-paid work (%)	3(2.38 %)	4(3.7 %)
Student (%)	3(2.38 %)	5(4.63 %)
Keeping house (%)	4(3.17 %)	3(2.78 %)
Retired (%)	2(1.59 %)	1(0.93 %)
Unemployed (health reasons) (%)	2(1.59%)	0
Unemployed (other reasons) (%)	14(11.11 %)	2(1.85 %)
Duration on HAART	5.36(2.01)	5.12(1.98)
Clinic ART Adherence	87%	89%
Baseline Clinical features		
AUDIT Score (SD)	14.9(6.3)	14.7(6.2)
Log10Viral load (SD)	1.86(1.12)	1.48(1.41)
CD4(SD)	338.7(234.6)	442.6(236.8)
WHODAS(SD)	14.6(3.0)	16.2(4.64)
WHOQoL (SD)	86.3(14.7)	84.4(9.5)

Table 3: The table presents the socio demographic characteristics and baseline clinical features of the study sample.

Condition	Frequency
Other substance use	71(30%)
Manic/Bipolar	64(27%)
Depression	117(50%)
Anxiety	126(54%)
PTSD	75(32%)

Table 4: The table shows the prevalence of substances use and mental illness at baseline. There is significant comorbities in PLWH with high levels of depression and anxiety.

Most participants had moderate to high level of support from significant others, friends and family (47% to 51%). Participants in both MI/CBT and mh GAP had rates of subthreshold PTSD as assessed by DTS with impairment of 29.8 95% CI (24.4;35.2) and 33.7 95% CI (29.6;37.8), respectively.

There were no baseline differences in coping strategies between the MI/CBT and mh GAP IG, although fewer participants (9.6% *vs.*9.7%) used behaviour disengagement, while active coping, religious coping and planning were favoured by more in the MI/CBT (12.0%*vs*. 10.9) Tables 5,6 and 7 give the moderator characteristics.

	Low	Moderate support	High support
Significant others	3(1%)	109(47%)	119(51%)
Family	8(3%)	110(47%)	116(50%)
Friends	6(3%)	114(49%)	113(48%)

Table 5: The table shows perceived support as assessed by the MSPSS. Most participants felt supported by family and friends.

Domain	MI/CBT	mh GAP IG
Positive reinterpretation	11.3 95%CI (10.8-11.8)	10.0 95% CI (9.6-10.4)
Mental disengagement	10.6 95%CI (10.2-11.0)	10.5 95%CI (10.2-10.9)
Focus and venting emotions	10.4 95%CI (9.9-10.8)	10.0 95%CI (9.6-10.4)
Instrumental social support	11.6 95%CI (11.1-12.1)	9.8 95%CI (9.4-10.3)
Active coping	12.0 95%CI (10.5-11.3)	10.9 95%CI (11.6-12.4)
Denial	9.5 95%CI (9.0-10.3)	10.4 95% CI (10.0-10.8)
Religious coping	12.8 95%CI (12.3-13.2)	11.5 95% CI (11.0-11.8)
Humor	10.1 95%CI9.5-10.7)	10.1 95% CI (9.5-10.7)
Behaviour disengagement	9.6 95%CI (9.0-10.1)	9.7 95%CI (9.3-10.1)
Restrain	10.4 95% CI (9.5-10.4)	10.0 95% CI (10.4-9.5)
Use of emotional social support	11.5 95%CI (11.1-12.0)	10.8 95%CI (10.3-11.2)
Substance use	10.2 95%CI (9.6-10.8)	9.3 95% CI (8.8-9.8)
Acceptance	11.8 95% CI (11.4-12.2)	11.2 95% CI (10.8-11.7)
Suppression	11.2 95% CI (10.8-11.6)	9.9 95% CI (9.4-10.4)
Planning	12.0 95% CI (11.4-12.5)	10.4 95% CI (10.0-10.8)

Table 6: Shows the coping mechanisms as assessed by the Cope 13.

Domain	MI/CBT	mh GAP IG
Frequency	15.2 95%CI (12.4-18.0)	17.2 95% CI (15.2-19.3)
Severity	14.8 95%CI (12.0-17.6)	17.0 95%CI (14.9-19.2)
Total	29.8 95% CI (24.4-35.2)	33.7 95% CI (29.6-37.8)

Table 7: This table shows experiences of trauma as assessed with the Davidson Trauma Scale

Intervention effects on alcohol use

At three months, as shown on Table 5, there were a statistically significant reductions in alcohol use in both MI/CBT and mh GAP IG groups mean diff. 3.33(1.88;4.78) p <0.001, and 2.53(1.25;3.81) p < 0.001. However, there were no statistically significant differences between the groups (p=0.85). However, at 6 months, the MI/CBT had a further reduction in AUDIT score that was statistically significant 2.41(0.99;3.83) p <0.001. There was a statistically significant difference between the MI/CBT and mh GAP IG at 6 months (p=0.05) as shown on Figures 2 and 3.

	MEAN	STANDRAD ERROR	STANDARD DEVIATION	95%CI	P-VALUE
MI/CBT n=102					
AUDIT					
Baseline	14.85	0.63	6.34	(13.60-16.10)	
3 months	11.51	0.54	5.46	(10.45-12.60)	
Mean diff	3.33	0.72	7.39	(1.88-4.78)	<0.001
mh GAP IG n=106					
AUDIT					
Baseline	14.29	0.58	5.96	(13.14-15.44)	
3 months	11.76	0.58	6.00	(10.60-12.92)	
Mean diff	2.53	0.65	6.66	(1.25-3.81)	<0.001
MI/CBT n=86					
AUDIT					
3 months	11.23	0.57	5.32	(10.09-12.37)	
6 months	8.82	0.47	4.37	(7.89-9.76)	
Mean diff	2.41	0.71	6.62	(0.99-3.83)	<0.001
mh GAP IG n=79					
AUDIT					
3 months	11.84	0.68	6.11	(10.47-13.20)	
6 months	10.81	(0)	5.63	(9.55-12.07)	
Mean diff	1.02	0.85	7.51	(-0.66-2.70)	0.1143

