Effectiveness and cost-effectiveness of group support psychotherapy delivered by trained lay health workers for depression treatment among people with HIV in Uganda: a cluster-randomised trial

Etheldreda Nakimuli-Mpungu, Seggane Musisi, Kizito Wamala, James Okello, Sheila Ndyanabangi, Josephine Birungi, Mastula Nanfuka, Micheal Etukoit, Chrispus Mayora, Freddie Ssengooba, Ramin Mojtabai, Jean B Nachega, Ofir Harari, Edward J Mills*

Summary

Background WHO recommends the use of psychological interventions as first-line treatment for depression in low-income and middle-income countries. However, evaluations of the effectiveness and cost-effectiveness of such interventions among people with HIV are scarce. Our aim was to establish the effectiveness of group support psychotherapy (GSP) delivered by lay health workers for depression treatment among people living with HIV in a rural area of Uganda on a large scale.

Methods In this cluster-randomised trial, we included 30 health centres offering HIV care. These were randomly assigned to deliver either GSP or group HIV education (GHE). Randomisation, in a ratio of 1:1, was achieved by health centre managers separately picking a paper containing the intervention allocation from a basket. Participants were people living with HIV, aged 19 years and older, with mild to moderate major depression assessed with the Mini International Neuropsychiatric Interview depression module, taking antiretroviral therapy, and antidepressant-naive. Group sessions were led by trained lay health workers once a week for 8 weeks. The primary outcomes were the proportion of participants with major depression and function scores at 6 months post-treatment, analysed by intention to treat by means of multilevel random effect regression analyses adjusting for clustering in health centres. This trial is registered with the Pan African Clinical Trials Registry, PACTR201608001738234.

Findings Between Sept 13 and Dec 15, 2016, we assessed 1473 individuals, of whom 1140 were recruited from health centres offering GSP (n=578 [51%]) or GHE (n=562 [49%]). Two (<1%) participants in the GSP group were diagnosed with major depression 6 months post-treatment compared with 160 (28%) in the GHE group (adjusted odds ratio=0·01, 95% CI 0·003–0·012, p<0·0001). The mean function scores 6 months post-treatment were 9·85 (SD 0·76) in the GSP group and 6·83 (2·85) in the GHE group (β=4·12; 95% CI 3·75–4·49, p<0·0001). 36 individuals had 63 serious adverse events, which included 25 suicide attempts and 22 hospital admissions for medical complications. The outcomes of these serious adverse events included 16 deaths, 4 of which were completed suicides (GSP=2; GHE=2), and 12 of which were HIV-related medical complications (GSP=8; GHE=4). Cost-effectiveness estimates showed an incremental cost-effectiveness ratio of US$13·0 per disability-adjusted life-year averted, which can be considered very cost-effective in Uganda.

Interpretation Integration of cost-effective psychological treatments such as group support psychotherapy into existing HIV interventions might improve the mental health of people living with HIV.

Funding MQ Transforming Mental Health and Grand Challenges Canada.

Introduction

The huge burden of mental health problems among people living with HIV is recognised as an obstacle to the successful implementation of the WHO Treat All policy, which recommends antiretroviral therapy (ART) for all people living with HIV regardless of their CD4 count.[1] In sub-Saharan Africa, most HIV treatment centres do not screen for mental health problems and yet substantial prevalence estimates of depression, symptoms of post-traumatic stress disorder, and hazardous alcohol use ranging from 13 to 78%, have been reported among people living with HIV, as compared with 5–10% in the general population.[2] Such untreated mental health problems have negative public health consequences including reduced engagement in care, delayed HIV diagnosis, and suboptimal ART adherence and virological suppression; hence affected individuals remain more likely to transmit the virus.[3] Because of this, integration of mental health care into routine HIV care is crucial.

Lancet Glob Health 2020; 8: e387–98

Published Online February 5, 2020 https://doi.org/10.1016/S2214-109X(19)30548-0

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Department of Psychiatry, College of Health Sciences, Makerere University, Kampala, Uganda (E Nakimuli-Mpungu PhD, Prof S Musisi FRCP[C]); **Department of Psychology, Center for Victims of Torture, Gulu, Uganda** (K Wamala MSc); **Department of Mental Health, Faculty of Medicine, Gulu University, Gulu, Uganda** (J Okello PhD); **Mental Health Program, Ministry of Health of Uganda, Kampala, Uganda** (S Ndyanabangi MPH); **The AIDS Support Organization, Kampala, Uganda** (J Birungi MPH, M Nanfuka MPH, M Etukoit MPH); **Department of Health Policy Planning and Management, School of Public Health, Makerere University, Kampala, Uganda** (C Mayora MPH, F Ssengooba PhD); **Department of Mental Health** (Prof R Mojtabai PhD), **Department of International Health** (Prof J B Nachega PhD), **Department of Epidemiology** (Prof J B Nachega), **Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA; Department of Epidemiology** (Prof J B Nachega PhD), **Infectious Diseases and Microbiology** (Prof J B Nachega), **University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA; Center for Infectious Disease, Department of Medicine, Stellenbosch University Faculty of Medicine and Health Sciences, Cape Town, South Africa** (Prof J B Nachega); **MTEK**

Sciences, Vancouver, BC, Canada (O Harari PhD, E J Mills PhD)**; and Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada** (E J Mills)

*Ms Ndyanabangi died Aug 25, 2018

Correspondence to: Dr E Nakimuli-Mpungu, Department of Psychiatry, College of Health Sciences, Makerere University, Old Mulago Hospital Complex, Mulago Hill Road, Kampala, 256 Uganda
ethelnakimuli@chs.mak.ac.ug

Research in context

Evidence before this study

van Luenen and colleagues reviewed 62 randomised clinical trials done since 1996, which investigated the effectiveness for people living with HIV of various psychosocial interventions aimed at decreasing depression and anxiety, and improving quality of life and psychological wellbeing. A range of psychosocial intervention types including cognitive behaviour therapy, supportive interventions, and meditation seemed to be helpful in improving the mental health of people living with HIV, although the effect size was small. Chuah and colleagues reviewed 45 studies published worldwide before October, 2015, and described interventions and approaches to integrating HIV and mental health services. Both reviews revealed a shortage of research in low-income and middle-income countries, and scarce data on longer-term effectiveness, cost-effectiveness, and effect on HIV treatment outcomes, particularly at the health system level. Chibanda and colleagues reviewed five randomised controlled trials based on the principles of cognitive behaviour therapy from low-income and middle-income countries for people living with HIV, which were effective in reducing depression and anxiety symptoms. None of the studies were from sub-Saharan African. Although there are several well-documented studies from non-HIV settings in low-income and middle-income countries that support the use of psychological interventions delivered by lay health workers, such task-shifting approaches have not been used to provide mental health care for people living with HIV.

