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PROTOCOL

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TABLE OF CONTENTS

1. Specific Aims …….....2
2. Background and Significance …….....2
    i. Figure 1: Conceptual Model ……4
3. Research Strategy …….....7
    i. Table 1: Overall Study Timeline ……..……9
    ii. Table 2: Original Relaxation Response Resiliency Program Chapters & Goals ….8
    iii. Table 3: Skills Table…….…….....10
    iv. Table 4: Study Event Timeline……...…..……...12
4. References……...22

1. SPECIFIC AIMS

Specific Aims. This is the second phase of a two-part study. In the first phase (MGH IRB Protocol #2017P000404), we adapted an existing resiliency intervention, the Relaxation Response Resiliency Program (3RP), to the needs of women ages 50 and over who are living with HIV. We conducted preliminary testing of the refined group intervention via an open pilot study (N=13 enrolled) across two sites, MGH and Boston Medical Center), and conducted individual exit interviews to solicit feedback on the intervention, including experiences with the assessment protocol, intervention content, and number and duration of sessions. Data from these interviews were used to make adaptations to the manual in an iterative fashion after each of the three open pilot groups, and the final product will now be tested via a small randomized controlled trial.

Specifically, we will conduct a randomized study (N=up to 60) of the adapted 3RP intervention among groups of women living with HIV, ages 50 and over. Our primary aim is to test the feasibility and acceptability of all study procedures; we hypothesize that our protocol will be both feasible and acceptable. We will also examine data on the effect of the intervention on primary (e.g., resilience) and secondary outcomes of interest, but these analyses are purely exploratory, and we are most interested in how well our selected measures may be sensitive to change. Secondary outcomes will include changes in measures of psychosocial distress (depressive symptoms, anxiety, social support, and quality of life) and HIV / physical health outcomes (suppressed viral load, decreased symptom burden, improved cognitive and physical status). We hypothesize that participants in the treatment condition will experience greater improvements in resilience, psychosocial distress, and HIV / physical health outcomes. Data from this second phase of the study will inform the eventual development of a full-scale randomized controlled trial.

2. BACKGROUND AND SIGNIFICANCE

2.1. SIGNIFICANCE

The number of older women living with HIV in the U.S. is growing. In many settings, people living with HIV/AIDS can expect to live close to a normal lifespan with ongoing medical care.[1–3] As of 2011, approximately 26% of people living with HIV/AIDS in the U.S. are over the age of 55; many of these individuals are among the first people in the U.S. to live with HIV over long periods of time.[4] Because new infections continue to occur among older adults (adults over 50 comprised 18% of new HIV/AIDS diagnoses in the United States in 2013), the population of older adults living with HIV will continue to grow in number.[4] It is estimated that approximately 50% of the population living with HIV will be over age 50 by 2020.[5] A significant percent of women, particularly women of color, continue to be impacted by HIV/AIDS. Twenty percent of new diagnoses in the United States in 2013 overall occurred in women,[4] and 23% of these new infections occurred in women over age 45; at the end of 2009 over 50,000 women over the age of 50 were living with HIV.[4] Overall, the proportion of women living with HIV has more than tripled in the past decade.[6,7] Thus, a significant percentage of older adults living with HIV/AIDS in the United States are women.

The experience of aging with HIV results in complex biopsychosocial challenges for women, which are experienced as stressors. The burden of managing a lifelong illness that is highly stigmatized creates an environment of chronic stress. Older adults living with HIV are at risk for additional medical illnesses that occur at disproportionate rates relative to individuals not living with HIV, including cardiovascular disease, diseases of bone health, various cancers,

and metabolic disorders.[5] The menopausal transition may also be more complicated for women living with HIV, as they experience more symptoms.[8] Older women living with HIV in particular experience greater levels of chronic pain and fatigue than their male counterparts.[9,10] Women living with HIV report lower levels of health related quality of life than men,[11] and experience greater numbers of HIV-related health events and greater mortality than men,[12] even when adjusting for use of antiretroviral therapy.[13] These biological factors serve to create a greater allostatic load than just managing HIV alone.

With respect to psychological and behavioral challenges, older women living with HIV experience high rates of anxiety and depression,[14,15] challenges negotiating healthy sexuality, and reduced adherence to antiretroviral therapy.[16,17] Fears about disclosing serostatus, potentially infecting sexual partners, negotiating safer sex practices, and rejection may deter older women living with HIV from engaging in sexual activity, which may lead to increased loneliness.[18,19] Previous literature suggests that women who are in midlife and older who experience high levels of HIV-related stigma have lower self-esteem, perform more self-silencing behaviors, and are less assertive in sexual situations.[20] This discomfort in discussing sexual behavior transcends interpersonal relationships, and older women may also fear initiating open discussions with healthcare providers about sexuality, due to concerns of that they will face prejudice and shame for being older and sexually active.[20] Many older women living with HIV choose celibacy to avoid rejection, but also to avoid HIV transmission.[19,21]

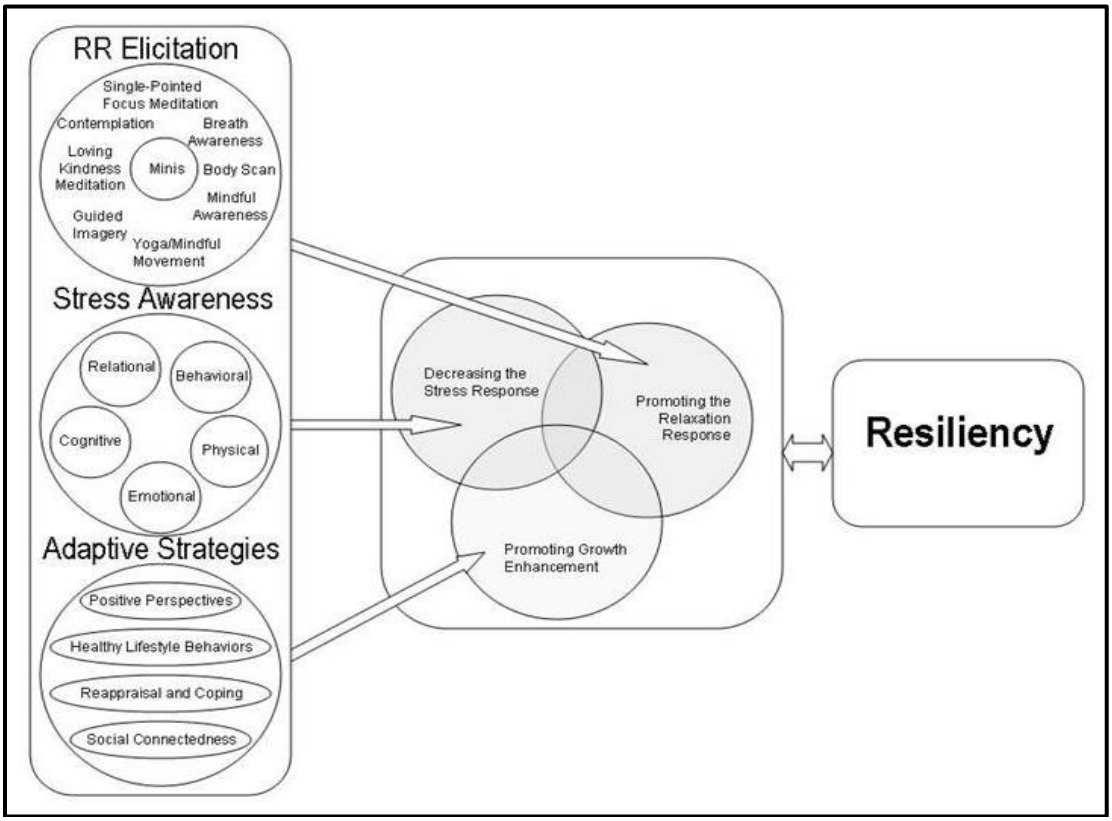
Socially, older women living with HIV report significant isolation,[22–24] which is often the result of HIV related stigma, age related stigma or both.[25,26] Older women living with HIV engage in deliberate attempts to avoid disclosing their HIV status,[25] which has been associated with increased social isolation and loneliness, even among women who report some level of social support. Fear of HIV-related stigma is heightened by age, as older women worry that it is more shameful to be an older woman living with HIV than a younger woman.[26] Older women living with HIV may also experience identity shifts, such as “empty nest” issues with the transition of adult children outside the home and serving as a caregiver to another person with chronic illness and/or grandchildren[27,28]; they may also have fewer surviving family members to rely on for support.[29]