Table 8: Comparison of effect of MI/CBT and mh GAP IG on AUDs

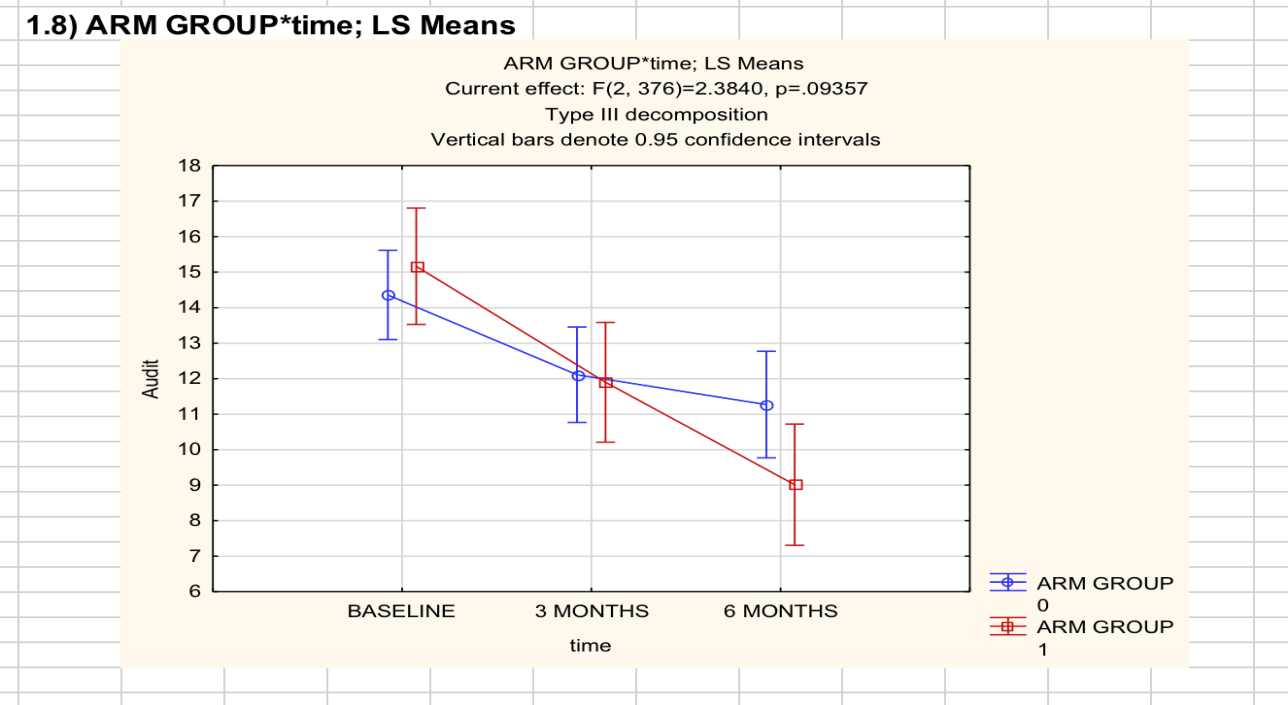

Figure 2: Compare MI/CBT and mh GAP IG interventions effects over 6 months. ARM GROUP 1 is the MI/CBT and ARM GROUP 0 is the mhGAP IG.

Viral load

There were statistically significant reductions in viral load at the end of 6 months for both the MI/CBT 0.77(0.41;1.13) p <0.001 and mh GAP IG 0.40(-0.51;0.84) p= 0.0408 with a greater reduction in the MI/CBT as shown on Table 9. However, group differences were not statistically significant (p=0.46) at 6 months. Figure 4 shows the change in viral loads change over 6 months comparisons. Figure 5 shows the viral loads changes for the whole sample by individual between baseline and 6 months. Of note is the fact that the majority of participants reduced their viral loads, however, a minority increased the viral loads.

MI/CBT n=85	MEAN	STANDARD ERROR	STANDARD DEVIATION	95%CI	P-VALUE
Baseline	1.85	0.12	1.11	(1.62-2.09)	
6 months	1.07	0.15	1.40	(0.78-1.39)	
Mean diff	0.77	0.18	1.66	(0.41-1.13)	<0.001
mh GAP IG n=81	**MEAN**	**STANDARD ERROR**	**STANDARD DEVIATION**	**95%CI**	**P-VALUE**
Baseline	1.51	0.14	1.25	(1.22-1.78)	
6 months	1.11	0.17	1.53	(0.78-1.45)	
Mean diff	0.40	0.22	2.02	(-0.51-0.84)	0.0408

Table 9: Shows intervention effects of the MI/CBT and mh GAP on viral loads from baseline to 6 months.

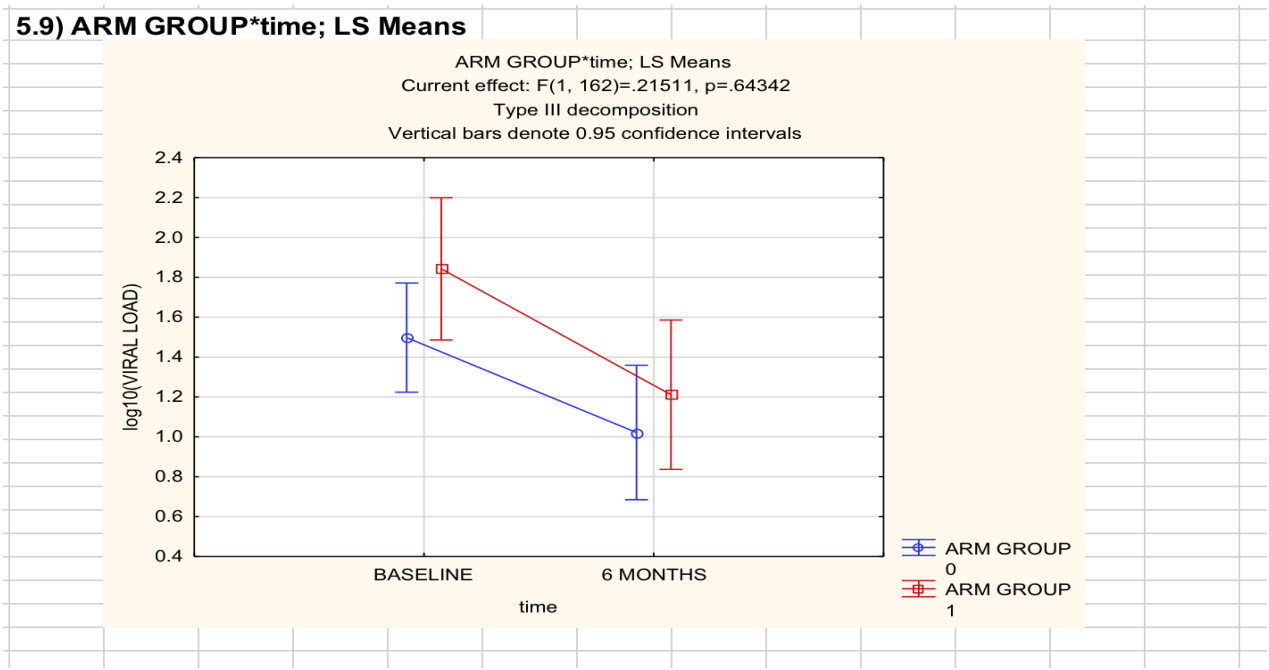

Figure 3: Shows comparisons of viral loads changes from baseline to 6 months between the arms.

ARM GROUP 1 is the MI/CBT and ARM GROUP 0 is the mh GAP IG.