Added value of this study

To our knowledge, this is the first study in sub-Saharan Africa to use task-shifting strategies to evaluate long-term effectiveness, cost-effectiveness, and HIV treatment outcomes of a culturally sensitive psychological treatment for mild to moderate major depression in a large sample of people living with HIV. Group support psychotherapy based on the principles of cognitive behaviour theory, social learning theory, and the sustainable livelihoods framework is not only effective against depression in the long term but also reduces post-traumatic stress symptoms, alcohol use, improves antiretroviral therapy adherence, and is cost-effective in a primary care setting. Also, the study shows that group support psychotherapy is attractive to men. Consequently, its integration into existing HIV care platforms might confer additional value, particularly in engaging men in HIV treatment services, thereby improving the health of the entire community.

Implications of all the available evidence

Study findings indicate that it is possible to overcome barriers of poverty, remoteness, mental health stigma, and cultural ignorance to provide a comprehensive HIV care model to people living with HIV in rural areas. Lay health workers delivering group support psychotherapy for depression care within routine primary HIV care in a low-resource setting might have the potential to accelerate the attainment of the UNAIDS 90-90-90 targets, which aim to diagnose 90% of all HIV positive people, provide antiretroviral therapy for 90% of those diagnosed, and achieve viral suppression for 90% of those treated.

WHO recommends the use of psychological interventions as first-line treatment for depression in low-income and middle-income countries. However, evaluations of the effectiveness and cost-effectiveness of such interventions among people with HIV are scarce.[4] HIV-positive populations across sub-Saharan Africa suffer an enormous socioeconomic disadvantage, with most having lower education, living in poverty, without an income-generating activity, with food insecurity, and potential exposure to a high amount of stigma and discrimination.[5] These environmental stressors precipitate and perpetuate mental health problems such as depression, which is often comorbid with post-traumatic stress, alcohol use problems, or both.[6]

To attend to the socioeconomic disadvantage among people living with HIV, we developed group support psychotherapy (GSP)—a culturally sensitive cognitive-behavioural-based intervention that treats depression by enhancing emotional and social support, positive coping, and livelihood skills.[7] The effectiveness of GSP in treating mild to moderate depression among people living with HIV has been shown in a series of pilot studies.[8–11] However, evaluation of its effectiveness and cost-effectiveness when delivered by trained lay health workers (LHWs) among people with HIV has not been shown to date.

The purpose of this study was to primarily establish the effectiveness of GSP delivered by lay health workers for depression treatment among people living with HIV in rural areas on a large scale. Secondary objectives included assessing the effect of GSP on comorbid mental health problems, HIV treatment outcomes (ART adherence and viral load), and the cost-effectiveness of implementing GSP. We hypothesised that GSP delivered by trained lay health workers would result in a greater reduction in depression cases and comorbid mental health problems, improved functioning, and better HIV treatment outcomes over the long term, and would be more cost-effective, than group HIV education (GHE) delivered by similar cadres.

Methods

Study design

This was a pragmatic two-arm cluster-randomised trial in which 30 primary health centres (clusters) across three districts (Gulu, Kitgum, and Pader) in post-conflict, rural northern Uganda were randomly assigned to deliver either GSP or GHE. The study protocol is published[12] and registered with the Pan African Clinical Trials Registry, PACTR201608001738234. The study was submitted to and approved by both the Makerere University College of Health Sciences Research Ethics Committee and the

Uganda National Council of Science and Technology. A Data and Safety Monitoring Board oversaw the study.

Participants

Health centres eligible for the trial had to offer HIV services, and nominate at least four LHWs who were actively involved in HIV care, able to read and write, and resided within the villages served by the centre. Participants were people living with HIV, aged 19 years and older, with mild to moderate depression assessed with the Mini International Neuropsychiatric Interview (MINI) depression module, taking ART, and anti-depressant-naive. Individuals with high suicide risk, a severe medical disorder such as pneumonia or active tuberculosis, psychotic symptoms, and hearing or visual impairment were excluded from the study. Details of the recruitment process and protocol deviations have been published elsewhere.[13] All study participants provided written informed consent. Each participant received UGX8000 (US$2·16) and the group facilitator received UGX80 000 ($21·62), at the end of treatment, to defray costs that they might have incurred to get to the group session (eg, childcare costs or income they might have foregone).

Randomisation and masking

Health centre managers were invited to a stakeholders' meeting held at the district's local government offices. Study purpose and procedures were explained to facilitate district leadership understanding of the trial activities. Randomisation of health centres was achieved by urn (health centre managers separately picked a paper containing the intervention allocation from a basket; ratio 1:1). By design, both experimental and control interventions were identifiable to participants and outcome assessors, but masked to the Data and Safety Monitoring Board, and data analysts up to 12 months post-treatment.

Procedures

Primary care health workers gave a health talk on depression to clients in the waiting area. Clients who felt that they had had the symptoms of depression described were invited for further evaluations on the same day. Clients diagnosed with major depression by the health worker who gave the health talk were approached by research assistants who explained study procedures, established eligibility, and then obtained informed consent. Each client who gave informed consent received baseline assessments with a standardised questionnaire. Recruited participants from the same village were assigned to a trained LHW residing in or near their village to receive either GSP or GHE.

The content of the GSP and GHE interventions has been described in previous publications.[10,11] Briefly, the first GSP session addressed issues relevant to group process, ground rules, and expectations. In the second session, participants were educated about triggers, symptoms, and treatment options for depression. Also, participants were educated on the relationship between depression and HIV. Participants were asked to share personal problems in the third and fourth sessions. In the fifth session, participants were taught positive coping skills, particularly skills to manage depressive thoughts and excessive worries. Problem-solving skills and skills for coping with stigma and discrimination were taught in the sixth session. The last two sessions were dedicated to training participants in income-generating skills.

GHE was designed and delivered in a similar format to GSP. The first session of GHE focused on introductory issues, the rationale of HIV education, and orientation. In the second session, participants were taught about the progression of HIV in the body. The third and fourth sessions covered transmission and prevention of HIV infection. Mother-to-child transmission and prevention were taught in sessions five and six. The last two sessions focused on basic facts about ART. Group members were allowed to ask questions at the end of every session. Details of the training of the LHWs are presented in the appendix (p 2).