While stress can worsen or perpetuate chronic illness,[30–33] interventions that foster resilience have the capacity to minimize the negative impact of illness-associated stressors and lead to successful aging. Resiliency is a “multidimensional construct that refers to the ability to maintain adaptation and effective functioning under significant adversity or challenging life conditions”[34] and has been identified as an important intervention when developing psychosocial treatments for older people living with HIV/AIDS,[27] particularly women. Skills that may foster resilience include increasing social support, mastery, optimism, acceptance, will to live, effective self-management, and generativity.[27,33] Resiliency interventions go beyond traditional stress management interventions by adding elements of positive psychology, which teach individuals not only how to manage immediate stressors, but also how to live purposefully, optimize health, and build “immunity” for better long term management of stress. Resilience, as well as hardiness, a construct closely related to resilience, has been associated with improved psychological and physical health, as well as overall quality of life in older individuals living with HIV.[35,36] Our team conceptualizes resilience as the ability to: (1) adapt to stress by purposefully utilizing stress reduction techniques (e.g., eliciting the relaxation response); (2) generate adaptive thoughts in response to stress; (3) actively engage in healthy lifestyle behaviors, even in the face of stress; (4) experience pleasure and appreciation, again, even in the face of stress; and (5) engage in pleasurable and empathic behaviors.[37] The 3RP intervention goes beyond traditional stress management interventions, by more explicitly

integrating positive psychology strategies (an outline of the 3RP intervention is provided) interwoven among traditional relaxation-based behavioral strategies and cognitive-behavioral skills. For example, Cognitive Behavioral Stress Management (CBSM) protocols make use of tools such as cognitive restructuring, guided imagery, breathing exercises, and communication skills, some of which are also contained in the 3RP. However, cognitive restructuring in the 3RP is focused not only on modifying maladaptive cognitions, but on eliciting a positive emotion to guide a more adaptive response and thus drawing meaning from stressful events. While CBSM focuses on enhancing social relationships, this is achieved primarily through improving communication skills. The social focus of the 3RP intervention involves an assessment of available types of social support, and in the proposed modifications, problem-solving ways to close perceived gaps in support to enhance one's sense of connectedness to themselves and others. The 3RP intervention also focuses extensively on mindful awareness skills to improve the experience of daily living.

Few interventions have been developed for older adults with HIV; none focus on women, nor do existing interventions use a "strengths based" approach. A recent review of interventions for older adults with HIV concluded that, overall, there is a dearth of interventions available for this population.[38] Of the six interventions reviewed, the study populations were all predominantly male, and none attempted to develop strengths that may affect the full spectrum of factors that influence healthy aging with a chronic illness. The authors conclude that subsequent interventions must be more "representative... of the older adult population living with HIV". Thus, the scientific community is compelled to develop interventions that may meet the specific needs of older women living with HIV.[36]

Figure 1: Conceptual model



Theoretical model: The Relaxation Response Resiliency Program (3RP).

The 3RP was developed by Dr. Elyse Park and colleagues at the Massachusetts General Hospital's Benson-Henry Institute for Mind Body Medicine (BHI).[34] It is a blending of stress management principles from the relaxation response,[39] cognitive behavioral treatment, and positive psychology. The goal of the 3RP is to decrease the physiological, emotional, cognitive and behavioral effects of the stress response by promoting the physiological, emotional, cognitive and behavioral effects of the relaxation response. To achieve these goals, the 3RP focuses on 3 major areas: (1) eliciting the relaxation response; (2) increasing stress awareness; and (3) promoting adaptive strategies (Figure 1). *Eliciting the relaxation response* involves learning strategies to reduce muscle tension, breathing rate, heart rate, and blood pressure, in order to help regulate cellular response to stress. *Decreasing stress reactivity* involves increasing one's awareness of being in the stress response (negative thoughts, emotions, physical reactions, and behaviors) and learning skills to change/alter these components (e.g., cognitive restructuring). *Adaptive strategies* focus on utilizing different techniques to promote positive growth and self-efficacy in response to stress and stressful life events. It is the learning and integration of these three core elements that enables individuals to adaptively cope with stressful situations and thus promote one's resiliency.

2.2 Preliminary Studies

The 3RP intervention. Over the past couple of years, BHI investigators have assessed the feasibility and acceptability of the 3RP with pilot trials among medical patients, clinical providers, and community cohorts. Pilot trials have shown that the 3RP is efficacious among participants, with reported post-treatment improvements in mood and positive affect, stress coping, life/work satisfaction, and resiliency. Following treatment, patients with neurofibromatosis (n=17) showed significant improvement in resiliency, satisfaction with life, stress, depression, anxiety, mindfulness and post-traumatic growth (Cohen's d=.73–1.33).[40] In terms of providers, the 3RP has been conducted with palliative care clinicians and medical interpreters. A pilot 3RP group was conducted with 16 palliative care clinicians from MGH. Clinicians completed a 3RP group treatment and showed a reduction in perceived stress (p=.03; Cohen's d=.65), an increase in perspective taking (p=.10; Cohen's d=.67) and improvements in positive affect (p=.17; Cohen's d=.42).[41] A 3RP treatment was modified to target the needs of medical interpreters (n=28) at three academic medical centers in Boston. At 4 weeks post-treatment, interpreters reported decreased stress reactivity (Measure of Current Status (MOCS-A)); specifically, participants reported feeling more assertive about their needs (p=.10; Cohen's d=.30), more able to relax at will (p=.10; Cohen's d=.35) and improvements in job satisfaction (p=.02; Cohen's d=.41).[42] We have conducted 3RP pilot work with two community samples – members of a World Trade Center cohort and veterans. Members of the World Trade Center cohort (n=27) showed post-treatment improvements in depression and PTSD symptoms (Cohen's d=.53 and .92, respectively), stress management skills (Cohen's d=1.36) and post-traumatic growth (Cohen's d=.92).[37] Sixteen veterans completed the 3RP treatment and showed improvements in post-treatment depression (p=.02; Cohen's d=.60), anxiety (p=.06; Cohen's d=.55), perceived stress (p=.04; Cohen's d=.62), and stress coping efficacy (p=.04; Cohen's d=.62).

Qualitative data to inform modification of 3RP. As part of a qualitative study funded by the Harvard University Center for AIDS Research, our team conducted semi-structured interviews with 19 purposively sampled women who were age 50 or older, had a diagnosis of HIV/AIDS, and were English-speaking to explore and understand how women living with HIV over 50 experience living with HIV.[19,43] Interviews began with a free-list activity whereby participants were asked to list the challenges faced by women over the age of 50 living with HIV. This was

followed by questions exploring the issues raised by the interviewee during the free-list activity as well as the following topic areas, which were selected after a review of the literature to identify areas important to those living with HIV, older women, or both: (1) mental health concerns/cognitive functioning, (2) sexual functioning, (3) menopause, (4) quality of life, (5) social support, and (6) management of multiple health conditions/adherence to care.