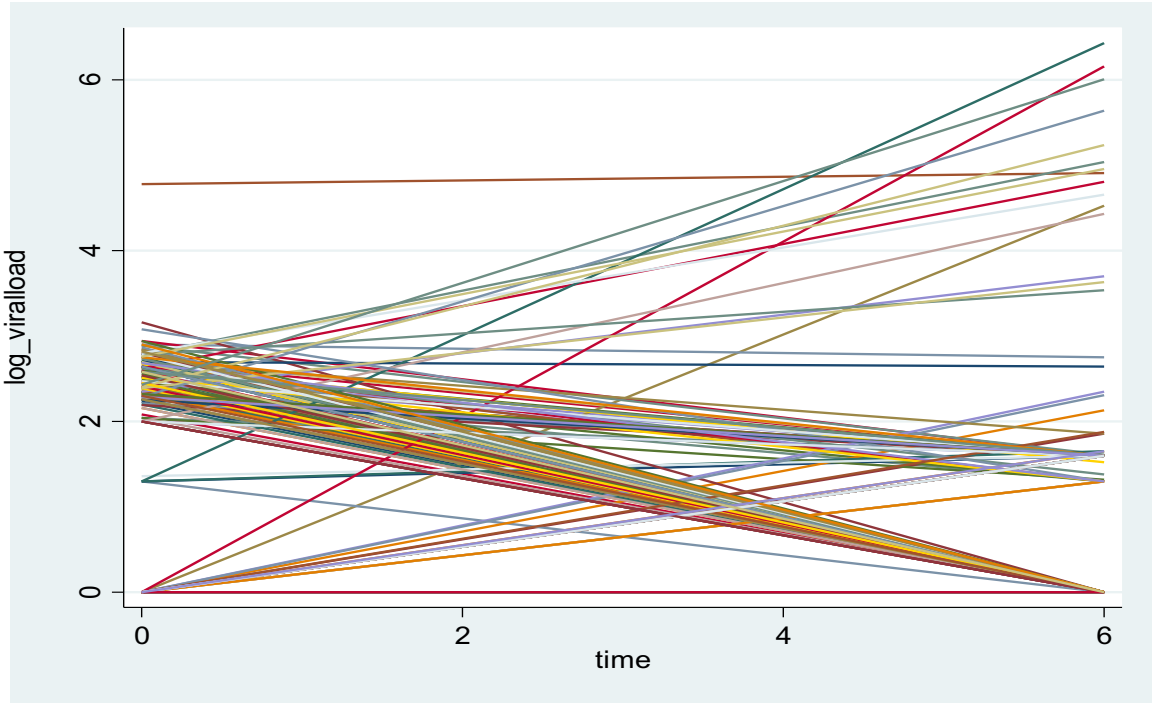

Figure 4: Spaghetti plot for overall viral load over 6 months.

CD4

At baseline, the MI/CBT arm had a lower CD4 compared to the mh GAP IG as shown in Table 10 and Figure 5. At 6 months MI/CBT group improved on CD4 by MD23(-72;26.08) p=0.8231 and mh GAP IG MD45.07(13.05;103,20), both which were however not statistically significant. This is shown on Table 10.

	Mean	Standard	Standard deviation	95%CI	P value
MI/CBT n=85					
Baseline	397.32	26.32	243.19	(344.87:449.79)	
6 months	420.35	25.58	235.85	(369.48:471.23)	
Mean diff	-23.02	24.69	227.64	(72.12;26.08)	0.8231
mh GAP IG n=81					
Baseline	463.61	25.37	228.31	(413.12:514.09)	
6 months	418.53	22.59	208.36	(373.56:463.50)	
Mean diff	45.07	29.21	262.88	(13.05:103.20)	0.0634

Table 10: Comparison of CD4 between MI/CBT and mh GAP IG over 6 months.

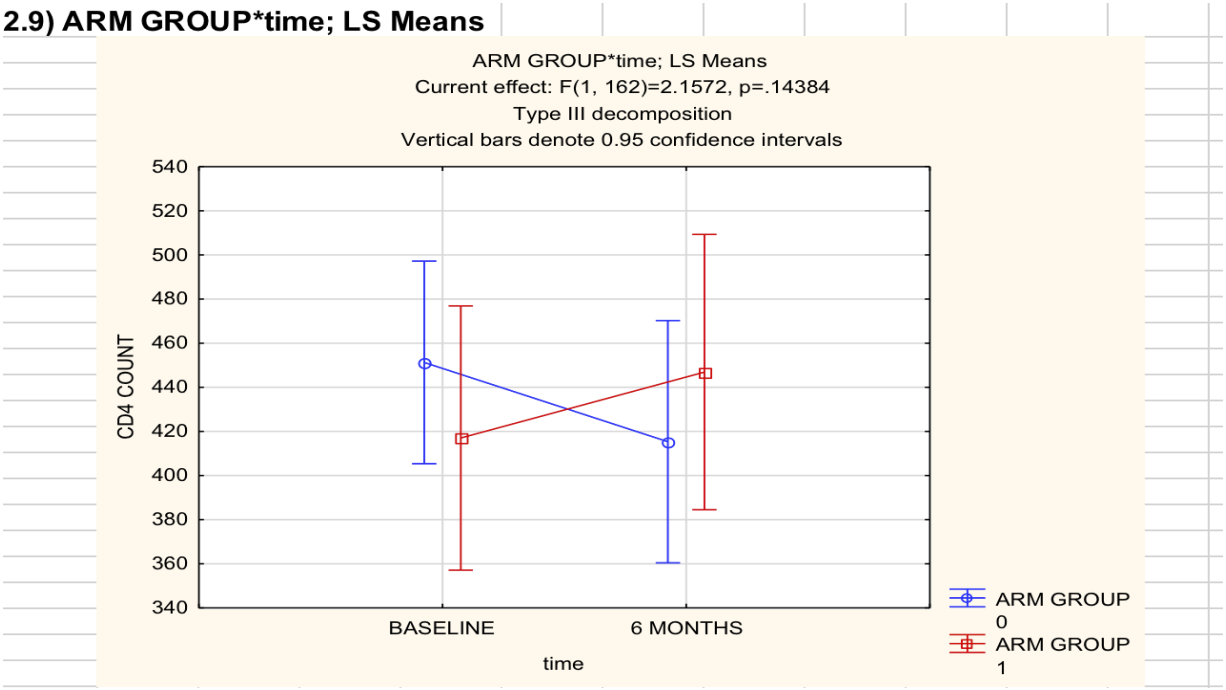

Figure 5: Comparison of intervention effects between MI/CBT and mh GAP IG over 6 months. ARM GROUP 1 is the MI/CBT and ARM GROUP 0 is the mh GAP IG.

Functionality

There were statistically significant changes in functionality for both MI/CBT (MD0.95 95% CI (0.10; 1.80) p=0.029) and mh GAP IG (MD 1.25 95%CI (0.39;2.52) p=0.008). However, there were no statistically significant differences between groups (p=0.67).