See Online for appendix

Strategies to ensure treatment fidelity in both treatment groups included the use of standardised intervention materials, structured health worker training, ongoing supervision, and training a larger number of LHWs than was required in order to avoid potential disruptions due to illness or job transfers.

Outcomes

The primary outcomes were major depression and functioning 6 months after the end of treatment. Major depression was assessed by means of the MINI.[14] A diagnosis of current major depression was made if a study participant positively endorsed five or more questions related to depression symptoms and the one question related to functional impairment over the 4-week period before the interview. Functioning was assessed by means of a five-item locally developed function assessment method.[15] Scores range from 0 to 10 and were modelled as a continuous variable. The measure attained a Cronbach α reliability coefficient of 0·86. Secondary outcome measures included symptoms of post-traumatic stress disorder, suicide risk, alcohol use, coping skills, HIV-related stigma, adherence to ART, viral load, and cost-effectiveness. Instruments used to measure these outcomes, and the measurement schedule, are shown in table 1.[16–21] Cost-effectiveness was also estimated.

The study cohort was monitored for suicide attempts continuously and when an attempt occurred it was reported to the group facilitator who in turn informed the study team, which took steps to confirm the incident. Once confirmed, the incident was recorded on an adverse event form which was forwarded to the principle investigator, the Institutional Review Board, and the Data and Safety Monitoring Board. Therefore, at each assessment timepoint, all participants received a suicide

	Instrument	Data collection schedule (months)			
		0	2	6	12
Sociodemographic variables	Standardised Demographic Questionnaire asked for descriptive information including age, gender, number of children, education, relationship, and employment status. Employment status was categorised into unemployed, employed, and peasant farmer. Relationship status was categorised into never married, married or living with a partner, divorced/separated, or widowed. Education status was categorised into primary or no formal education and secondary and above	X	..	..	..
Secondary outcomes					
Depression symptoms	Self-Reporting Questionnaire (SRQ-20)[16] scores were modelled as a continuous variable and the measure attained a Cronbach's α reliability coefficient of 0·77	X	X	X	X
Suicide risk	The SAD PERSONS scale was used to assess the suicide risk.[17] The total score ranges from 0 to 10. Scores of <4 (low risk); 5–7 (moderate risk); 8–10 (high risk)	X	X	X	X
Post-traumatic stress symptoms	Locally adapted Harvard Trauma Questionnaire.[18] The total score ranges from 16 to 64 and a total score ≥36 is indicative of post-traumatic stress disorder	X	X	X	X
Alcohol use	10-item alcohol use disorders identification test (AUDIT).[19] The total score ranges from 0 to 40 and a score of ≥8 is indicative of hazardous use. AUDIT scores were modelled as a continuous variable. In this study population, the measure attained a Cronbach α of 0·95	X	X	X	X
Coping skills	A modified coping inventory to assess a broad range of both positive and negative coping responses.[20] Responses were based on a four-point scale. For each coping strategy, the scores range from 2 to 8, with higher scores indicating frequent use of the coping strategy. A binary variable was created whereby frequent use of 1 or more coping skills was coded 1 while non-use was coded 0	X	X	X	X
HIV-related stigma	To measure internalised stigma, we used the brief AIDS-related stigma scale.[21] Responses were based on a four-point Likert scale. The scores ranged from 8 to 32 with high scores indicating higher levels of internalised stigma	X	X	X	X
Adherence to antiretroviral therapy	One question—during the past week, on how many days have you missed taking all your medication doses?	X	..	X	X
Viral load	HIV clinics routinely assess viral load of clients once a year. Measures of viral load were obtained from the medical charts of study participants, but the actual assay used to measure viral load in the laboratory was not recorded. Viral load was treated as a categorical variable indicating suppression (coded 1) or non-suppression (coded 0) of viral load	X	..	..	X

Table 1: **List of study measures and data collection schedule**

risk assessment and the total attempts that had occurred before that timepoint were recorded.

Intervention costs were analysed by means of ingredient-based costing from the health-care-sector perspective.[22] Programme costs were taken to be third-party payer costs. Programme activities were valued according to reimbursement agreements between the programme and service providers or participants. Other items used in the programme were valued according to market prices. Costs were classified according to major expenditure lines and estimated retrospectively by means of programme accounting and financial and administrative records. Additional cost data were identified from grey and published literature. The main programme costs were related to training (both primary health centre health workers and LHWs), ongoing support supervision and follow-up, development of learning materials (including training manuals), and facilitation of Community Advisory Boards. Time spent by LHWs during the programme, especially on facilitating group sessions, was also established and valued based on their estimated earnings. The value of voluntary time for LHWs in Uganda has been estimated at $199 per month, which translates into about $7·0 per full-time equivalent (FTE) day.[23] A total of 60 LHWs attended a 5-day training course under GSP (5 FTE days per LHW), and each facilitated eight group sessions of 3 h (3 FTE days per LHW). The LHWs were compensated $21·62 for their time spent on group sessions under GSP. Under GHE, a total of 60 LHWs attended the 2-day training course (2 FTE days per LHW) and facilitated eight group sessions of 3 h (3 FTE days per LHW); they were equally compensated with $21·62 at the end of the treatment. The health workers who facilitated the training of trainers were provided with a facilitation allowance to compensate for their effort beyond their routine work. We included health-care costs due to hospitalisation estimated on the basis of inpatient bed days in a public health facility.[24] All costs were standardised and reported in 2017 US$, by use of the exchange rate of $1=UGX 3500. Total costs attributable to implementing GSP and GHE were established. In addition, the unit cost of achieving a reduction in the mean depression score for the participating cohort was derived by comparing baseline depression scores and those at endline (12 months).

Whereas the primary outcomes of this study included depression cases and function scores, the cost-effectiveness analysis (CEA) used depression as the only primary measurement outcome. The effectiveness measure we adopted for the CEA analysis—the mean scores of depression—was an intermediate outcome measured at baseline, 6 months, and 12 months to ascertain the effect of the intervention on depression control. This intermediate outcome was then mapped on to a long-term outcome—disability-adjusted life-years (DALYs). The DALY is a measure that combines years of life lost owing to premature mortality (YLL), and years of life lost

owing to time lived in states of less than full health or disability (YLD).