In addition to identifying challenges, participants were also able to articulate facilitators to coping well in the context of aging with HIV. With age came knowledge and understanding of what it means to live well and be resilient in the face of HIV. Participants often initially assumed that life was over at diagnosis, but the experience of growing older with HIV caused women to re-examine those beliefs. This often spurred a desire to begin "living" again. In order to live well and cope with the demands of HIV, women made their health a priority and sought ways to maximize well-being. This encompassed taking care of both body and mind by seeking emotional support from friends, family, and therapy, and making efforts to exercise and eat well. Women emphasized the need to eliminate "toxic" forces in their lives, such as drug abuse and relationships with "toxic" people. Another aspect of living well with HIV involved making meaning of their diagnosis; this was often accomplished by acts of service to the HIV community. Some women began attending support groups to offer their support to those recently diagnosed with HIV. Others participated in research, or educated family and friends about HIV prevention. These findings are consistent with recent studies that have examined aging among older people living with HIV/AIDS and highlight the importance of concepts such as resilience, optimism, and problem-focused coping to facilitate successful aging and better quality of life.[27,35,44,45] We describe how we use these findings to inform our modifications to the 3RP intervention to better meet the needs of this population below.

Phase I open pilot study findings.

Recruitment and screening. Participants were recruited through community outreach, posting of IRB-approved flyers, and approaching patients at the Infectious Disease Clinic (BMC). At MGH, 19 participants were screened. 9 participants were eligible and were then consented/enrolled, although 3 of these participants were lost to follow up. At BMC, 20 participants were screened and 9 were eligible. Of these 9 participants, 4 were consented/enrolled and 5 were not consented due to lack of availability for group sessions and/or difficulty reaching via phone. 1 participant was lost to follow up due to over-commitment in research and scheduling difficulty.

Feasibility and acceptability metrics. 39 total participants were screened and 18 were found to be eligible (46.1%). Of these, 13 were consented/enrolled and 10 participated in the intervention (76.9%). The duration of the baseline assessment averaged 1.8 hours, ranging from 1.25 hours to 3.0 hours (N=13). Post-treatment assessments averaged 1.5 hours and ranged from 56 minutes to 1.57 hours (N=6). Exit interviews averaged 36.8 minutes and ranged from 12 minutes to 1.03 hours (N=6). Reasons for declining enrollment included work schedule, the number of group sessions, transportation cost and distance, medical reasons (e.g., surgical procedures limiting mobility), and other life circumstances. Of the 3 participants that were lost to follow-up, 2 noted that they were unable to participate due to medical reasons. Participants who have completed the intervention to date showed decreases in depressive symptoms as measured by the Center for Epidemiologic Studies Depression (CES-D) scale and increases in resiliency scores as measured by the Connor-Davidson Resilience Scale (CD-RISC). At the end of the intervention, participants reported being "very satisfied" with the program overall and stated that they would recommend it to others, although one participant noted the program was moderately burdensome as measured by the Perception of Study Assessments survey.

Demographics. Of our 13 participants, the mean age was 58, with women ranging from 50-68 years of age. 61.5% of participants were black or African American (N=8), and 30.8% had completed some high school (N=4), while 38.5% had completed some college (N=5). 92.3% (N=12) of participants reported that they were diagnosed with HIV more than 5 years ago. Additionally, 53.8% (N=7) of participants reported being on disability, and 69.2% (N=9) reported $10,000 or less as their total annual income.

Protocol changes. Changes resulting from our pilot study findings include adapting and shortening the assessment battery to reduce participant burden, adapting the intervention content and length to better meet the needs of our target population, and removing the resilience score criterion to decrease screening and enrollment barriers. Other changes include providing participants the option of attending up to 3 make-up sessions to accommodate scheduling conflicts, which were common in Phase I, and allowing participants to call into group sessions by phone after having attended at least one session in-person.

Exit interview data. Participants shared a desire for longer and/or more sessions, as well as an appreciation the overall support received. Data collection in the open pilot is still ongoing, though an informal review of the qualitative interviews shows that participants have reported substantial benefit from the program, specifically in their ability to manage and respond to stress adaptively. They identified the in-session breathing exercises and discussions of healthy sexuality, social support, and stigma as particularly helpful. Data from participant exit interviews indicated general satisfaction with session content, so no substantial changes were made to session content (i.e., adding to deleting content) following the final open pilot group.

3. RESEARCH STRATEGY

Overview. The goal of this phase of the project is to conduct a randomized pilot study (N=up to 60) of an adapted mind-body resiliency intervention (3RP) among biologically-born women living with HIV, ages 50 and over. Based on exit interviews from the first phase of this study (open pilot), as well as qualitative work conducted previously with this population, we will conduct a small, randomized pilot of the intervention in groups of up to 10 women with HIV (total N=up to 60) to assess feasibility and acceptability of study procedures. Participants will be recruited from Boston-area hospitals and health care settings, including, but not limited to MGH and MGH satellite clinics, Brigham and Women's Hospital, Boston Medical Center, as well as community organizations serving individuals living with HIV. Participants will be screened for eligibility either by phone or in person by a study staff member. Eligible and interested participants will attend an individual study visit (either in person or via Zoom), during which they will sign informed consent (or provide verbal consent if the assessment is conducted via Zoom) and complete a baseline assessment. Following completion of this visit, participants will be randomized to either the intervention or control arm. The intervention groups will participate in the adapted 3RP intervention, while the control groups will participate in a supportive psychotherapy therapy program that is time-matched to the intervention. Participants will attend up to 10 group sessions (either in person or via Zoom), with opportunities to attend up to 3 make-up sessions in cases of scheduling conflict or missed sessions. At the end of the program, participants will complete a qualitative exit interview to provide feedback on the intervention (either in person or via Zoom). They will also complete a post-treatment assessment, and a 3-month follow-up assessment (either in person or via Zoom).

Study setting and participants.

Participants will be recruited from the Boston-area hospitals and health care settings, including but not limited to MGH and MGH satellite clinics, Brigham and Women's Hospital, Boston Medical Center, as well as community organizations serving individuals living with HIV. The Infectious Disease clinic at MGH serves over 1,000 individuals living with HIV per year. Approximately 36% of female patients identify as White/Caucasian, 40% identify as Black/African-American, and 12% identify as Hispanic/Latina.

Inclusion and exclusion criteria:
We will recruit and enroll up to 60 individuals meeting the following criteria:
(1) biologically born/cisgender women who endorse a female identity;
(2) living with HIV
(3) age 50 or over;
(4) English speaking;
(5) able and willing to sign informed consent.

We believe that non-cisgender women may experience unique and/or additional challenges than cisgender women (i.e., stigma related to sexual and/or gender identity, mode of HIV infection, etc.); thus, we have excluded them from the study at this time.

Exclusion criteria include: (1) presence of an active (i.e. untreated) and interfering psychiatric disorder (e.g., bipolar disorder, schizophrenia, substance abuse) that, in the opinion of the principal investigator or appropriate clinical staff, would compromise the individual's ability to participate in and benefit from the intervention; (2) have participated in structured cognitive behavioral therapy and/or a comprehensive mind-body intervention (including both mindfulness and behavioral therapy components) in the past year, also in the opinion of the principal investigator or appropriate clinical staff. By sampling from an array of medical centers, small clinics, and community organizations, we expect to recruit a representative sample of older women living with HIV.

If people are ineligible for the study at screening and ask for resources, we will refer them additional services in the community, including, but not limited to the following:

(1) stress reduction groups at the Benson-Henry Institute for Mind Body Medicine at MGH;
(2) mindfulness-based stress reduction and mindfulness-based cognitive therapy programs at the Center for Mindfulness at the University of Massachusetts Medical School;
(3) "Find a Therapist" tool on the American Psychological Association website;
(4) their primary care provider and/or their insurance company for a therapy referral

Recruitment procedures.