Table 11: Comparison of arms for WHODAS 2.0

	Mean	Standard error	Standard deviation	95%CI	P-value
MI/CBT n=102					
Baseline	14.6	0.27	4.05	14.00;16.02)	
3 months	14.6	0.29	3.01	(14.05;1519)	
6 months	15.71	0.35	3.56	(15.01:16.40)	
Mean diff	-1.05	0.46	4.64	(-1.96: -0.14)	0.025
Mh GAP IG					
Baseline	16.5	0.38	4.10	(14.60;16.80	
3 months	15.82	0.42	4.27	(14.99:16.65)	
6 months	14.87	0.40	3.66	(14.06:15.67)	
Mean diff	1.45	0.54	4.70	(0.39:2.52)	<0.001

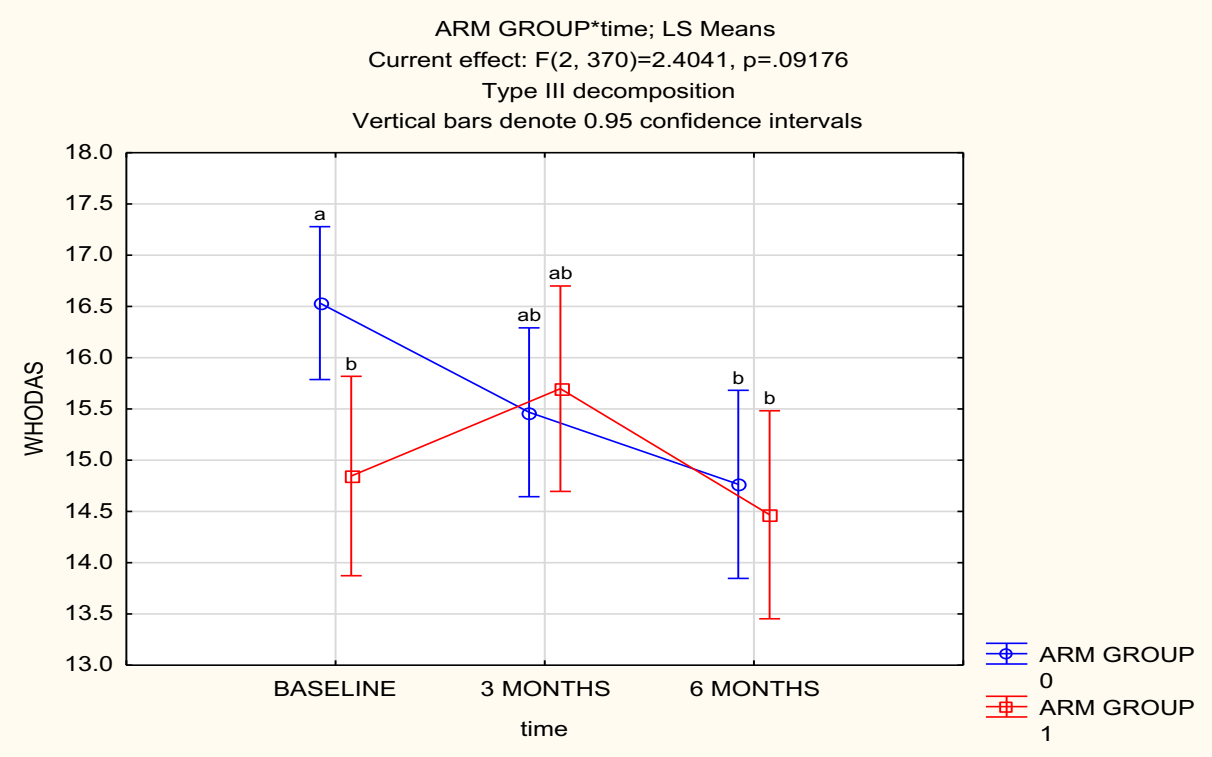

Figure 6: Comparison of WHODAS at baseline, 3 months and 6 months for both arms. ARM GROUP 1 is the MI/CBT and ARM GROUP 0 is the mh GAP IG.

Quality of life (QoL)

There were statistically significant changes in the quality of life for both arms between 3 and 6 months (MI/CBT MD-13.63 95%CI (-17.05; -10.21, p <0.001; mh GAP IG MD -12.21 95% CI (-14.71; -9.72) p<0.001) However, there were no statistically significant differences between groups p=0.51.

	Mean	Standard error	Standard deviation	95%CI	P value
MI/CBT					
Baseline	69.80	0.85	8.90	(82.85;88.10)	
3 months	73.22	0.96	9.08	(83.89;89.08)	
6 months	71.68	0.89	8.98	(69.91;73.44)	
Mean diff	1.48	1.37	12.67	(-1.24;4.19)	0.283
MI/CBT					
Baseline	71.00	0.75	8.45	(69.00;73.22)	
3 months	71.63	0.89	8.98	(69.91;73.44)	
6 months	86.28	1.14	14.66	(83.48;86.08)	
Mean diff	-13.63	1.72	17.41	(-17.05; -10.21)	<0.001
mh GAP IG					
Baseline	69.70	0.75	7.30	(70.32;73.40)	
3 months	71.81	0.80	7.29	(70.23;73.39)	

6 months	71.59	0.71	7.32	(70.19;72.99)	
Mean diff	0.46	1.17	10.39	(-1.87;2.78)	0.698
mh GAP IG					
Baseline	71.25	0.62	7.15	(69.18;73.28)	
3 months	71.59	0.71	7.32	(70.19;72.99)	
6 months	84.38	0.86	9.64	(82.68;86.08)	
Mean diff	-12.21	1.26	13.03	(14.71; -9.72)	<0.001

Table 12: Showing a comparison of arms for WHOQoL at baseline, 3 months and 6 months

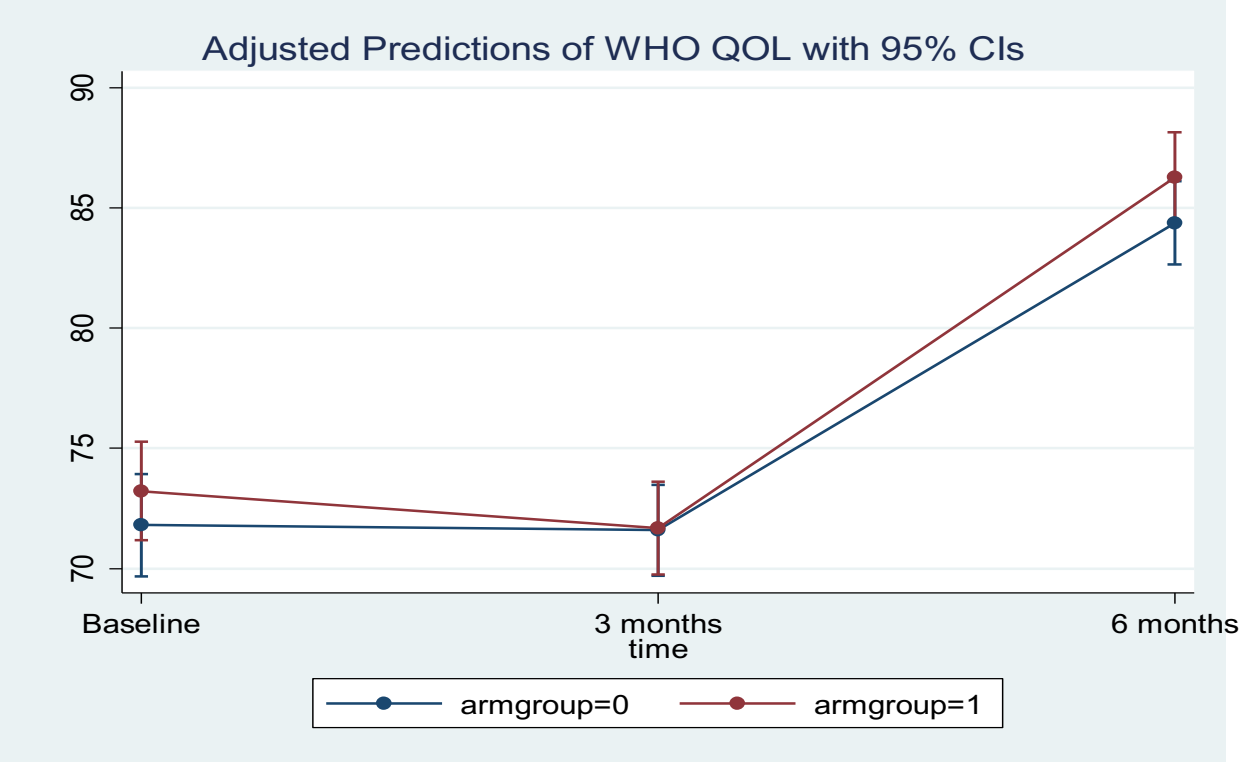

Figure 7: Showing an adjusted prediction of WHOQoL with 95% confidence intervals of both arms for baseline, 3 months and 6 months