The YLD component of the DALY was estimated by means of several parameters, including disability weights for depression.[25] Several studies have indicated that most depression cases among HIV patients are diagnosed when they are mild or moderate.[26,27] On the basis of these studies, we used the WHO disability weights for both mild and moderate depression. Other parameters used include: age at onset of depression, duration of disability, and the target population. The YLL is based on the number of deaths and the standard life expectancy at age of death in years. For the CEA analysis, participants were categorised into five age groups of varying intervals, with the lowest age group being 19–29 years, and the highest being 70–79 years. On the basis of expert opinion we assumed an average of 5 years for each age group since the onset of the condition. The DALYs were estimated by means of the WHO DALY calculator, an Excel-based model,[28] and later discounted at a 3% rate.

Incremental CEA was done to compare the GSP and the GHE study groups by estimating the difference between baseline DALYs and endline DALYs and comparing across the two intervention groups, to derive an estimate of DALYs averted (ie, incremental effects). The difference between each intervention group's costs was also estimated (ie, incremental costs). The difference in the study groups' costs was divided by the difference in the groups' outcomes or DALYs averted. This yielded the incremental cost-effectiveness ratio (ICER), which represents cost per additional DALY averted. The ICER was compared with WHO's threshold values for interventions that are cost-effective.

Given that intervention costs are specific to the treatment package being offered and were compiled from the same sources, very little uncertainty was expected from the design and inputs, except for probable changes in the market prices of cost items that could introduce uncertainty to the estimate. We varied the cost estimates, the outcomes, and discount rate by plus or minus 20% in a one-way sensitivity analysis and analysed the effect on the ICER and the consequent decision.

Statistical analysis

Based on results from our pilot randomised controlled trial,[10] we assumed that the absolute difference in proportion of major depression cases at 6 months follow-up between the intervention (15%) and control groups (25%) would be 10%. By use of the formulae proposed by Hayes and Moulton,[29] and assuming the between-cluster coefficient of variation k of 0·25, a study with 12 non-matched pairs of clusters, and a cluster size of 32 people living with HIV would have 80% power of detecting a 10% reduction in major depression cases at the 5% significance level. The number of clusters was increased to 15 pairs to allow for individual-level analyses by means of multilevel random effect regression models, and the cluster size was increased to 40, accounting for a potential 20% loss to follow-up.

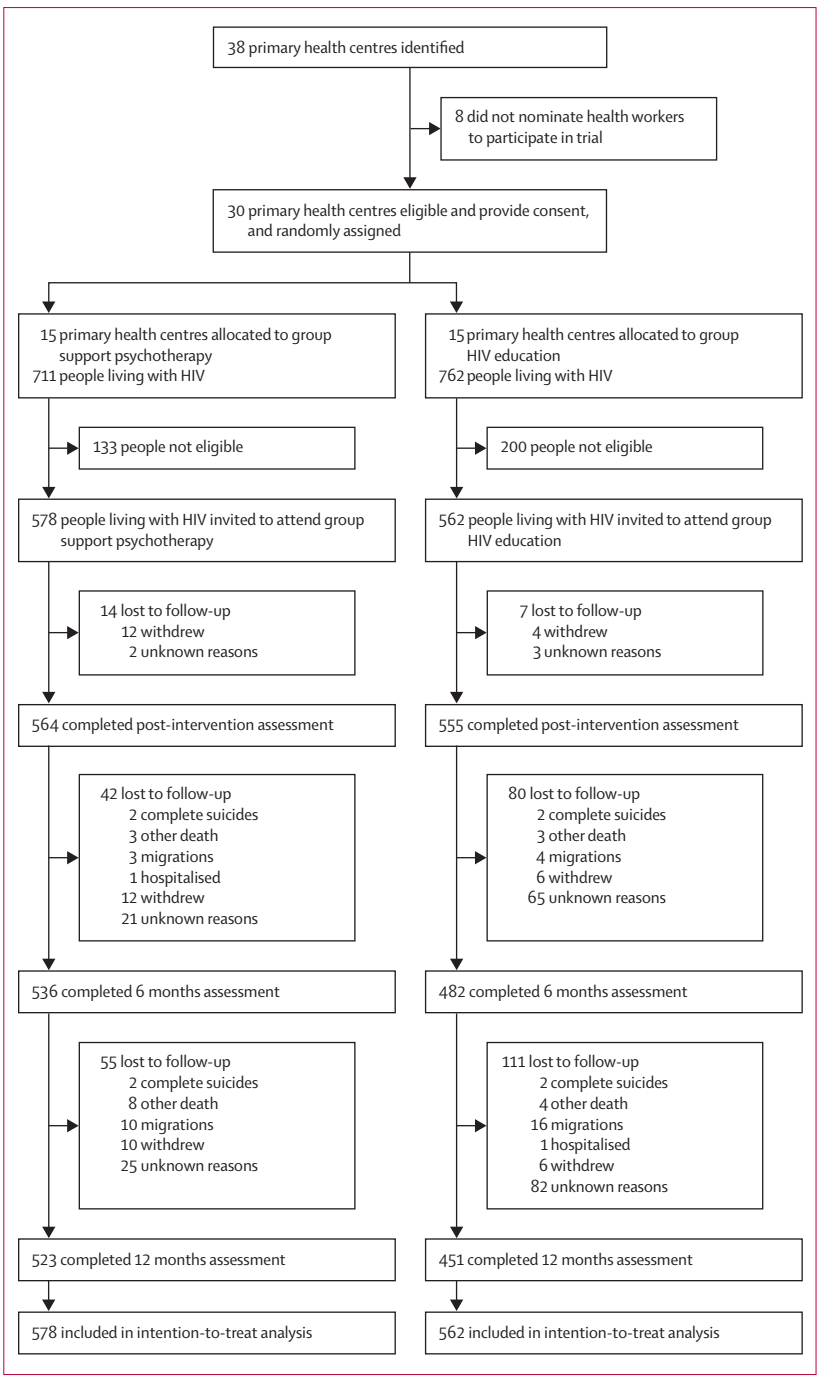

Figure 1: **Trial profile**

We analysed data in three steps. First, we did cluster-level bivariate analyses to compare baseline demographic and psychosocial characteristics between intervention and control group participants. Specifically, we used the STATA clttest command to compare cluster means across treatment groups for continuous variables and the clchi2