At MGH, a research assistant or other study staff member will review lists of potentially eligible patients, and ask providers to introduce the study, and obtain permission to be contacted by a study staff member. Participants may also be directed referred to the study by a health care provider. Flyers advertising the study will also be posted in patient waiting areas in Boston area hospitals (as described above) and health centers and distributed to Boston-area community organizations serving persons living with HIV (e.g., AIDS Action and The Living Center). Rally, the Partners Healthcare online recruitment platform, will also be used to aid in recruitment efforts. Additionally, study staff will use the MGH Research Patient Data Registry (RPDR) to identify patients who meet eligibility criteria and have previously indicated their interest in research participation, and conduct direct patient outreach via letters. The study team will attend meetings of the clinics from which patients are recruited to discuss the study as needed. These

methods have been used successfully in other projects, including Dr. Psaros' Harvard University Center for AIDS Research Scholar Award (P30 AI060354) with a similar population, and Phase I of this study (2017P000404).

Consent procedures.

After eligibility has been determined and interest in participation has been verified, participants will be scheduled to attend a baseline assessment (either in person or via Zoom) during which the informed consent document will be reviewed in a private setting.

If the baseline assessment is conducted in person, a detailed consent form will be signed by each participant following an explanation of the study procedures. The consent form will include all study procedures, information about potential risks and benefits of participation, and information regarding who they can contact for further questions. It also will state that participation is voluntary, that participants can refuse to answer any question, that they can withdraw from the study at any time, and that study participation is in no way related to their health care. The participant will also be asked to provide permission to receive a reminder call from a study staff member before each study visit and that it is permissible to leave a message, or if they prefer, to receive a confirmatory email with appointment time and location. We will share the "Partners Required Warning Language for Email Correspondence" if they elect to receive email communication to ensure their full understanding of potential confidentiality risks associated with unencrypted emails. Participants will be given as much time as needed to review the consent form before signing, even if it means postponing the baseline assessment.

If the baseline assessment is conducted via Zoom, study staff will email each participant a copy of the study fact sheet prior to their assessment, and then review the fact sheet in full with the participant via Zoom in order to obtain verbal consent. Verbal consent will be documented in a password-protected participant tracking spreadsheet, which will be saved on the Partners secure shared drive and accessible only to members of the study team. Participants will also be given the option to receive a signed copy of the study fact sheet via email or mail for their personal records.

Study procedures and data collection.

Table 1: Approximate Study Timeline for Phase II

Months	Activity
1-16	• Conduct of the randomized pilot trial groups. • Complete all recruitment activities.
17-20	• Complete all participant activities, including post-treatment assessments and follow-up visits. • Data analysis and write-up.

An approximate timeline for Phase II of the study is provided in Table 1. We have tailored the existing treatment manual to more specifically meet the needs of older women living with HIV based on the first phase of this study, as well as our prior qualitative work with the same population. The original 3RP intervention consisted of eight, 90-minute weekly group sessions and is described in Table 2. We expanded the number of sessions from 8 to 10 to

accommodate the HIV-specific elements and skills added to the original intervention content. A more detailed description of the intervention modules is provided below.

Table 2: Original Relaxation Response Resiliency Program Chapters and Goals

Chapter Title	Goals
Chapter 1 The Relaxation Response Resiliency Program	○ Introduce the Relaxation Response Resiliency Program (3RP) and its 3 components ○ Discuss how to elicit the RR ○ Introduce RR-elicitation method: single pointed focus meditation ○ Introduce the concept of appreciation ○ Establish program and weekly goals ○ Identify individual's sources of stress and coping
Chapter 2 The Relaxation Response	○ Introduce RR-elicitation method: breath awareness ○ Describe the relationship between the RR, health and wellness ○ Introduce 'Minis' as a method to reduce tension and anxiety through the day ○ Assess recuperative sleep
Chapter 3 The Four Components of Stress: Emotional and Behavioral	○ Introduce RR-elicitation method: autogenic training ○ Learn the four-component model of stress ○ Identify individual's emotional and behavioral components of stress
Chapter 4 The Four Components of Stress: Physical and Cognitive	○ Introduce new RR-elicitation method: chair yoga ○ Describe cognitive and physical components of stress ○ Describe automatic, self-defeating thoughts ○ Define different types of cognitive distortions, and learn how to identify them
Chapter 5 Building a Positive Perspective	○ Introduce new RR-elicitation method: joyful place imagery ○ Use cognitive reappraisal as a way to build adaption ○ Identify how positivity can increase resiliency in the long term ○ Learn concepts and strategies for enhancing positivity
Chapter 6 Mindful Awareness and Acceptance	○ Introduce RR-elicitation method: mindful awareness ○ Use strategies for applying mindful awareness in daily living ○ Learn about different coping styles: problem-solving and acceptance-based coping ○ Explore the development of acceptance, an essential quality of acceptance-based coping
Chapter 7 Healing States of Mind	○ Introduce RR-elicitation method: loving-kindness meditation ○ Introduce and evaluate types of social support ○ Learn how to select coping strategies: problem-solving and acceptance ○ Practice using humor to enhance processes of appreciation and acceptance ○ Introduce RR-elicitation method: idealized self

Chapter 8 **Staying Resilient**	○ Identify how empathy can increase resiliency in the long term ○ Review 3RP strategies learned ○ Develop a plan for continuing to use program strategies ○ Set goals for the future

Optimizing health can facilitate psychological resilience. Because successful management of HIV requires ongoing contact with the medical system and lifelong adherence to antiretroviral therapy, and because older women with HIV often have to navigate additional medical comorbidities,[46,47(p)] information on how to manage health in the context of HIV has been added to content from the *"Healing States of Mind"* module, in addition to information on activity and nutrition. We expanded upon the *"Building a Positive Perspective"* content to include material on valued action based on our finding that living a meaningful life and finding meaning from an HIV diagnosis is important to aging well with HIV.[43] The concept of valued action is derived from Acceptance and Commitment Therapy[48] and involves identifying values across multiple domains of life and assessing current satisfaction with each domain.

Our prior data also suggested that capitalizing on positive social supports and minimizing contact with negative social supports is important.[43] Thus, we expanded the content contained in the *"Healing States of Mind"* module to include an exercise that involves identifying positive and negative social influences, and using problem-solving skills to formulate plans to develop greater positive social support, and reduce the impact of negative social influences. Given the data on challenges with sexuality and the high levels of stigma and social isolation in this population, sexuality will also be directly targeted in combination with content from the *"Healing States of Mind"* module. Updated education on risks of HIV transmission (particularly in the era of treatment as prevention and biomedical HIV prevention)[49,50] will be shared. Goals around sexuality will be discussed, and problem-solving skills will be used to overcome barriers to healthy sexuality.

Throughout the program, participants will set goals for their weekly relaxation practice, in addition to other self-determined goals related but not limited to healthy lifestyle behaviors, HIV management, social support, and valued action. Progress on goals will be evaluated and new goals will be set over time. For example, if an individual articulates that she values service to the HIV community, but is not currently engaged with that community, goals may include researching options for involvement, contacting agencies of interest, and eventually applying to serve as a volunteer.

As described above, some of the most common challenges for older women living with HIV are anxiety, depression, loneliness, managing multiple medical comorbidities, chronic pain, fatigue, sexuality, and stigma. In Table 3, we highlight how the skills contained in our modified 3RP intervention target these issues.