AUDIT	MD	S.E	SD	95%CI	P-value
At 3 months					
MI/CBT	3.33	0.72	7.39	(1.88-4.78)	< 0.001
Mh GAP IG	2.53	0.65	6.66	(1.25-3.81)	< 0.001
At 6 months					
MI/CBT	2.41	0.71	1.66	(0.41-1.13)	< 0.001
Mh GAP IG	1.02	0.85	0.71	(-0.51-0.84)	0.0408
Viral load At 6 months					
MI/CBT	0.77	0.18	1.66	(0.41-1.13)	< 0.001
Mh GAP IG	0.40	0.22	2.02	(-0.51-0.84)	0.0408
CD4 at 6 months					
MI/CBT	-23.02	24.69	227.64	(-72.12; 26.08)	0.8231
Mh GAP IG	45.07	29.21	262.88	(-13.05;103.20)	0.0634
WHODAS at 3 months					
MI/CBT	-1.05	0.46	4.64	(-1.96; -0.14)	0.025
Mh GAP	0.26	0.69	7.07	(-1.10;1.62)	0.706
At 6 months					
MI/CBT	0.95	0.43	3.97	(0.10;1.80)	0.029
Mh GAP IG	1.45	0.54	4.70	(0.39;2.52)	<0.001
WHOQOL					
At 3 months					
MI/CBT	1.48	1.37	12.67	(24;4.19)	0.283
Mh GAP IG	0.46	1.17	10.39	(-1.87;2.78)	0.698
At 6 months					
MI/CBT	-13.63	1.72	17.41	(-17.05; -10.21)	<0.001
Mh GAP IG	-12.21	1.26	13.03	(-14.71; -9.72)	<0.001

Table 13: is showing a summary of outcomes. The outcomes include AUDIT, VIRAL LOAD, CD4 and WHOQOL for 3 months and 6 months.

Discussion

This two-arm study demonstrated significant effects on alcohol use reduction in PLWH. Further, interventions showed effects on viral loads and the MI/CBT caused some modest improvement in CD4 count. The interventions for problematic alcohol use led to improvement in functionality and quality of life. These are significant findings in light of a few trials that have been done that showed no effects on alcohol use in PLWH(22, 28, 56). More important is the fact that the intervention was delivered within the usual HIV care setting, by nurses who are involved in the day-to-day care of HIV patients. This finding suggests that, integration of management of alcohol use within the usual care for HIV is feasible. The effects of the study may be related to it being “imbedded” within the day to day HIV care. Task sharing and integration have been key in the success of not only

HIV care upscaling but also stigma reduction(57-59). The same success in task sharing and integration in alcohol use management are possible and can give equally good results. This may eliminate stigma associated with both HIV and alcohol use. Stigma for both HIV and alcohol consumption have been shown to be some of the barriers to uptake of interventions for problematic alcohol use by PLWH(30).

The participants were in the mh GAP IG in our study benefited from the intervention up to three months. Current research data shows that the effects of interventions for problematic alcohol use are not prolonged beyond three months(22, 60). It also seems that in this study exposure to intervention was good enough to cause effects on alcohol use and other treatment outcomes. The prolonged effects in the MI/CBT arm maybe due to booster sessions. These findings have important implications. They demonstrate the need for booster sessions through continued contact and feedback. This is in keeping with recent recommendations about booster sessions by a recent systematic review(22). These booster sessions can come in the form of brief discussions of current alcohol consumption at medication refill encounters or through use of mobile mHealth technologies. Mobile health technologies have been shown to be low cost and aid the effects of motivational interviewing (61). Besides the need for booster sessions, the findings of this study suggest that the mh GAP IG is able to reduce the AUDIT score, but only for a period. Even though the periods were short, as the country roles out the mh GAP IG, emphasis should be made on reaching all individuals and conditions. This will also help in integration of mental health in HIV care and primary health care.

Further, the success of our intervention can be attributed to provision of feedback on the patients' viral loads and CD4. This is especially so, as the usual HIV care in Zimbabwe did not include this feedback as the viral loads. Personal feedback especially using mobile health technologies can be a key component of motivating desire for change in future interventions(62, 63). Exposure to alcohol intervention and feedback has been shown to lead to change in the drinking behaviour(64). This approach is feasible as mobile phone penetrance improve in LMIC.

This study demonstrated a statistically significant drop in the viral load of both the MI/CBT and mh GAP IG, although it was more so on the MI/CBT. The change in the viral loads is important especially in Zimbabwe, where a recent population based survey on HIV care and 90-90-90 targets were assessed that showed that 75% had viral suppression, that fall short of the 90% as required by 90-90-90 UNAIDs strategy(2, 65). This reduction in viral loads suggest that the adherence to treatment improved as a result of the interventions. Virological control is key in the HIV treatment cascade (66). Viral load reduction reduces infectiousness thus it is useful in preventing new infections(67). Addition of interventions for problematic alcohol use in the HIV care program in Zimbabwe and other HIV high burden countries is essential for them to reach the 2020 goal of 90-90-90.

There was some modest improvement of CD4 in the MI/CBT. Overall, this suggest that intervention for alcohol use have the effect of improving HIV treatment outcomes. The magnitude of CD4 change is however not unexpected given the recent findings in similar studies Wandera et al(2017) from Uganda found hazardous alcohol consumption not related to CD4 suggesting that CD4 count measure may not be an important marker of poor adherence (68) and initiation of HIV treatment in individuals with alcohol consumption did not affect the CD4 cells count in another study(69). However, a study in Brazil found alcohol consumption associated with low CD4 count(70). This suggests that there may exist some ways that alcohol use interacts with CD4 independent of ART and adherence(71). These findings suggest that CD4 on its own is not a good measure of effectiveness of HIV treatment.

Our study showed that intervention for problematic alcohol use lead to improvement in the functionality as measured by WHODAS 2.0 score. This is an important finding and suggest that validation and use of such scales needs to be done in the HIV clinics. Functionality in PLWH on ART has been known to be compromised especially in patients with poor adherence and depression(72).

In addition presence of physical symptoms has also been shown to lead to reduced function in the domains of participation and mobility in PLWH(73). As PLWH frequently face a reduction in function and limited activity, which also affect adherence, routine monitoring of functionality has been recommended(72). In HIV care clinics like in Zimbabwe, this may need a small, but important cost of validation of the tools.