	Group support psychotherapy (n=578)	Group HIV education (n=562)	Cluster-adjusted χ-squared or mean difference	p value
Age (years)	38·85 (10·44)	38·06 (11·50)	−0·58	0·56
Gender				
Female	317 (55%)	295 (52%)	0·41	0·52
Male	261 (45%)	267 (48%)	..	..
Educational background				
Primary education or lower	503 (87%)	480 (85%)	0·27	0·60
Secondary education or higher	75 (13%)	82 (15%)	..	..
Occupational status				
Not employed	221 (38%)	184 (33%)	0·27	0·88
Employed	49 (8%)	64 (11%)	..	..
Peasant farmer	308 (53%)	314 (56%)	..	..
Relationship status				
Never married	57 (10%)	94 (17%)	3·52	0·32
Married or living with partner	422 (73%)	394 (70%)	..	..
Separated or divorced	44 (8%)	43 (8%)	..	..
Widowed	55 (10%)	31 (6%)	..	..
Post-traumatic stress symptoms				
Yes	443 (77%)	404 (72%)	0·57	0·54
No	135 (23%)	158 (28%)	..	..
Hazardous alcohol consumption				
Yes	166 (29%)	160 (28%)	0·00	0·97
No	412 (71%)	336 (60%)	..	..
Suicide risk				
Low	242 (42%)	244 (43%)	0·93	0·63
Moderate	309 (53%)	308 (55%)	..	..
High	27 (5%)	10 (2%)	..	..
Depression score	13·92 (4·00)	13·15 (3·92)	−1·16	0·12
Function scores β	4·35 (2·83)	5·56 (2·86)	1·58	0·18
Social-support scores	39·03 (19·62)	48·62 (18·92)	2·14	0·04
Self-esteem scores	12·60 (7·81)	14·87 (8·20)	1·08	0·29
HIV-related stigma scores	21·91 (5·61)	21·65 (4·96)	−0·25	0·80
Use of >1 positive coping skill	281 (48·62)	365 (64·95)	1·66	0·19
Use of >1 negative coping skill	420 (72·66)	430 (76·69)	0·46	0·49
Undetectable viral load (<1000 viral copies per mL)	509 (88·06)	492 (87·54)	0·01	0·93
Adherence rate to antiretroviral therapy	87% (0·75)	90% (0·65)	1·02	0·31

Data are n (%) or mean (SD).

Table 2: **Baseline study population demographic and psychosocial characteristics**

command to compare proportions across treatment groups for categorical variables.

Second, intervention effects on primary outcomes (depression and function scores) measured across three time periods (2 months, 6 months, and 12 months after treatment) were analysed by intention to treat by use of multilevel mixed effect linear regression models. In these models we adjusted for clustering in primary health centres by modelling the primary health centres as a random effect variable.[30] Two separate models were analysed in which the dependent variables were change in depression symptom scores and change in function scores. In each model, the independent variables included intervention status (representing whether there is a group difference in the dependent variable at baseline), time (ordinal variable representing the change in the dependent variable for each additional unit of time over the three periods) and the interaction of intervention status by time (representing the additional change in the dependent variable with each additional unit of time among intervention participants relative to non-participants). Potential confounders including perceived social support, stigma, negative coping skills, positive coping skills, employment status, marital status, socioeconomic status index, and adherence to ART were added to each model. The socioeconomic status index was created by doing principal component analysis of the variables of various household assets, income generated, and savings. The socioeconomic status index was modelled as a continuous variable.

We assessed moderation effects of gender, hazardous alcohol use, and probable post-traumatic stress disorder by inclusion of a three-way interaction term (intervention status×time×moderator variable) to the mixed effects linear regression models (appendix pp 4–5).

Third, secondary outcomes at 6 and 12 months after treatment were compared between the GSP and GHE group by means of cluster-level bivariate analyses. Missing data were handled directly through maximum likelihood estimation in mixed modelling. We constructed five imputed datasets assuming that data were missing at random. All participants had rich baseline data that we used to create the multiple imputation datasets. We verified that mixed model-based results were not sensitive to violations of model assumptions with permutation tests. Lastly, for primary outcomes, Cohen's *d* effect sizes were computed for the effect estimates to establish the size of the intervention effect.[31] STATA 15 statistical software was used to do all analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Between Sept 13 and Dec 15, 2016, we assessed 1473 individuals, of whom 1140 were recruited from health centres offering GSP (n=578) or GHE (n=562). Figure 1 illustrates the trial profile. Baseline socio-demographic and psychosocial characteristics are shown in table 2. 33 (6%) of 578 GSP and 15 (3%) of 562 GHE participants missed all sessions. Individuals who did not attend any group session were not excluded from follow-up assessments. 450 (78%) of 578 GSP and 502 (89%) of 562 GHE participants attended all eight group sessions. Details of group session attendance by intervention group are included in the appendix (p 1). Attrition from

	Group support psychotherapy (n=578)	Group HIV education (n=562)	Cluster-adjusted χ-squared test	Mean difference (95% CI)	p value
6 months primary outcomes					
Major depression	2 (<1%)	160 (28%)	11·20		<0·0001
Function scores	9·85 (0·76)	6·83 (2·85)	2·98	(2·16 to 3·67)	<0·0001
12 months primary outcomes					
Major depression	3 (1%)	225 (40%)	6·32		0·012
Function scores	9·87 (0·86)	5·94 (2·94)	3·93	(3·68 to 4·18)	<0·0001
6 months secondary outcomes					
Post-traumatic stress symptoms	2 (<1%)	114 (20%)	8·40		0·004
Hazardous alcohol consumption	5 (1%)	10 (2%)	0·65		0·419
Moderate suicide risk	2 (<1%)	66 (12%)	12·5		0·001
≥95% antiretroviral therapy adherence	578 (100%)	550 (98%)	18·32		0·076
SES index (lowest quintile)	238 (41%)	408 (73%)	29·34		<0·0001
Social-support scores	79·62 (6·21)	59·38 (15·46)	−20·24	(−26·81 to −13·14)	<0·0001
HIV-related stigma scores	9·07 (2·78)	16·67 (6·61)	7·50	(4·48 to 10·29)	<0·0001
Self-esteem scores	28·1 (3·71)	18·45 (9·64)	−9·64	(−13·31 to −5·64)	<0·0001
Use of >1 positive coping skill	576 (100%)	442 (79%)	12·5		0·004
Use of >1 negative coping skill	11 (2%)	220 (39%)	9·98		0·002
12 months secondary outcomes					
Post-traumatic stress symptoms	1 (<1%)	225 (40%)	10·56		0·0001
Hazardous alcohol consumption	15 (3%)	86 (15%)	6·15		0·013
Moderate suicide risk	3 (1%)	115 (20%)	8·23		0·02
Undetectable viral load (<1000 viral copies per mL)	512 (88%)	463 (82%)	0·01		0·93
≥95% antiretroviral therapy adherence rate	551 (95%)	495 (88%)	3·60		0·057
SES index (lowest quintile)	11 (2%)	386 (69%)	29·34		<0·0001
Social-support scores	78·15 (7·95)	52·45 (17·89)	−25·69	(−27·29 to −24·09)	<0·0001
HIV-related stigma scores	9·16 (5·61)	18·92 (4·96)	9·76	(9·08 to 10·43)	<0·0001
Self-esteem scores	29·62 (2·42)	13·90 (9·49)	−15·71	(−16·52 to −14·92)	<0·0001
Use of >1 positive coping skill	578 (100%)	329 (59%)	9·38		0·002
Use of >1 negative coping skill	1 (<1%)	314 (56%)	17·20		<0·0001