Table 3: Skills Table

Common concerns for older women living with HIV	Current intervention skills	Additional skills added to existing intervention
Stress of managing a chronic long-term, life threatening illness; toxicities associated with long term use of ARVs; additional medical comorbidities	Eliciting the relaxation response (e.g., meditation, chair yoga; imagery); optimizing recuperative sleep; cognitive reappraisal; building a positive perspective; acceptance based coping skills; physical activity and nutrition recommendations	Supporting healthy lifestyle behaviors (e.g., how to manage health in the context of HIV); self-compassion
Pain and fatigue	Eliciting the relaxation response (e.g., meditation, chair yoga; imagery); cognitive reappraisal	Supporting healthy lifestyle behaviors (e.g., pacing); self-compassion
Stigma and social isolation	Evaluation of current social support; cognitive reappraisal; building a positive perspective; acceptance based coping skills	Valued action; problem-solving around developing healthy social supports; self-compassion
Depression and anxiety	Eliciting the relaxation response (e.g., meditation, chair yoga; imagery); cognitive reappraisal; building a positive perspective; acceptance based coping skills; physical activity and nutrition recommendations	Valued action; problem-solving around developing healthy social supports; self-compassion
Sexuality concerns	Cognitive reappraisal	Education around HIV prevention; development of sexuality goals; problem-solving barriers to goals; self-compassion

In the present phase of this study, we will conduct a randomized pilot of the revised intervention and all assessments among groups of up to 10 participants. Prior to beginning the revised intervention, participants will complete a baseline assessment lasting approximately 45-60 minutes (either in person or via Zoom). At the baseline assessment visit, participants will complete a series of quantitative self-report measures (described below), including sociodemographic information and data on resilience, antiretroviral adherence, stress reactivity, HIV disclosure status, anxiety, depression, social support, health-related quality of life, symptom distress, coping, substance use, perceptions of HIV stigma, and sexual functioning and communication. Participants will also complete a cognitive assessment. All questionnaires will be completed on either a touchscreen tablet or on paper (if the assessment is conducted in person) or verbally via phone or directly in REDCap (if the assessment is conducted via Zoom). For participants for whom questionnaires must be read aloud, response option cards will be provided (either in person or via email) for each instrument to serve as a visual reminder of the response options for scales on different questionnaires. Study staff will be available to assist in completion of the self-report questionnaires when needed. Participants will also be asked to have their blood drawn at the MGH Clinical Research Center (CRC), located in the White

Building 12 on the main hospital campus. In order to minimize inconvenience, participants will be provided with information about the on-call MGH shuttle service that can transport them to the main hospital campus from One Bowdoin Square. All blood draws are optional; participants may opt out and still participate in the study. Note: Study blood draws will not be conducted for the duration of virtual conduct of study procedures (i.e., assessment visits and group sessions). If and when it becomes safe for participants to receive blood draws in-person, scheduling of study blood draw visits will resume.

If participants who have completed a baseline assessment are unable to participate in the group (e.g., due to changes in availability), study staff will re-do the informed consent process and baseline assessments before participants join a subsequent group.

Following completion of this initial baseline visit, participants will be randomized (1:1) to the intervention or control arm. Random assignment to condition will minimize the likelihood of bias in either condition. A study research assistant or staff member not involved in the actual therapy will hold the randomization scheme, which will be developed by the study biostatistician (Dr. Mark Vangel). Baseline characteristics for each group will be examined for significant differences.

The control condition will be a supportive therapy program that is matched to the intervention for number and length of sessions. A version of this intervention has been used in a randomized controlled trial evaluating the efficacy of a combined depression and adherence treatment intervention, on which Dr. Psaros worked (R01MH084757). Basic principles of supportive psychotherapy will be followed [51,52], and the interventionist will facilitate discussion around what it is like to live with HIV as an aging woman. Sessions will be delivered by a study staff member (either in person or via Zoom) who will be thoroughly trained on the intervention or control condition material (e.g., predoctoral psychology intern, postdoctoral psychology fellow, junior psychologist). All group facilitators will receive supervision on a weekly or biweekly basis.

Participants will be given the opportunity to attend up to 3 make-up sessions (either in person or via Zoom) if they are unable to attend the originally scheduled session. For the control condition, makeup sessions will entail individual supportive psychotherapy. We will also allow participants to call into up to 3 group sessions by phone after having attended at least one session in-person. This will allow for more flexibility in scheduling and facilitate better overall attendance over the duration of the program. Additionally, participants in both the intervention and control groups will receive a schedule of all group sessions in order to minimize confusion about session dates and maximize efficiency of make-up scheduling.

Following completion of the intervention or the control group sessions, participants will complete a post-treatment assessment (either in person or via Zoom). Apart from the sociodemographic information, participants will complete all the same quantitative self-report measures (described below) as in the baseline assessment. Additional measures assessed at post-treatment include a measure of client satisfaction and a measure of perceptions regarding study assessments. All questionnaires will be completed on either a touchscreen tablet or on paper as described above (if the assessment is conducted in person) or verbally via phone or directly in REDCap (if the assessment is conducted via Zoom). We will also conduct semi-structured, individual qualitative exit interviews (either in person or via Zoom) to evaluate participants' perceptions of their experience in the study. Interviews will explore treatment content, satisfaction with group format (including group versus individual delivery), length of individual sessions, scheduling and location of sessions, adherence to the skills covered in the sessions, length of the overall group intervention, and perceptions of the assessment experience, including length of battery. In

addition to the qualitative interviews, the randomized pilot trial will provide information relevant to manual revisions in the form of audio recordings of sessions, weekly progress notes, therapist and patient ratings of satisfaction with and helpfulness of treatment procedures, and participant ratings of out of session practice of skills. Audio recordings of selected sessions will be made available for download from a secure, password-protected, HIPAA-compliant website and viewed by the study team.

Finally, we will conduct 3-month follow-up assessments (either in person or via Zoom), during which participants will complete all the same quantitative self-report measures (described below) as in the post-treatment assessment, apart from the sociodemographic information, client satisfaction measure, and measure of perceptions regarding study assessments. All questionnaires will be completed on either a touchscreen tablet or on paper as described above (if the assessment is conducted in person) or verbally via phone or directly in REDCap (if the assessment is conducted via Zoom).

Retention. The research assistant will track participant retention, which will be reviewed weekly by the principal investigator. We will collect extensive locator information at baseline (that contains contact information for at least two individuals with whom the participant is in regular contact) for participants in the event that they move or discontinue HIV care at the recruitment site, or become lost to follow-up from study procedures. Locator form information will be collected either in person or via Zoom. Should the individuals listed on the locator form be contacted, reference to HIV will never be made. We will make concerted efforts to maintain contact with individuals who discontinue the intervention but are still willing to complete follow-up assessments. To facilitate such retention, if necessary we will meet with participants at any confidential location that is comfortable for them for study assessment visits. Additionally, we have budgeted for financial incentives and public transportation costs.

Fidelity: All sessions led by the group facilitators will be audio-taped. Monitoring of the intervention will take into account both therapist adherence as well as competence.[53] We have developed a rating checklist for therapist adherence including whether the specific components of the modules of treatment were delivered, as well as a contamination checklist to measure the degree to which group facilitators introduced intervention content into the control sessions. This will be done by the PI (Psaros) or clinical supervisor. At least ten percent of the sessions will be reviewed.

Assessment instruments: All assessments that occur post treatment will be conducted by a study team member who did not serve as the group facilitator to minimize the risk of bias. We expect the baseline assessment, post-treatment assessment, and 3-month follow-up assessment to each last approximately 45-60 minutes.

Sociodemographic data: Data on age, race/ethnicity, relationship status, occupational status, and socioeconomic status will be collected at baseline, as will disclosure of HIV status and history of exposure to traumatic events, including interpersonal violence. Participant zip codes will also be recorded to account for time traveled to study visits.

Feasibility: To assess feasibility, we will track the number of potential participants we screen, the number of potential participants who meet study inclusion criteria, the number of participants who meet study criteria and then enroll (and the time it takes to complete these steps), and the number of treatment and assessment sessions completed by all enrolled participants. We will also track the duration of assessments, reasons for declining enrollment and for prematurely leaving the trial, and make-up sessions attended. The study team will review these data and

determine the degree of feasibility, though we will consider these feasibility/retention outcomes in the context of what other trials conducted with older individuals living with HIV have achieved.[38]

Acceptability: Acceptability will be assessed at post treatment using the eight-item Client Satisfaction Questionnaire (CSQ-8),[54] a measure of how much an individual values a treatment. Items assess factors such as the perceived quality of the services, how much the services met needs, satisfaction with the help received, and others. Items are scored from 1 (poor) to 4 (excellent), with higher scores indicating greater satisfaction. We will also ask participants about their perceptions of the burden of the study assessment battery.

