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# Multi-Component Intervention to Improve Health Outcomes and Quality of Life Among Rural Older Adults Living With HIV

**ClinicalTrials.gov Study Protocol and Statistical Analysis Plan**

**May 23, 2023**

## METHODS

### Participants and Procedures

Inclusion criteria for the study were (1) 50 years of age or older; (2) self-reported HIV-positive status; (3) residence in a rural zip code or county within 9 southern US states, including Alabama, Arkansas, Georgia, Kentucky, Mississippi, Missouri, Oklahoma, South Carolina, and Tennessee; (4) self-reported willingness to participate in support groups and to provide a dried-blood spot sample; (5) access to a telephone at home; and (6) ability to provide informed consent. Participants met the rural residence eligibility criteria if they resided in a zip code classified as a "Small and Isolated Small Rural Town" area by Rural-Urban Commuting Area Codes (RUCAs),[1] and/or in a county classified as rural based on RUCAs, and/or in a county with a score of .4 or higher on the index of relative rurality (IRR).[2]

We recruited participants using several passive mechanisms. We engaged in partnerships with 15 AIDS service organizations (ASOs) that serve rural clientele in the target southern US states. Partner agencies distributed recruitment materials by mail and/or displayed materials within their facilities. We also placed advertisements on social media sites, using targeted algorithms to deliver ads based on age and geographic location. Ads were also placed on two HIV-specific informational websites. Finally, we used a research registry of participants engaged in research previously to invite potential participants, based on demographic information, to be screened for eligibility for this study.

Interested individuals completed screening either online—by directly clicking on an online ad, or by entering the website listed on recruitment materials—or by calling the study phone number, after which study staff would verbally complete the screener with participants. For eligible participants, informed consent was subsequently completed either online or over the phone.

Following consent, patients completed a baseline survey either online or through a paper survey mailed to them (see Measures) and self-collected and returned a dried blood spot (DBS) kit to assess HIV viral load (see HIV Viral Load Testing). Following baseline survey and DBS completion, participants were randomized to one of 16 conditions (see Study Design and Randomization) and invited to participate in 0, 1, 2, 3, or 4 of the interventions (see Interventions). Following intervention delivery and at least 90

days after baseline survey completion, participants were invited to complete a follow-up survey and DBS kit.

This research was approved by the Medical College of Wisconsin Institutional Review Board (protocol #PRO00037672), and the trial was registered at ClinicalTrials.gov (protocol #NCT04549259).

## Measures

Unless otherwise detailed, measures were completed at both baseline and follow-up.

### *Demographics*

Participants reported their state of residence, age, gender identity, race and ethnicity, sexual orientation, education, annual income, work status, insurance type, and year of HIV diagnosis. Participants reported whether or not they currently had each of 16 comorbid health conditions (e.g., cancer, diabetes, heart disease, etc.). We coded the mode of data collection (online or on paper).

### *Primary Outcomes*

***Health-related quality of life.*** Quality of life (QOL) was assessed with 31 items from the WHOQOL-HIV BREF[3] (e.g., "How would you rate your quality of life?"). Domains assessed include physical health; psychological health; level of independence; social relationships; environmental health; and personal beliefs. Additionally, two individual items focus on overall quality of life and general health. Items focus on the past 2 weeks, and all items are responded to using 5-point Likert scales. Domain scores were created as described by the WHO, with scores within each domain ranging from 4 to 20.[4] We also created a composite quality of life score by equally weighting the 6 domains, overall quality of life item, and general health item. This composite score is in line with research supporting a single quality of life factor[3]; additionally, there was good reliability ($\alpha$ = .87-.90) for these 8 indicators. The composite score was rescaled such that overall scores ranged from 0 to 100, with higher scores indicating better health-related QOL. We focus here on overall QOL and on the personal beliefs subscale (e.g., "To what extent do you feel your life to be meaningful?").