Data are n (%) or mean (SD).

Table 3: **Cluster-level bivariate analyses of outcomes**

the study was significantly more common in the GHE than GSP group at 6 months' follow-up (79 [14%] *vs* 41 [7%]; p=<0·001) and at 12 months follow-up (111 [20%] *vs* 55 [10%]; p<0·001). Participants lost to follow-up at both periods of assessment did not differ significantly on baseline sociodemographic variables; however, there were differences in baseline psychosocial and HIV treatment outcomes. Overall, those lost to follow-up at 12 months had reported significantly lower suicide risk, fewer traumatic experiences, lower prevalence of adherence to ART, and higher viral loads at baseline than those retained in the study. Details of differences between study completers and non-completers are presented in the appendix (pp 6–8).

Regarding primary outcomes, two (<1%) participants in the GSP group were diagnosed with major depression 6 months post-treatment compared with 160 (28%) in the GHE group (adjusted odds ratio=0·01, 95% CI 0·003–0·012, p<0·0001 [Cohen's *d*=1·28]; table 3). Similarly, those in the GSP group reported higher mean function scores 6 months post-treatment (9·85 [SD 0·76]) than did those in the GHE group (6·83 [2·85]; β=4·12; 95% CI 3·75–4·49, p<0·0001 [Cohen's *d*=1·44]; table 3). than did participants in the GHE group. β coefficients refer to the two-way interaction of intervention status by time (representing the additional change in the primary outcome with each additional unit of time among GSP participants relative to non-participants). Figures 2 and 3 illustrate mean depression symptom scores and mean function scores from baseline to 12 months post-treatment. These effects were modified by gender and baseline probable post-traumatic stress disorder but not baseline hazardous alcohol use in the long term. Results of moderator analyses are included in the supplementary materials.

Regarding secondary outcomes, substantially fewer GSP than GHE participants reported post-traumatic stress symptoms, suicide risk, and hazardous use of

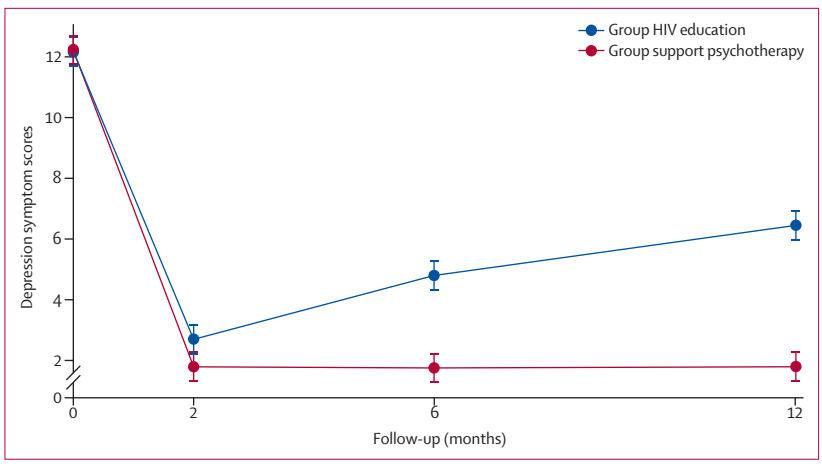

Figure 2: **Effect of group HIV education and group support psychotherapy on mean depression symptom scores**
Error bars=95% CI.

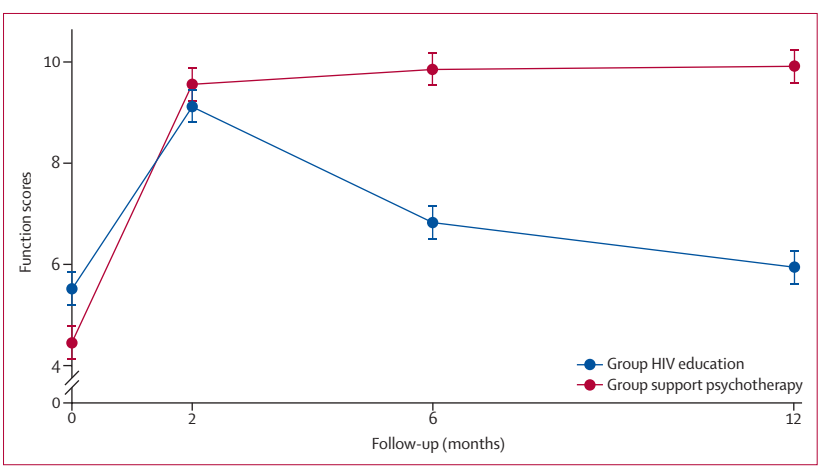

Figure 3: **Effect of group HIV education and group support psychotherapy on function scores**
Error bars=95% CI.

alcohol, and GSP participants had better adherence to ART. Viral load suppression was similar between the two groups. Details are shown in table 3.

As of Dec 30, 2018, a total of 36 individuals had 63 serious adverse events. These included 25 suicide attempts and 22 hospital admissions for medical complications. The outcomes of these serious adverse events included 16 deaths (GSP=10; GHE=6), four of which were completed suicides (GSP=2; GHE=2), and 12 of which were HIV-related medical complications (GSP=8; GHE=4). All participants who attempted suicide were referred to the district hospital or health centres with mental health workers for hospitalisation but only 12 made it to the hospital. 13 could not afford or refused hospitalisation owing to lack of transportation costs and inadequate social support. These participants were kept under close observation by relatives or group members and received home visits from trained LHWs who facilitated their groups. Overall, 20 affected individuals recovered from the serious adverse event.