Resilience.
Resilience: The Connor-Davidson Resilience Scale (CD-RISC)[55] is a self-report measure of resiliency comprised of 10 items rated on a five-point scale (0 = not true at all, 1 = rarely true, 2 = sometimes true, 3 = often true, 4 = true nearly all the time). Items capture various aspects of resilience including adaptability to change, availability and use of social support, and problem-solving style. Total scores range from 0-40; high scores indicate greater resilience. The CD-RISC has demonstrated good psychometric properties in previous research, including among medical populations.[55]

Measure of Current Status (MOCS-A): The MOCS-A is a 13-item self-report measure of stress reactivity and coping, which will be administered at baseline and post treatment. It was developed to assess one's current self-perceived status on several skills targeted by the intervention, including the ability to relax at will, recognize stress-inducing situations, restructure maladaptive thoughts, be assertive about their needs, and choose appropriate coping responses. Statements are rated from 0 (I cannot do this at all) to 4 (I can do this extremely well). Scores range from 0-52; higher scores suggest better coping skills.

Secondary Outcomes: Psychosocial.
Anxiety: Anxiety symptoms will be assessed using the State form of the State-Trait Anxiety Inventory (STAI).[56] The STAI State form is a 20-item self-report measure that has been used successfully to measure state anxiety in clinical and research settings. Respondents report the intensity of their current anxiety on a 4-point scale (1 = not at all, 2 = somewhat, 3 = moderately so, 4 = very much so). Scores range from 20-80, with higher scores indicating greater anxiety. This measure has been widely researched and used, and previous studies have found that the STAI is consistently reliable and valid.[57]

Depression: Depressive symptoms will be assessed using the Center for Epidemiologic Studies – Depression scale (CES-D).[58] This is a 20-item self-report measure that screens for depression and depressive episodes. Respondents report how often they experienced symptoms associated with depression on a 4-point scale (0 = rarely or none of the time, 1 = some or a little of the time, 2 = occasionally or a moderate amount of the time, 3 = most or all of the time). Scores range from 0 to 60; high scores reflect greater depressive symptoms. The CES-D has been found reliable (Alpha >.85) in previous research among medical populations, women in midlife, and older adults.[59–61]It has also been found to have good sensitivity and specificity.[61]

Social support: Social support will be assessed using the Medical Outcomes Study Social Support Survey.[62] The Medical Outcomes Study Social Support Survey is a 20-item self-report measure of emotional/informational support, tangible support, and positive social interaction. Respondents rate on a 5-point scale (1 = none of the time, 2 = a little of the time, 3 = some of the time, 4 = most of the time, 5 = all of the time) how often each type of social support is

available to them if they need it. The measure has good reliability and was found be fairly stable over a one-year period.[63]

Quality of life: Health related quality of life will be assessed using the AIDS Clinical Trials Group quality of life assessment, the Multidimensional Health Status Assessment. This is a self-report measure, in which individuals report the effect of their health on their quality of their existence across multiple domains including physical and psychological functioning. Items on this scale also assess the extent to which pain and fatigue have a negative impact on quality of life. Previous research has consistently confirmed that the assessment is highly reliable and valid, and it is used extensively in HIV research.[64,65]

HIV stigma: HIV stigma will be assessed using the HIV Stigma Scale,[66] a widely used measure of personalized stigma, disclosure concerns, negative self-image, and concern with public attitudes toward people with HIV. Respondents report their experiences of stigma on a 4-point scale (strongly disagree to strongly agree), with a total score ranging from 0 to 75. The measure has been validated among adults living with HIV (alpha = 0.88).[67]

Substance use: The Addiction Severity Index-Lite (ASI-Lite)[68] will be used to assess lifetime and recent substance use, including severity. It also asks about route of administration and if any substance use is prescribed. The number of items depends on substances endorsed. It has good internal consistency (alpha = 0.61 – 0.89).[69]

Coping: Coping strategies will be assessed using the Brief COPE.[70] This is a 28-item measure rated on a 4-point scale (I haven't been doing this at all to I've been doing this a lot) evaluating how often individuals engage in specific strategies in response to specific stressors. It consists of 14 subscales (self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, venting, behavioral disengagement, positive reframing, planning, humor, acceptance, religion, self-blame). Total scores range from 28 to 112, with higher scores indicating greater use of the coping strategy.

Sexual functioning: Sexual functioning will be assessed using the Female Sexual Function Index,[71] a 19-item gender-specific measure that asks about sexual functioning across six domains (desire, arousal, lubrication, orgasm, satisfaction, pain). Total scores range from 2 to 36, with higher scores representing higher sexual functioning. The measure was developed for women with female sexual arousal disorder but has also been validated in the general population.[72] It has good internal consistency (alpha = 0.78 – 0.84).[73]

Sexual communication: Sexual communication will be assessed using the 6-item version of the Dyadic Sexual Communication (DSC) Scale,[74] a measure of how individuals perceive discussions surrounding sexual matters with their partners. Items are rated on a 6-point Likert scale from 1 (disagree strongly) to 6 (agree strongly), with total scores ranging from 13 to 78, and higher scores indicating higher quality of communication. The original measure has been found to have good internal consistency (alpha = 0.81).[74]

Secondary Outcomes: HIV/Physical Health.

The proposed content on how to manage health in the context of HIV (See Table 3) provides information on the importance of sustained adherence to antiretroviral therapy and continued engagement in HIV care, as one must adequately manage their disease to be truly resilient in the face of HIV infection. Individuals will generate plans and back-up plans on how to manage common barriers to antiretroviral adherence, as well as engagement in HIV care. Thus, we will assess variables related to HIV management, to measure the performance of this content. Data

on time since HIV diagnosis will be assessed at baseline. The following variables will be assessed: current antiretroviral therapy regimen, adherence to antiretroviral therapy regimen, and engagement in HIV care.

Engagement in HIV care: On average, persons living with HIV should meet with their HIV provider four times per year.[75] We will ask participants when they last saw an HIV care provider.

Adherence to antiretroviral therapy: Adherence will be assessed via self-report. Data on self-reported adherence will be collected each week using the participant "weekly adherence to skills" forms described below. The questions will be based on standardized questions for self-report assessment of adherence to antiretroviral therapy.[76] A list of common antiretroviral medications will be provided along with the adherence assessment in order to facilitate participant memory and enhance self-report.

CD4 and viral load: CD4 count will be assessed at baseline only, while viral load will be assessed at baseline, post-treatment, and 3-month follow-up visits. At the baseline assessment, patients will have two tubes drawn by a phlebotomist at the MGH Clinical Research Center (CRC), located in the White Building 12 at 55 Fruit Street, Boston, MA 02114. One EDTA (lavender top) tube will be used for HIV viral load measurements (10 ml of blood) and another for CD4 (3 ml of blood). Per hospital clinic protocol, each visit will include an intake and measure of vital signs prior to the blood draw. At subsequent major assessment visits (post-treatment and three-month follow-up), only one tube will be drawn. All blood samples will be analyzed at the MGH Core Lab, located in the Warren Building 225 at 55 Fruit Street, Boston, MA 02114, and results will be available within 5-7 business days for the viral load, and 24-48 hours for the CD4 count. Recent viral load and CD4 count will be abstracted from participants' health records if they are patients at MGH. The purpose of this is to save participants an unnecessary blood draw if they have recently had these tests done during a clinical visit. Both MGH patient registration status and recent clinical blood draw history will be determined during screening process. All blood draws are optional; participants may opt out if they so choose.