***Depressive symptoms.*** Depressive symptoms during the past 2 weeks were assessed with the 9 items from the Patient Health Questionnaie-9 (PHQ-9)[5] ($\alpha$s = .87-.90). Participants indicated how often

they had experienced different depressive symptoms (e.g., "Feeling down, depressed, or hopeless"). Responses ranged from not at all (0) to nearly every day (3). Items were summed; higher scores indicated more depressive symptoms.

***ART adherence.*** Adherence to HIV antiretroviral medications in the past 30 days was assessed with the 3 items from the Wilson adherence scale[6] (e.g. "In the last 30 days, on how many days did you miss at least one dose of any of your HIV medication(s)?", αs = .71-.79). This scale was scored in line with Wilson et al.,[6] with scores ranging from 0 to 100 and higher scores indicating better adherence. Due to significant skew in this outcome, we created a binary variable indicating perfect adherence to HIV medications (0 = imperfect adherence, 1 = perfect adherence).

***Mediating Mechanisms***

We also assessed several factors we viewed as potential mediating mechanisms. Theorized mechanisms for the social support and stigma reduction groups were social support, loneliness, and internalized stigma. Theorized mechanisms for strengths-based case management (SBCM) were accessing needed services and the personal beliefs subscale of the quality of life measure (discussed above). Finally, a theorized mechanism for the technology detailing intervention was eHealth literacy.

***Social support.*** Social support was assessed with 19 items from the MOS Social Support Scale[7] (αs = .98). Participants indicated how often different kinds of support were available to them (e.g., "Someone who understands your problems") on a scale from none of the time (1) to all of the time (5). Items were averaged; higher scores indicated more support.

***Loneliness.*** Loneliness was assessed with 5 items from the Loneliness survey from the NIH Toolbox (αs = .95-.96).[8] Participants indicated how often during the past month they had felt various ways (e.g., "I feel isolated from others.") on a scale from never (1) to always (5). Items were averaged; higher scores indicated greater loneliness.

***Internalized stigma.*** Internalized stigma was assessed with 6 items from the internalized stigma subscale of the HIV Stigma Mechanisms scale (e.g., "I feel ashamed of having HIV," αs = .95).[9]

Responses were on a scale from *strongly disagree* (1) to *strongly agree* (5). Items were averaged; higher scores indicated more internalized stigma.

***Accessing needed services.*** Participants reported which of 12 HIV-related social and medical services they had needed during the previous 12 months (e.g., mental health counseling, help finding meals and food, transportation, etc.).[10] For those services they reported needing, participants indicated whether or not they had been able to obtain that service. A composite variable was created indicating whether participants had obtained at least one needed service (0 = no, 1 = yes).

***eHealth literacy.*** eHealth literacy was assessed with 8 items from the eHealth Literacy Scale (e.g., "I know what health resources are available on the Internet," αs = .92-.94).[11] Responses were on a scale from *strongly disagree* (1) to *strongly agree* (5). Items were averaged; higher scores indicated greater literacy.

***Feasibility and Acceptability***

These items were included only in the follow-up assessment.

***Feasibility.*** To contribute additional information related to intervention feasibility, participants provided information on why they did not participate in or complete programs (when relevant) and reasons for missing sessions. In relation to the HemaSpot kits, participants provided open-ended information on issues they encountered before, during, or after collecting their blood sample.

***Intervention acceptability.*** Participants separately evaluated the acceptability of each individual program they were randomly assigned to by indicating how much they agreed or disagreed with 6 statements (e.g., "The stigma reduction group sessions have helped me" and "I would recommend the strengths-based case management sessions to other people living with HIV"). Participants also provided open-ended responses regarding what they liked and disliked and suggestions for improvement.

**HIV Viral Load Testing**

At baseline and follow-up, participants were sent dried blood spot (DBS) kits by mail to complete self-collection of blood samples for HIV viral load testing. Each DBS kit contained a HemaSpot™ collection container, alcohol pads, lancets, gauze pads, bandages, a biohazard bag labeled with participant

ID, a postage paid envelope for specimen return, and an instruction card, written at an 8th grade reading level, that described how to collect the specimen. Participants could also call the study coordinator for additional assistance. Following specimen collection, participants placed the filled HemaSpot™ container into the shipping envelope, which sent the specimen directly to the clinical laboratory for testing. Shipping was tracked by the study team and the laboratory also logged the arrival of each specimen.