The total cost of implementing the GSP programme was estimated at $29 718, compared with $24 580 for the GHE programme. Up to 22 study participants were hospitalised at the district hospital for various adverse events. The 2014 survey in Uganda reported that the average length of stay for inpatients at district hospitals in Uganda was 10 days.[32] Relatedly, the ABCE study reported that an inpatient bed day at a district hospital costs $17 (provider costs).[22]

Using these estimates, we found that up to $3740 was spent on health-care or hospitalisation costs. Hospitalisation costs were borne by the health-care sector and not the third-party payer (programme), or the patient. Based on the assumption that 50% of hospitalised participants belonged to either of the groups, the hospitalisation costs are shared between the GSP and GHE programmes ($1870 for each group). A summary of the intervention costs is in the appendix (p 9). The highest share of costs for the GSP programme was for training of trainers and the LHWs to implement the programme (66·5%), followed by facilitation of group sessions of people living with HIV (9·2%). For the GHE programme, the highest share of costs was for training (32·8%), followed by supervision costs (28·8%) and facilitation of group sessions (10·8%). The reduction in mean depression scores between baseline and 12 months was 13·68 for GSP and 6·19 for GHE, resulting in an estimated average cost per mean depression score decline of $2172 for GSP, and $3970 for GHE.

For CEA, we used the DALY estimates (YLL+YLD) averted as a long-term measure of programme effectiveness. In estimating the YLL, we used standard life expectancy and mortality. From the available data, up to 16 participants died in the follow-up period. All mortality occurred within the age group of 30–49 years, with an average of 39 years at death. The average life expectancy for Uganda in 2016 was 62·5 years.[33] Applying this data to the WHO DALY estimator shows 282 YLL under the GSP compared with 169 YLL under GHE. The baseline mortality among the GSP and GHE groups was assumed to be zero. The study found a reduction in DALYs, from 961·4 at baseline to 347·9 at endline under the GSP programme, and from 891·4 at baseline to 685·9 at endline under the GHE programme. Compared with baseline, there were reductions in DALYs across both treatment groups, although the reductions were more under the GSP compared with the GHE. The GSP intervention achieved 595·6 DALYs averted compared with 199·5 DALYs averted for the GHE intervention, after discounting at 3%. The difference between the two intervention programmes was 396·1 DALYs averted (table 4). The cost-effectiveness estimates show an ICER of $13·0 per DALY averted, from the health care sector perspective. According to WHO, interventions are very cost-effective if the ICER is lower than the gross domestic product (GDP) per capita, cost-effective if less than three times the GDP per capita, and not

	YLD* (baseline)	YLD (12 months)	YLL (at 12 months)	DALYs (at 12 months) YLL + YLD	DALYs averted (3% discount)	Total cost (US$)	Incremental cost (US$)	Incremental YLDs averted (discounted 3%)	ICER (per DALY averted)
Group support psychotherapy	961·4	65·9	282	347·9	595·6	29 718	..	..	..
Group HIV education	891·4	516·9	169	685·9	199·5	24 580	5138	396·1	$13·0

YLD=years of life lost owing to time lived in states of less than full health or disability. YLL=years of life lost owing to premature mortality. DALYs=disability-adjusted life-years. *Both mild and moderate depression conditions and their disability weights were used in the estimates of YLD.

Table 4: **Incremental cost-effectiveness ratio**

cost-effective if greater than three times the GDP per capita. The Uganda GDP per capita in 2017 was estimated at $606 (World Bank 2017).[34] Thus, a $13·0 ICER is considered very cost-effective, implying that compared to the GHE intervention, the GSP intervention programme was more cost-effective with an ICER per DALY averted of $13·0 (table 4).

A univariate sensitivity analysis was done by use of major ICER parameters—the costs, discount rate, and outputs (DALYs averted). A Tornado plot (not shown here) showed that costs and discount rate had little influence on the ICER; rather, it is the outcome (DALYs averted) that had the biggest effect. Any changes in costs and discount rates do not necessarily have a huge effect on the estimated ICER. For example, 20% reduction in discounting outcomes would lead to an ICER of $13·04 (20% increase in discount rate) and $12·9 (for a 20% reduction in discount rate). In addition, a 20% reduction in DALYs would lead to an ICER of $13·2. This implies that changes in considered parameters by 20% would not alter the decision about cost-effectiveness. In fact, under the circumstances, programme costs would need to increase by more than 1000% to hit the threshold of not cost-effective.

Discussion

GSP delivered by trained LHWs in routine HIV care settings is effective in the treatment of mild to moderate major depression. GSP produced a profound effect on major depression, with almost all participants achieving remission by 6 months after treatment and remaining depression free 12 months later. Similarly, the effect on functioning was equally profound with GSP participants achieving and sustaining higher function scores 12 months later.

Such strikingly positive results could be explained in several ways. First, unlike the GHE intervention, GSP has known active ingredients (emotional and social support, positive coping skills, and income-generating skills) which are potent buffers against depression. The active ingredients not only address emotional symptoms but also major risk factors for depression including stigma, discrimination, and socioeconomic disadvantage (poverty).

Furthermore, people with HIV and depression were involved in the development of GSP. They endorsed the active ingredients and suggested the cultural aspects to be considered during delivery of group sessions. Also, previous research indicates that group therapeutic processes including catharsis, altruism, and socialisation techniques were encountered by GSP participants.[11] Therefore, it should not be surprising that they effectively pushed back depression more than GHE participants.

The effects of GSP treatment on depression and functioning were present among both men and women, but unlike other trials in Uganda,[35] the magnitude of the effects was largest among male participants. Given the low participation of men in health interventions in low-resource settings,[36] this finding suggests that integrating GSP for depression treatment into existing HIV service delivery platforms might confer additional value, particularly in attracting men and engaging them in HIV treatment services, thereby improving the health of the entire community.