Symptom burden: Symptom burden will be assessed using the using the AIDS Clinical Trials Group Symptoms Distress Module,[77] an instrument that measures distress related to HIV symptoms, and asks participants to rate on a 5-point scale (0 = I do not have this symptom, 1 = it doesn't bother me, 2 = it bothers me a little, 3 = it bothers me, 4 = it bothers me a lot) how much each of 20 symptoms (e.g., fatigue, nausea, muscle aches) bothered them during the past four weeks. The instrument is reliable and valid, is used extensively in HIV research and has also demonstrated cross-cultural validity.[78,79]

Cognitive status: Cognitive status will be assessed using the Mini-Cog.[80] The Mini-Cog can quickly detect cognitive impairment through its three-item recall test and a clock-drawing test (CDT) administered by a clinician. Respondents score as positive for cognitive impairment if they recall no words, or recall 1 or 2 words with an abnormal CDT. Both measures have been used with older adults in various health care settings, and previous research has found consistently good reliability and validity.[81,82]

Weekly adherence to skills: Practice notes have been developed to correspond with each module of the 3RP treatment. Participants will be asked to keep brief daily diaries of their out of session practice (e.g., completion of 15 minutes of meditation, engaged in activities to foster social connectedness, engaged in a desired lifestyle behavior, etc.). These diaries will be used to generate a rating of adherence to out of session practice guidelines. If group sessions are conducted virtually via Zoom, participants in the intervention group will be mailed an envelope

containing weekly practice notes to be completed during the 10-week group program. Participants will then be asked to mail back the completed practice notes (via a pre-paid envelope) at the end of the program.

Treatment Credibility and Expectancy: The Treatment Credibility/Expectancy Questionnaire (CEQ)[83] is a widely used 6-item measure that assesses treatment credibility and expectancy. Participants are asked to rate the treatment from 1 (not at all) to 9 (very much) and from 0% (not at all) to 100% (very much). The percentage ratings are subjected to linear transformation with a minimum of 1 and a maximum of 9. We will administer the scale after the first treatment session.

COVID-19-related: Quantitative assessments and the qualitative exit interview will contain COVID-19-related items in order to better understand the impact of COVID-19 and corresponding public health restrictions on participants' lives (e.g., mental health, ability to adhere to HIV medications), and their experience participating in this study.

Participant remuneration.

Participants will receive up to $293 over the course of the study, including $25 for their time after each of the assessment visits (i.e., baseline, post-treatment, 3-month follow-up, and optional qualitative exit interview), $25 for interview questions related to COVID-19, as well as $12 reimbursement for attending all study visits (either in person or via Zoom).

Participants may be remunerated via eCheck or Forte cards. If study visits are conducted virtually, Forte cards will be mailed to participants' homes for the purposes of remuneration during the study.

Foreseeable risks and discomforts.

It is unlikely that participants will be at any risk for physical harm resulting from study participation. Participants may find some of the questions covered in the assessments to be emotionally upsetting. Participating in a counselling study (for resilience) can be difficult, because it may involve discussing personal matters. As with any study, there is always the risk of inadvertent breach of confidentiality. This is of particular importance here because participants are living with HIV, which may be stigmatizing. An additional discussion of how we minimize these risks is described below.

Minimization of risks.

It is unlikely that participants will be at any risk for physical harm resulting from study participation. In the event that any study procedures result in significant distress, the participant will be given the opportunity to cease study participation. All research study staff will be thoroughly trained in assessment procedures. If a participant is determined to be in distress or actively suicidal and at risk for self-harm during any study procedure, study staff will contact the PI (Psaros) or another trained clinician, so that appropriate clinical intervention is executed. Any participant who scores greater than or equal to a 23 on the CES-D will be evaluated (either in person or via Zoom) by a licensed psychologist or another qualified provider/clinician and referred for additional services as needed.[84] The group facilitators will participate in regular supervision. We have added a DSMB that will convene at least annually to afford additional, external review of study procedures, participant safety, and adverse events.

Additionally, Dr. Psaros has been involved with numerous local and national studies of persons with HIV and has considerable experience implementing measures to protect confidentiality. Some of these steps include in-service trainings on confidentiality and the assignment of study ID numbers. Staff at all sites who conduct participant recruitment, screening, enrollment, and assessments will have been trained in ethical human subjects research, screening and interviewing techniques, to minimize participant risk as much as possible; this includes all staff at non-Partners sites. All data will be kept confidential, under lock-and-key, accessible only to trained study staff. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept separately under lock and key. Any paper-based assessments will be stored under lock and key within a secure office space accessible only to approved study staff. The study database will be secured with password protection and accessible only to approved study staff. Participants will be asked to sign a confidentiality statement prior to the inception of group sessions (if the baseline assessment is conducted in person) or verbally consent to such an agreement (if the baseline assessment is conducted via Zoom).

Expected benefits.

It is possible that there will be no direct benefit to participants in the current study. However, participants may benefit from participation via an increased understanding of how to optimize well-being among older women living with HIV, and that may improve the care of this population in the future. Participants may also feel a sense of purpose that they are contributing to work that may help others. Participants are also provided financial remuneration for their participation.

Equitable selection of participants.

Participants will be biologically born women, living with HIV, age 50 years or older, and English speaking. Participants must be able to provide informed consent and agree to study procedures (e.g. completion of assessments and intervention program). The patient population will be comprised of individuals of varied racial/ethnic and socioeconomic backgrounds. All participants meeting inclusion criteria will be offered the opportunity to participate. We will not exclude participants based on minority status.

Data analytic plan.

Quantitative data will be entered in an on-going fashion (into REDCap data management system), and will be analyzed using SPSS, "R", and QSR NVivo qualitative software, version 9, after being thoroughly checked and cleaned as appropriate. Dr. Psaros has the full support of a biostatistician (Dr. Mark Vangel) for all statistical analyses. We will compile descriptive statistics to examine intervention acceptability and feasibility as described above, as well as to examine indicators of change on measures of various psychosocial outcomes. We will compare each outcome between groups using mixed model regression analyses, with subject as a random effect. Fixed covariates will include time in study (baseline, end of treatment, 3-month follow-up) and time since diagnosis. Other covariates, such as education, socioeconomic status, and history of exposure to traumatic events will also be considered. We will consider exploratory mediational and moderational analyses, based on procedures outlined by Hayes.[85] We will assess adherence in the active treatment arm, in particular to determine if adherence is related to change in the primary outcome. We will perform exploratory multivariate analyses among the outcomes, including graphical methods and the calculation and testing of correlations and partial correlations. We will examine patterns in missing data in order to see if missingness is related to measured patient characteristics. We will adjust for missing data using multiple

imputation as appropriate. We will adjust for multiple comparisons using the method of Hothorn, Bretz and Westfall.[86] Statistical analyses will be performed using "R" software.[87]

All qualitative data resulting from exit interviews will be analyzed using standard qualitative methodologies described by the Office of Behavioral and Social Sciences Research at the National Institutes of Health. Specifically, data will be analyzed using content analysis, an iterative, multi-step process as described by Miles and Huberman[88] and Strauss and Corbin.[89] The investigators will use NVivo software (version 10) to organize data and to facilitate analyses. Two study team members will independently review the transcripts in order to generate an overarching thematic framework for data interpretation, in which major and minor themes are identified. Using multiple coders also enhances the validity of the analysis.[90] The investigators will compare their thematic frameworks for consistency, and any discrepancies will be discussed until there is agreement on the thematic framework. Data will be reexamined, messages will be extracted and highlighted, and ongoing discussion between coders will allow for further theorizing and making interconnections between research questions, coding categories, and raw data.[88]

Mechanisms for reporting adverse events.