**Study Design and Randomization**

This pilot was designed to test the feasibility and acceptability of both the interventions and of a multiphase optimization strategy (MOST) design. MOST involves testing the impact of multiple interventions or intervention components simultaneously using a factorial design.[12] Therefore, using the REDCap randomization module, participants were randomly assigned to 1 of 16 conditions in a 2 (social support groups) x 2 (stigma reduction groups) x 2 (SBCM) x 2 (technology detailing) between-participants factorial design. Based on condition, participants were invited to participate in 0, 1, 2, 3 or 4 of the interventions. Information on the 16 conditions is provided in Table 1. To balance the number of participants in groups over time, randomization occurred in blocks of 32. Neither participants nor study staff were blinded to participant randomization.

**Interventions**

Prior work of our team and others identified factors that may affect health-related quality of life, engagement in medical care, medication adherence, and viral suppression. We chose interventions that aimed to increase social support, decrease HIV-related stigma, overcome participants' structural barriers to care, and increase technology use to engage in healthcare for this study. We aimed to identify evidence-based interventions—that could potentially be delivered remotely— to target each domain. Prior to enrolling participants, we conducted interviews with staff members at our community partner agencies to discuss our proposed interventions and receive input on how best to adapt their implementation for our target population. Following this input, each intervention was fully manualized and staff members were trained on the interventions they delivered.

Participants were randomly assigned to participate in zero to four of the interventions. All participants also received written information on healthy aging with HIV. Receipt of this information served as the control condition for those not assigned to any intervention group.

***Social support group-based intervention***. Social support has been identified as a factor that could affect medication adherence among older people living with HIV (PLH).[13] Researchers have demonstrated that many PLH lack needed social support, and low levels of perceived social support, isolation, and loneliness can impede medication adherence among older PLH.[14] Social support availability and satisfaction can contribute to positive health outcomes as well as reduce internalized HIV-related stigma.[15] A review of social support group interventions for PLH found they have a high impact on morbidity and retention in care as well as a positive impact on mortality and quality of life. However, the availability of support groups are limited for PLH in rural areas, and access to such services is hampered by long distances and limited transportation options. In-person groups may exclude the most vulnerable adults and may not be practical for geographically isolated rural PLH.

Based on this foundation, we adapted a supportive-expressive group therapy (SEGT) intervention[16] for online delivery to rural older PLH. This telephone-administered intervention was previously shown to reduce depressive symptoms among older PLH. However, the efficacy of SEGT for improving viral suppression, medication adherence, and quality of life among rural older PLH has not been tested.

The intervention was designed to generate social support among participants and provide them with skills and resources needed to identify and enhance other sources of social support in their lives. We adapted the intervention to allow video or telephone-only participation. The 8 weekly 90-minute sessions were held on an online platform, allowing video and telephone connectivity, and were facilitated by a licensed psychiatrist who assisted with adapting the intervention manual. Each of the 8 sessions had a specific focus: (1) introductions, overview, goal setting; (2) “Why did HIV happen to me?”; (3) values and life priorities; (4) uncertainty and lack of control; (5) doctor-patient relationship; (6) friend/family

relationships; (7) self/body image; and (8) summary and closure. We ran 3 waves of this intervention with between 9 and 11 participants in each group.