This study showed that reduction in alcohol use and clinical improvement was associated with improvement in quality of life. It has been shown that poor quality of life is associated with reduced adherence to treatments of other chronic conditions such as hypertension and other chronic conditions(74). Quality of life reduces adherence and poor adherence leads to poor quality of life. Improved quality of life has been shown to promote adherence to HIV treatment(75). It is essential that the PLWH have both physical recovery and experience good quality with their lives.

Participants in this study had substantial comorbidities especially depression and anxiety. Future interventions for problematic alcohol use must include sections that target both depression and/or anxiety as well. The psychological treatments that target several comorbities have already been done. These comorbities need to be reconsidered at scale-up as they may have influenced the outcomes from this study. A study in India by Patel V et al (2017) showed that depression and alcohol can be treated in the same clinic using manualised interventions(76). The RGNs in the HIV care clinics can thus be trained to deliver HIV care and psychological treatments for depression and/or anxiety and alcohol in an integrated setting. Calls have indeed been made to integrate mental health services into the existing primary health care services in order to narrow the mental health treatment gap(77). The present study findings should be taken together with other on-going initiatives in mental health in Zimbabwe. These include the TENDAI studies and the Friendship Bench, both of which aim to utilise lay-health care workers to treat depression in PLWH and common mental disorders in the general population respectively(78-80).

This study has several limitations. First, the RCT was a cluster randomised controlled trial and the clusters were different in sizes, resulting in failing to recruit same numbers of participants in the clusters. This has the effect of loss of power in the study. Selection of cluster was however, by randomisation and participants were randomly selected using computer databases to reduce selection bias. Secondly, the study had significant loss to follow up especially in the mh GAP IG arm. This could have resulted in the loss of power. Third, the alcohol use measure was the AUDIT score. This is a self-report questionnaire which is subject to social desirability bias(81). Methods such as use of automated computer assisted self-interview (ACASI) or electronic assessments maybe useful in reducing social desirability bias(82). Fourth, the mh GAP IG experienced more loss compared to the MI/CBT and resulting in attrition bias. Lastly, the AUDIT, the WHODAS 2.0 and WHOQOL have not been validated in Zimbabwe PLWH.

Notwithstanding these limitations, we believe our study has findings that are important. As the country continues to improve HIV care treatments in order to attain the 90-90-90 targets, problematic alcohol use maybe the next frontier. Most levels of HIV care were represented so the findings can be generalised for all the clinics in Zimbabwe.

Conclusion

This is the first study in Zimbabwe to demonstrate the effectiveness of a psychological interventions for problematic alcohol use in PLWH delivered in a task sharing model within HIV clinics. This has important implications. Alcohol use in HIV infected patients can be managed in clinics by nurses who have been trained. More staff need to be recruited though, as the participants will require additional time with RGNs. The additional time required for HIV/alcohol use counselling may affect nurse's routine duties. As a result, the clinics may need adjustment to accommodate the changes. The interventions led to improvement in functionality and quality of life. This is important as quality of life and functionality are important determinants of HIV treatment outcomes.

As the AUDIT is a self-report, it is not the ideal tool to use alone especially in these populations whose alcohol consumption though low or moderate may lead to more damage in the body. Use of alcohol biomarkers is thus recommended.

Finally, as the study experienced significant loss to follow up, mechanisms to retain participants need to be developed. Use of mobile technology may also be employed to reduce the need of patients face-to-face with intervention staff. We therefore call for effectiveness trials that consider current HIV treatment settings complexity, current staffing and their knowledge of alcohol use/HIV interface and involvement of patients in design and participants retention techniques.

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Contributors

MM and SS conceived the study and developed the study protocol. MA, AC and DC critically reviewed the protocol. SR and MZ developed the statistical plan and provided critical input on study design and data analysis. MD and WM adapted the mh GAP IG for this study. MM, BD and TM developed the MI/CBT and prepared it for use in the field. MM and SS drafted the manuscript. All authors revised the manuscript and approved it for submission.

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CHAPTER SEVEN

CONCLUSION

Although alcohol use is associated with HIV transmission, adherence to treatment, increased physiologic harm and worse retention in care yet, few clinical trials targeting unhealthy alcohol use in people living with HIV (PLWH) have been undertaken (Brown, DeMartini, Sales, Swartzendruber, & DiClemente, 2013; Justice et al., 2016; Marshall et al., 2017; Monroe et al., 2016). A recent systematic review found alcohol use was one of the key determining factors of adherence to HIV treatment(Azar, Springer, Meyer, & Altice, 2010; Heestermans, Browne, Aitken, Vervoort, & Klipstein-Grobusch, 2016). Research on psychological or behavioural interventions for alcohol use have not provided consistent evidence for their effectiveness in PLWH(Brown et al., 2013; Samet & Walley, 2010). While, Zimbabwe has 1.6 million PLWH and 6.0 litres per capita alcohol consumption and the deleterious effects of the combination of HIV and alcohol use are known, the Zimbabwe National AIDS Council 2015-2020 HIV Strategy, has no policy initiatives that address alcohol use (nac.org.zw/hiv-and-aids-situation/; www.who.int/substance_abuse/publications/global_alcohol_report/profiles/en/). The aim of this dissertation was to assess the effectiveness of psychological interventions for alcohol use in PLWH through a cluster randomised controlled trial (RCT) in order to inform future policy on interventions for them in Zimbabwe.

Systematic review of interventions for alcohol use disorders

A systematic review to synthesize the evidence of the effectiveness of psychological interventions for unhealthy alcohol use in PLWH was carried done. The primary outcome for the review was a reduction in the frequency of alcohol use. The secondary outcomes were the effects of the interventions on CD4 count, viral load, other substances use, risky sexual behaviour and quality of life. The participants were PLWH receiving care at hospitals, clinics and communities. Experimental studies have shown that the daily allowable alcohol intake for PLWH, especially if they have not achieved viral suppression, needs to be lower than 21 units per week for males and 14 units per week for females as PLWH, they need less alcohol to get intoxicated and suffer physiologic harm from a lower quantities of alcohol(Braithwaite et al., 2008; Cook et al., 2017; Justice et al., 2016; McGinnis et al., 2016). Damage to the liver due to alcohol use and hepatitis C, which are both associated with HIV, have been associated with a reduction in the effectiveness of antiretroviral therapy and poorer treatment response(Fuster et al., 2016; Kresina et al., 2002; Sonderup & Wainwright, 2017). Both the quantity and the frequency of alcohol intake have been found to adversely affect viral suppression(Braithwaite et al., 2005; Canan et al., 2017).

Our review identified 14 studies that met the eligibility criteria, three from Africa and the rest from US. Heterogeneity in the measurement of alcohol use outcomes did not allow for a meta-analysis to be carried out. The overall quality of studies was moderate to low on account of selection and attrition biases. The main findings of the review were that (i) motivational interviewing alone and with adjunctive mobile technology and (ii) cognitive behavioural therapy alone reduced alcohol consumption frequency. The findings of our review are similar to two previous systematic reviews(Brown et al, 2013 and Samet et al, 2010) but differed from a recent systematic review by Scott-Sheldon et al (2017), who found evidence for behavioural/psychological interventions on alcohol consumption, condom use and adherence to treatment in PLWH(Brown et al., 2013; Samet

& Walley, 2010; Scott-Sheldon, Carey, Johnson, Carey, & Team, 2017). More randomised controlled trials are needed in low- and medium-income countries (LMIC) that have high HIV disease burden(Brown et al., 2013). We also recommend that effectiveness trials target alcohol use specifically and use uniform alcohol use measures.