The effects of treatment on secondary outcomes related to suicide risk, post-traumatic stress symptoms, and hazardous use of alcohol suggests that GSP has adequate intensity to resolve mental health difficulties in people with multiple psychosocial challenges. This is particularly important for communities facing adverse living circumstances such as refugees or those residing in post-conflict areas where depression and comorbid mental health problems are generally the rule rather than the exception.[37]

Initially, major improvements in depression, hazardous alcohol use, and post-traumatic stress symptoms were observed in both intervention groups; however, these improvements were sustained more among GSP than GHE participants. Initial improvements could be explained by therapeutic factors common to both interventions such as a supportive environment, and therapeutic alliance, which generate positive feelings. However, since GHE lacks the active elements of GSP such as opportunity to express emotions, and acquisition and practice of positive coping skills and livelihood skills, positive feelings generated might not be sustained.

Previous longitudinal studies from high-income countries have long established the detrimental effects of depression, hazardous alcohol use, and post-traumatic stress symptoms on the progression of HIV disease.[38] Since improvement in depression and comorbid mental health problems coincides with improvement in ART adherence, a causal association is probable between these mental health problems and ART adherence.

Future secondary data analyses will explore the mediating role of these mental health issues in the observed association between GSP and ART adherence.

The complication of attempted suicide was expected given that 10–15% of outpatients with major depression attempt suicide in their lifetime.[39] Although our study population had a low suicide attempt rate (2·2%), the risk for suicide risk persisted and increased more in GHE than GSP participants, thereby rendering GSP the safer intervention to use in the long term.

A similar lack of improvement in viral suppression was observed in the long term for both interventions. Intervention differences in the effect on viral suppression might have been missed by the use of 1000 viral copies per mL, which is a conservative threshold to define ART failure. Studies in low-resource settings have shown that this threshold misclassifies patients who harbour resistant virus as non-failing.[40]

The gains in reduced depression can be considered cost-effective because the ICER of $13·0 per DALY averted by GSP compared with GHE is less than the Ugandan GDP per capita of $606. Sensitivity analysis showed that modifying programme cost estimates that affect the ICER by plus or minus 20% would not alter the cost-effectiveness decision, and would have to increase substantially by more than 1000% for GSP to become not cost-effective. The main factor that would substantially alter the ICER is the changes in health outcomes—in this case the DALYs averted. One of the main factors that could have contributed to the cost-effectiveness of this programme is the reliance on LHWs, who are essentially volunteers and are generally not paid any monthly stipends, but rather small incentives in appreciation of their engagement with programmes. The study was done in an area that is recovering from armed conflicts and among the poorest areas in Uganda. This partly explains the low market values for labour. Likewise, the policy environment of the study has low market prices for community volunteers. For instance, Ministry of Health guidelines for community health volunteers propose an allowance of $3 per month to LHWs.[41] This substantially reduces the cost that would be spent on professional trained health workers, yet it delivers the same package of services. In India, two trials of depression treatment among non-HIV populations reported reduced depression when LHWs or counsellors were used to deliver psychological or psychotherapy treatment to affected individuals. When the quality-adjusted life-year was used as the outcome measure, the India study, however, found that the Healthy Activity Program was cost-effective only if broader societal effects were considered.[42] Another task-shifting study found greater improvements in health outcomes among the intervention group compared with the control; time costs were also found to be significantly lower in the intervention group than in the control. However, health system costs were not significantly different between the two groups.[43]

Although GSP produced a significant reduction in depression at a cost that is acceptable compared with GHE, these results should be viewed in light of the following limitations. First, outcome assessors were not masked; therefore, detection bias could have affected the outcome measurement. Second, self-report is not the most reliable measure of ART adherence; therefore, our adherence estimates might represent an overestimate. However, a gold standard for adherence assessment does not exist and different assessment methods have been used in different studies.[44] Third, the retrospective use of conservative viral load suppression threshold results from clinical files which are only taken once a year might not represent an accurate measure of viral loads for the assessment period. However, the study could not afford viral load measures which cost up to $400 per person. Also, the cost-effectiveness analyses from a societal perspective were impossible to do, given limitations in data captured through the study. In addition, costs on food and other related non-health out-of-pocket patient expenses were not included because they were negligible given the low number of hospitalisations reported. Lastly, given a follow-up period of only 1 year, extrapolation of costs over the future to rhyme with the computation of outcomes was not done because it would not give a reliable picture. Nonetheless, the approach taken in the CEA analysis, although it might not have been so robust, still provides policy and programmatic insights, especially for data challenged settings.

Despite these limitations, the study had several strengths. First, it was a cluster randomised trial with a real-world sample of people living with HIV with multiple socioeconomic disadvantages that are often screened out of randomised trials. Second, the study includes an endpoint of 12 months. Moreover, follow-up of study participants will continue until 2 years after the end of treatment. This allows for evaluation of sustainability of intervention effects. Third, the study included a large sample size with a male to female ratio of almost 1:1. Developing GSP in consultation with community members with depression and tailoring it to the social context might explain its success in attracting both men and women living with HIV.[8] Fourth, similar to the previous pilot trial,[10] the study achieved a high proportion of treatment completion, which confirms the feasibility and acceptability of GSP in the targeted population. Lastly, the use of an active control group—GHE—ensured that both intervention groups were exposed to the group dynamics of simply meeting together, the attention of a group facilitator and education about HIV, its relationship with depression, and the importance of ART adherence. Therefore, we can confidently attribute the effects of GSP to its active ingredients: learning to seek emotional

and social support, and practising positive coping skills and income-generating skills.

These findings indicate that it is possible to overcome barriers of poverty, remoteness, mental health stigma, and cultural ignorance to provide a comprehensive HIV care model to people living with HIV in rural areas. Integrating GSP into existing HIV service delivery platforms is an important step in helping treat and manage mild to moderate major depression in this population.

Contributors

EN-M, KW, JO, SM, SN, RM, JB, EJM, and JBN conceptualised the study and EN-M sought and obtained funding. EJM and OH did statistical analyses. FS and CM did the cost-effectiveness analyses. EN-M and JO managed the literature searches. EN-M, RM, EJM, and JBN wrote the initial manuscript. SM, RM, MN, ME, EJM, and JBN revised the manuscript critically for important intellectual content. All authors contributed to the final manuscript.

Declaration of interests

EN-M holds the copyright for the group support psychotherapy manual. All other authors declare no competing interests.

Data sharing

The de-identified data set and a data dictionary will be made available with publication of the trial after obtaining relevant Institutional Research Ethics Board approval of a proposal and signed data access agreement.

Acknowledgments

The SEEK-GSP study is funded by Grand Challenges Canada (grant #0770-05) and the MQ Mental Health Fellowship Award (grant #MQ15FIP100024).

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