***Stigma reduction group-based intervention***. Prior work has demonstrated high levels of HIV-related stigma in rural PLH and its association with poorer care engagement and viral suppression (R01 3,14,15,16), Lucksted and colleagues published results from a 9-session group intervention, Ending Self Stigma, that successfully reduced internalized stigma related to mental illness and increased perceived social support.[17] This intervention was based on the Social-Cognitive Model of Internalized Stigma. Additional cognitive restructuring interventions have also used affirmative and validating approaches shown success in reducing internalized stigmas and improving participants' confidence and ability to cope with stigma and discrimination. (R01 29, 3). We adapted the Ending Self Stigma intervention to focus on reducing internalized stigma related to HIV. The six weekly 90-minute sessions were held online and were facilitated by a licensed psychiatrist who assisted with adopting the intervention manual for this study. Each session had a specific focus: (1) introducing stigma and eliciting participants' experiences with stigma; (2) interrupting "automatic thoughts" that perpetuate stigma; (3) strengthening self-concept; (4) increasing belonging; (5) handling disrespect and discrimination; and (6) summary and next steps. We ran 3 waves of this intervention with between 7 and 11 participants in the groups.

**Strengths-based case management (SCBM)**. Practical and logistical challenges, and other individual-level barriers can pose obstacles to care engagement and medication adherence. SBCM interventions address participants' proximal life stressors by assisting them to recognize their personal abilities and prior successes to establish self-efficacy for current and future problem solving. In practice, this may include empowering a participant to navigate issues related to employment, interpersonal relationships, medical insurance, general health, mental health, housing, or transportation. The strengths model of case management has been successful in linking recently diagnosed or out-of-care PLH to care and reducing HIV transmission risk among PLH.[18-22]

Based on the previous success of SBCM, we adapted an SBCM intervention focused on STI acquisition[23] to address barriers to HIV medical care and medication adherence. The adapted intervention

used an individually-tailored approach to address barriers elicited from each participant and was delivered by a trained study staff member through one-on-one telephone or Zoom video sessions.

The adapted intervention involved an initial session where rapport was developed between the staff member and participant, the participant's background and life challenges were discussed, and the participant was assisted in eliciting and then ranking stressors or obstacles they perceived as barriers to HIV care or medication adherence. Then, the most prominent stressor was discussed and strategies for overcoming it were developed, along with a specific action plan. A longer session was held approximately one week later, where progress was reviewed, strengths in overcoming barriers or taking action were identified, and lessons to use for future challenges were elicited. Then, new short and intermediate term goals were identified to overcome additional identified barriers. Up to 3 additional brief follow up sessions were conducted over the next three to five weeks, as needed, to check on progress on the identified action steps and tweak individual goals.

***Personalized technology detailing***. Medication adherence and care engagement can be affected by internet access and technology use among older rural PLH.[24] Technology can be leveraged to improve access to HIV and mental health care for patients in rural areas who may face challenges traveling longer distances to treatment. However, telehealth, online prescription access, or electronic medical records may be more difficult to access for older adults with lower technology literacy.[25] We developed this intervention based on the information-motivation-behavioral skills (IMB) model[26] and provided each assigned participant with individual sessions wherein they were provided with information on utilizing the internet for health-related purposes; motivating them by discussing how they could utilize the internet for learning more about their health, accessing medical or pharmacy services, and finding social or practical support; and assisting them in building their skills in using technology. The intervention used a framework viewing technology use for healthcare purposes as a continuum, as follows: (1) technology literacy or awareness; (2) access to the internet at home (including device and service); (3) use of the internet in general; and the ultimate goals of (4) utilization of the internet for obtaining medical care, pharmacy services, health-related information, and social support.

Up to 5 sessions were held with each participant assigned to this intervention. In the initial session, an assessment of current technology use was conducted. For those participants who were already at goal of technology utilization for healthcare information and services, no additional sessions were held. Up to a total of 5 sessions were held for those participants not already at goal technology utilization. The content of each session was individualized based on the participant's current status, and included education on the utility of technology in accessing health care or health information, understanding how to obtain internet access and an appropriate device (cellular-enabled tablets were made available to participants who could not otherwise afford equipment or internet access), accessing the participant's electronic health record and their pharmacy online, conducting a virtual visit with a provider, and utilizing the internet to find social support and educational materials on health topics.