Development of the intervention protocol

There is evidence that motivational interviewing is effective in improving adherence to ART, reduction in risky sexual behaviour, reduction in substance abuse and can lead to reduction in viral load(Hasin et al., 2013; Parsons, Golub, Rosof, & Holder, 2007). Alcohol use can be a maladaptive coping mechanism for the psychosocial stressors that PLWH face(Elliott, Aharonovich, O'Leary, Wainberg, & Hasin, 2014). As such, adaptive skills to cope with mental health problems and other stressors based on cognitive behavioural therapies(CBT) and problem-solving techniques are needed(Sikkema et al., 2015). CBT, combined with motivational interviewing or motivational interviewing combined with problem solving techniques have been used in some studies(Parry et al., 2014; Parsons et al., 2007).There is therefore heterogeneity in the interventions content. Specialist psychosocial workers are needed to deliver these interventions. However, there is shortage of specialized skilled personnel such as psychologists in most countries and the World Health Organisation has called from task sharing as a solution(Organization, 2008).

The experience of adapting evidence-based therapies is essential. This because, there are contextual factors such as language, cultures and traditions that need to be considered(Bernal & Adames, 2017; LeBron et al., 2014).

Alcohol use is associated with non-adherence to HIV treatment, sexually transmitted infections (STIs), HIV spread and poor HIV treatment outcomes(Fisher, Bang, & Kapiga, 2007; Hahn & Samet, 2010; Heestermans et al., 2016). Recommendations to develop and implement interventions for unhealthy alcohol use in PLWH have been made(Brown et al., 2013; Chander, Hutton, Lau, Xu, &

McCaul, 2015). A review of literature on interventions for unhealthy alcohol use, in-depth interviews with experts and focus group discussions with PLWH were some of the activities undertaken in the formative work. Further, a qualitative study on the perceptions, barriers and facilitators to interventions for unhealthy alcohol use in PLWH, a pilot and feasibility study of intervention for unhealthy alcohol use in PLWH and meetings with experts were held to come up with the final version that was to be used in the Cluster randomised controlled trial (RCT). A cluster RCT design was chosen for the delivery of a community-based motivational interviewing/cognitive behavioural therapy (MI/CBT) intervention to reduce the risk of contamination and to improve administrative efficiency (Hayes R). To permit generalizability, all HIV clinics in Zimbabwe were eligible to take part in the study.

The control in the study protocol was the World Health Organisation mental health GAP Intervention Guide (mh GAP IG) for patients with mental, neurological and substance use disorders, as has been employed in other studies(Nadkarni et al., 2015; Organisation, 2010).

Perceptions of alcohol use in PLWH

A qualitative study was conducted as part of the formative work for the intervention for alcohol use. The aim of the study was to understand patients' perceptions of alcohol use in the context of HIV treatment. Clinics were chosen to represent the tertiary care, secondary care and church related institutions or district hospitals, the current set-up in HIV care in Zimbabwe. The main findings were that (i) participants had adequate knowledge of the effects of alcohol use when one is on HIV treatment. (ii) Participants were able to identify direct effects of alcohol use on the body such as liver disease. (iii) Indirect effects of alcohol use when one is on HIV treatment such non-adherence to treatment and involvement in risky life styles such as involvement in sex without protection. (iv) Stigma that HIV and alcohol face. Participants also proffered solutions such as (i)additional training of nurses in HIV and alcohol use interface (ii)use of primary care counsellors in providing interventions (iii) need for change in attitudes towards HIV and in the HIV care staff.

These findings suggest that the HIV health education that is provided to patients is accurate and probably sufficient. It also suggests that HIV literacy levels were high among PLWH. However, there are high levels of stigma towards alcohol use and HIV. Person-cantered interventions for alcohol use which do not have diagnostic 'labels' such as 'alcoholic' or similar need to be implemented in order to reduce stigma(Robinson, 2017). Further, offering HIV treatment and interventions for alcohol use within the same premises and by the same staff attending to other health conditions may help reduce stigma(Church et al., 2013). Integration of mental health services with other health care services has been recommended as a way to improve treatment, reduce the treatment gaps, treatment outcomes and reduction of stigma(Patel et al., 2016). Due to the high levels of knowledge about the effects of alcohol consumption on HIV care, interventions for alcohol use can be made a routine practice in HIV care clinic without need for additional staff. More research in effectiveness trials of interventions for unhealthy alcohol use need to be done incorporating stigma reduction strategies in HIV care. These interventions must incorporate the views of patients in order to improve their acceptability(Fredericksen et al., 2015).

Pilot and feasibility study

In preparation for the main trial, a pilot and feasibility study were carried out. The aim was to assess (i) the feasibility of screening for alcohol use, (ii) the utility of the assessment tools, and the (iii) delivery of the interventions using a task sharing model. At the end of three months there was statistically significant change in AUDIT score and CD4. However, the study had a small sample size of 40 and was not adequately powered. This study however provided initial evidence of feasibility of the intervention (MI/CBT or MH GAP IG) in an HIV care clinic. The study found that it was feasible to recruit HIV positive individuals with unhealthy alcohol use among PLWH. Further, nurses were trained in delivering an unhealthy alcohol use intervention. Owing to significant loss to follow up, the main trial had to incorporate strategies to retain participants.

The findings from this study are important given that most of the studies have been shown to lack effectiveness in reducing alcohol consumption in PLWH(Brown et al., 2013; Samet & Walley, 2010). As the registered general nurses were selected to deliver the interventions for unhealthy alcohol use, the study findings showed that it was feasible to deliver the interventions within the same setting delivering HIV care. The amount of time to deliver MI/CBT intervention requirements were determined and helped in the planning of the RCT. Loss to follow-up was a limitation of the pilot and feasibility study. This helped the main trial to finalize the sample size by incorporating loss to follow up percentage in the sample size.

Intervention for unhealthy alcohol use: a cluster randomised controlled trial

The formative studies outlined above culminated in a cluster RCT to assess the effectiveness of a motivational interviewing- cognitive behavioural (MI/CBT) intervention. 234 PLWH were enrolled from randomly selected 16 HIV care clinics across Zimbabwe. The intervention used a task-sharing model to deliver the intervention. Our RCT blended motivational interviewing and CBT in the intervention for alcohol use based on this evidence. As the HIV care program includes counselling and testing, ART initiation and follow up and is nurse-led, registered general nurses (RGN) were chosen to deliver the intervention. Participants were followed up for 6 months post-intervention. This is the first study to test the effectiveness of interventions for alcohol use in PLWH in Zimbabwe.