**Fidelity**

Fidelity was monitored using checklists that facilitators would complete at the end of each session of each intervention tracking whether all components of the session were implemented. Early sessions of each intervention were reviewed by the principal investigators to ensure fidelity and provide feedback.

**Debriefing Interviews**

We conducted debriefing phone interviews with 14 randomly selected participants to obtain additional acceptability data and identify potential areas for modification. Debriefing interviews lasted approximately 20 minutes and were conducted by study staff not involved in delivering the interventions.

**Data Analysis**

Statistical analyses were performed with SPSS and R.[27,28] We analyzed data using an intent-to-treat principle, with participants analyzed based on the interventions they were assigned to regardless of intervention participation.

Descriptive statistics were used to summarize sample characteristics and intervention feasibility and acceptability. T-tests and Fisher's exact tests were used to compare baseline characteristics of participants who did and did not complete the follow-up assessment as well as participants assigned vs. not assigned to each intervention.

To test preliminary impact, we fit linear and generalized linear mixed models using the R package lme4. For continuous outcomes (QOL, depressive symptoms, social support, loneliness, internalized stigma, QOL personal beliefs, and eHealth literacy), we fit linear mixed models with the *lmer* function, and for categorical outcomes (medication adherence, DBS VL, and service utilization), we fit generalized mixed-effect logistic regression models with the *glmer* function and a logit link. Models included a random effect for participant and utilized all available data, including baseline data from participants missing follow-up data. Predictors (fixed effects) included time (baseline vs. follow-up), random assignment to each of the 4 interventions, and interactions between assignment to the 4 interventions and time. We adjusted for mode of survey completion, which differed for those with and without follow-up data as well as for those assigned vs. not assigned to the stigma reduction groups. Interaction terms were of primary interest, with significant interactions indicating differential changes in outcomes over time for those randomly assigned vs. not randomly assigned to different interventions. Due to the small sample size, we did not test interactions between different interventions. For continuous outcomes, we calculated Cohen's *d* as a measure of effect size using the R function *lme.dscore* in the EMAtools package, which calculates Cohen's *d* from the mixed model results. For categorical outcomes, we report odds ratios as a measure of effect size.

Given that our factorial design resulted in many "control" participants who were assigned to alternative interventions, for this pilot we also report on changes over time in outcomes for participants randomly assigned to each intervention. These changes were once again tested with mixed models that contained only participants assigned to each intervention. Here, time was the predictor of interest, and we again controlled for mode of survey administration.

All tests performed were 2-sided. Given that the study was a pilot, we used $\alpha = .25$ as a significance level cutoff and focus primarily on patterns in the data and effect sizes.

Table 1

Random Assignments in the Full Factorial Multiphase Optimization Strategy (MOST) Design

| Condition # | Social Support | Stigma Reduction | SBCM | Tech Detailing | HIV Info | *N* Assigned |
|---|---|---|---|---|---|---|
| 1 | OFF | OFF | OFF | OFF | ON | 4 |
| 2 | OFF | OFF | OFF | ON | ON | 4 |
| 3 | OFF | OFF | ON | OFF | ON | 4 |
| 4 | OFF | OFF | ON | ON | ON | 4 |
| 5 | OFF | ON | OFF | OFF | ON | 4 |
| 6 | OFF | ON | OFF | ON | ON | 4 |
| 7 | OFF | ON | ON | OFF | ON | 3 |
| 8 | OFF | ON | ON | ON | ON | 4 |
| 9 | ON | OFF | OFF | OFF | ON | 4 |
| 10 | ON | OFF | OFF | ON | ON | 4 |
| 11 | ON | OFF | ON | OFF | ON | 4 |
| 12 | ON | OFF | ON | ON | ON | 4 |
| 13 | ON | ON | OFF | OFF | ON | 3 |
| 14 | ON | ON | OFF | ON | ON | 3 |
| 15 | ON | ON | ON | OFF | ON | 4 |
| 16 | ON | ON | ON | ON | ON | 4 |

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