The two arms showed statistically significant changes in AUDIT scores (MD) at 3 months. However, the MI/CBT showed further improvement at 6 months, with the change between 3 and 6 months being statistically significant. The lack of a further improvement between 3 and 6 months in the mh GAP IG with continued improvement in the MI/CBT may be attributed to booster sessions given to MI/CBT arm. A number of studies have shown that intervention for unhealthy alcohol use have reduced effects over time and booster sessions have been recommended (Parsons et al., 2007; Samet & Walley, 2010). The mh GAP IG was developed for primary care settings

(www.who.int/mental_health/publications/mhGAP_intervention_guide/en/). The findings on the mh GAP IG effectiveness, albeit for 3 months is important as it can be adopted at HIV care clinic settings allowing for integration of mental, neurological and substance use in routine HIV treatment thus, to narrowing the treatment gap(www.who.int/mental_health/publications/mhGAP_intervention_guide/en/). Due to multiple comorbidities such as depression identified in this population, an intervention for unhealthy alcohol use should include treatment for depression using a transdiagnostic approach in HIV care patients as has been recommended by recent systematic reviews(Balhara, Gupta, & Elwadhi, 2017; Vujanovic et al., 2017).

There were reductions in viral loads for both the MI/CBT and the mh GAP IG at 6 months. However, there were modest changes in CD4 for both the MI/CBT. Functionality also improved for both arms at 6 months. Quality of life also improved over the follow-up period for both MI/CBT and the mh GAP IG interventions.

Findings from this study are important. They suggest that interventions for unhealthy alcohol use in PLWH can be effective in improving HIV viral loads through improvement in adherence. Such a finding is similar to findings from other studies(Naar-King et al., 2008; Parsons et al., 2007). Many studies have shown a strong relationship between the viral loads increase and alcohol use, both the in terms of quantities of alcohol taken and frequency of drinking(Braithwaite et al., 2005; Cook et al., 2017; Williams et al., 2016). Research suggests that PLWH with alcohol use require low daily allowable quantities of alcohol as compared to those living without HIV (Braithwaite et al., 2008). Further PLWH with detectable viral loads require less quantities of alcohol to get intoxicated(McGinnis et al., 2016). PLWH have also been shown to suffer more physiologic harm at low levels of alcohol consumption(Justice et al., 2016). Yet viral load suppression is associated with reduced HIV transmission and lack of viral suppression may increase HIV transmission(Ross et al., 2018).

Adherence is the most important determinant of treatment outcomes and unhealthy alcohol use have been associated with poor adherence and non-engagement with treatment(Azar et al., 2010; Galvan et al., 2002).

The findings on CD4 are in keeping with other studies from elsewhere. Wandera et al (2017) showed that hazardous alcohol use is not associated with lower CD4 count, yet Malbergier et al (2015)(Malbergier, Amaral, & Cardoso, 2015) found alcohol dependence to be associated with lower CD4 count (Wandera et al., 2017). Hahn et al (2018) found unhealth alcohol having apparent effect on CD4 in the short term(Hahn et al., 2018) while Kolwaski et al (2012) found alcohol consumption having no effect on people initiating antiretroviral therapy(Kowalski et al., 2012). However, findings from other studies are contrary. In a study that used the AUDIT score as a measure da Silva et al (2017) found that a high AUDIT score was associated with a low CD4(da Silva, Mendoza-Sassi, da Mota, Nader, & de Martinez, 2017). Both MI/CBT and mh GAP IG led to improvement in functionality and quality of life. Good quality of life has been shown to improve adherence to HIV treatment(Aranda-Naranjo, 2004).

Evidence for the effectiveness of alcohol use reduction interventions in HIV is weak, in spite of the burden and need(Brown et al., 2013; Samet & Walley, 2010). This dissertation demonstrates the feasibility of adapting an evidence-based intervention for alcohol use disorders that can be delivered in a low resource setting. However, it is important to incorporate patients' perceptions and expectations in the development of any intervention. Further, brief interventions for unhealthy alcohol use such as the mh GAP IG can result in reduction in alcohol use over a short period as shown in this study. It may however require booster sessions that may come in the form of short messages using mobile platforms such found by Hasin et al (2013) in the use of HealthCall(Hasin, Aharonovich, & Greenstein, 2014). Functionality and quality of life also improve with improved HIV treatment

adherence. It is thus essential to incorporate functionality and quality of life measures in routine HIV treatment settings.

Overall, this is the first study to enrol nurses to deliver an intervention for unhealthy alcohol us at HIV care clinics using a task sharing model. With the results achieved in this study, there is scope for upscaling MI/CBT intervention for unhealthy alcohol use to include more clinics. Further, the improvement in viral load control will go a long way in helping the country achieve the UNAIDS 90-90-90 goals(Organization, 2017; UNAIDS, 2018). Program planning for PLWH must include interventions for unhealthy alcohol use, substance use disorders and common mental disorders treatments in order to improve treatment HIV treatment outcomes.

This project had substantial limitations. The RCT was a cluster randomised controlled trial and the clusters were different in sizes, resulting in failing to recruit same numbers of participants. This has the effect of loss of power in the study. Selection of cluster was however, by randomisation and participants were randomly selected using computer databases to reduce selection bias.

Further there is paucity of intervention studies in low- and medium-income countries with a high HIV disease burden. As a result, most of the studies reviewed came from high income countries and most of the evidence was indirect. The Alcohol Use Disorders Identification Test (AUDIT) that was used in assessing alcohol use is a self-report questionnaire and suffer from social desirability bias. Besides, the AUDIT has not been validated in PLWH in Zimbabwe. This is the same case as other tools used in this project such as the WHODAS 2.0 and the WHOQOL. The RCT had significant loss to follow-up especially in the mg GAP IG arm and could have lost power.

However, despite these limitations, we believe the study makes a significant contribution to HIV care in Zimbabwe. The study showed that even with minimum funding and no increase in personnel, an intervention for alcohol use is feasible. This intervention resulted in reduction in alcohol use and reduction in viral load. Nurses provide HIV care services in many high HIV burden countries,

and the study showed that they can also deliver interventions for unhealthy alcohol use effectively. As adherence to ART is an important predictor of HIV treatment outcomes and alcohol has been shown to impact negatively on adherence, the findings in this study will improve the HIV treatment outcomes if implemented.

This study is one of a few interventions for problematic alcohol use to demonstrate effectiveness in alcohol use reduction, viral load reduction, functional improvement and improvement in quality of life in a LMIC. More effectiveness trials of interventions for unhealthy alcohol use need to be carried out, as these improvements will go a long way in helping the countries in achieving the 90-90-90 UNAIDS targets. HIV care programs must incorporate interventions for unhealthy alcohol use in order to improve HIV treatment outcomes. Unhealthy alcohol use and HIV treatment collaborations provide an opportunity for integrating mental health in other health care programs that may result in narrowing the mental health treatment gap. Problematic alcohol use has been associated with virological failure, suggesting that when doing HIV treatment outcome assessment, assessment of unhealthy alcohol use must be done concurrently. A brief intervention for unhealthy alcohol use such as mh GAP IG resulted in improved viral suppression. Effectiveness trials that target unhealthy alcohol use outcomes must include treatment outcomes such as viral loads. Quality of life and functionality must be measured routinely in HIV care programs, as improved function and better quality of life are associated with better adherence to HIV treatment.

As a way forward, the findings from this study may help inform other initiatives such as the Friendship Bench and Tendai that aim at treating common mental disorders and depression in HIV that are ongoing in a as synergistic way. This will also help in scaling up psychological therapies.

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