Adverse events are defined as harmful occurrences to study participants, either study related or non-study related, during participation in the clinical intervention study. As a result of participation in the intervention or qualitative interviews, study staff may become aware of an adverse event, including participant distress or disclosure of violence or abuse, or suicidal ideation. Study staff will be trained to make appropriate referrals for clinical care in consultation with the PI and co-investigators. All adverse events will be reported by the PI to the IRB within the required reporting periods as outlined by the PHRC policy, and these will be discussed during team meetings. Anticipated or unrelated adverse events will be reported to the DSMB and the annual summary, the DSMB report will state that the board has reviewed all AE reports. These will be discussed on weekly calls / in-person meetings with Dr. Psaros and key study staff. Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCIH Program Officer within 15 days. To ensure confidentiality during reporting, adverse event reports and annual summaries will not include identifiable information. Each report will only include the participants' ID numbers.

Data monitoring.

Data collection occurs in the form of a series of quantitative assessments and qualitative interviews. The principal investigator (Psaros) will work closely to oversee all data management and analysis issues, along with the project statistical (Vangel) and the rest of the study team. The study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. Data verification will be performed weekly by a study research assistant who will not be involved in data collection or have any direct contact with study participants. All intervention sessions and exit interviews will be audiotaped (participant consent will be obtained). Intervention fidelity will be assessed by randomly selecting approximately 10% of sessions and assessing adherence to the protocol based on checklists and scales specifically developed for this study. The group facilitator will also participate in weekly supervision with Dr. Park, Dr. Traeger or a study staff psychologist, where audio of sessions will also be reviewed.

Project organization.

A timeline of study procedures is provided in Table 1 and a timeline of study assessments is provided in Table 4. Dr. Psaros, as the principal investigator and overall project director, will oversee all aspects of the project. She will supervise the research assistants at MGH, and oversee the data management and data analyses. Lastly, Dr. Psaros will serve as a liaison among the other investigators, and together with the co-investigators, will prepare manuscripts and present findings at national conferences.

Training of study staff.

All proposed staff have participated in the NIH required trainings in participation and conduct of studies that involve human subjects, and any future study staff will do so upon hiring. Training for all staff includes (but is not limited to) Human Subjects, Informed Consent, Good Clinical Practice, Quality Management, Confidentiality and Reporting of Adverse Events. If any study staff discovers any untreated condition (e.g., a metal health condition), they will refer participants to appropriate treatment immediately.

STATISTICAL ANALYSIS PLAN

Table 4: Study Event Timeline

Phone Screening	Evaluation	Baseline Visit and Enrollment	Treatment Phase - Group Participation (10, 90-minute sessions)										Post Treatment Assessment	3-Month Follow-up Assessment
			1	2	3	4	5	6	7	8	9	10	10	22
			Weeks										+ 14 Days	± 14 Days
	Sociodemographics	X												
	Treatment Credibility / Expectancy		X											
	Client Satisfaction												X	X
	Resilience and MOCS-A	X											X	X
	Psychosocial Distress	X											X	X
	HIV / Physical Health Outcomes	X											X	X
	Adherence to Antiretroviral Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
	Adherence to Intervention Skills			X	X	X	X	X	X	X	X	X	X	X
	Qualitative Exit Interview												X	

Statistical Plan for Analyses

Power: PAR-14-182 states, "...the R34 should ... enhance the probability of reaching more definitive outcomes in a larger trial... by working out the details of the experimental protocols, including the assessment protocol, the...intervention protocol, as well as the comparison intervention protocol and randomization procedures; examining the feasibility of recruiting and retaining participants into the study conditions; ... collection of preliminary data regarding feasibility, acceptability, safety, tolerability, and target outcomes is appropriate. Given the limited sample sizes that can be supported under this...mechanism, proposing the use of a comparison group for conducting fully powered tests of outcomes (i.e., efficacy) or attempting to utilize the highly variable point estimate of an effect size for power calculations would not be appropriate." As stated in the specific aims, we aim to test the feasibility and acceptability of all study procedures as a primary goal; we will not attempt to use our data to estimate an effect size. We are interested in the sensitivity of our selected measures to detect change. Thus, as an exploratory outcome, we propose to examine the intervention effect of resilience and other secondary outcomes. We have conducted power calculations to ensure any lack of effect would be unrelated to power. We also explored current funded R34 studies of similar scope that are currently funded by NCCIH, and our sample size is well within the range of what is documented in these studies (e.g., 5R34AT008423, 1R34AT007935).

Power calculations are based on samples of older, HIV-infected women when available. When data from older HIV-infected women were not available, data from samples of older women, women, or HIV-infected populations were used. We also examined data from community samples. We calculated power estimates for the primary outcome (resilience as measured by the CD-RISC) and for two of the secondary outcomes, depressive symptoms and health related quality of life. With respect to resilience, from Dodding et al.,[87] we estimate the standard deviation of change due to the intervention to be 11.8. With 30 patients per group, we will have 80% power to detect a change in resilience of 6.2 points or greater, in absolute value, based on a paired t-test at the 0.05 two-tailed significance level. We estimate the population mean and standard deviation to be approximately 76+/-13 for community-based controls,[88] and 71.7+/-12.5 for a community-based sample of post-menopausal women with sub-clinical depression[89] (N=401). A change of 6.2 points corresponds to approximately 1/2 of a standard deviation for both of these populations (i.e., an effect size of 0.5). Comparing the post-pre differences between treatment arms, we estimate that we will have 80% power to detect an absolute difference of 8.7 on the CD-RISC, based on a two-sample t-test at the 0.05 two-tailed significance level (an effect size of 0.7, which corresponds to a medium-large effect size.[90]

For depressive symptoms, Ickovics et al.[91] reported that 42% of HIV seropositive women were depressed, based on reporting a CES-D score of >16 for 75% of more of study visits. Assuming that the population proportion of participants with elevated depressive symptoms in the placebo arm at the end of the study is 0.42, then with 30 participants per arm, we will have 80% power to detect that the corresponding treatment proportion is <0.12 or >0.76. For health related quality of life, Mrus et al.[92] reported a mean for the overall health domain of HRQoL in women engaged in HIV treatment of 71.4, with a standard deviation of 13.8. Using this standard deviation, with 30 participants per arm, we will have 80% power to detect if the absolute mean between-group difference in this quality of life measure at the end of the study is 10.2 points or greater, based on a two-sample t-test at the 0.05 two-tailed significance level. In summary, we are confident that we can achieve a medium to large effect size[90] across multiple outcomes with the proposed N.

Analyses: With respect to quantitative data, we will compare each outcome between groups using mixed- model regression analyses, with subject as a random effect. Fixed covariates will include time in study (baseline, end of treatment, 3 month follow-up) and time since diagnosis. Other covariates, such as education, socioeconomic status, and history of exposure to traumatic events will also be considered. We will consider exploratory mediational and moderational analyses, based on procedures outlined by Hayes.[93] We will assess adherence in the active treatment arm, in particular to determine if adherence is related to change in the primary outcome. We will perform exploratory multivariate analyses among the outcomes, including graphical methods and the calculation and testing of correlations and partial correlations. We will examine patterns in missing data in order to see if missingness is related to measured patient characteristics. We will adjust for missing data using multiple imputation as appropriate. We will adjust for multiple comparisons using the method of Hothorn, Bretz and Westfall.[94] Statistical analyses will be performed using "R" software.[95]

All qualitative data will be analyzed using standard qualitative methodologies described by the Office of Behavioral and Social Sciences Research at the National Institutes of Health. Specifically, data will be analyzed using content analysis, an iterative, multi-step process as described by Miles and Huberman[96] and Strauss and Corbin.[97] The investigators will use NVivo software (version 10) to organize data and to facilitate analyses. Two study team members will independently review the transcripts in order to generate an overarching thematic framework for data interpretation, in which major and minor themes are identified. Using multiple coders also enhances the validity of the analysis.[98] The investigators will compare their thematic frameworks for consistency, and any discrepancies will be discussed until there is agreement on the thematic framework. Data will be reexamined, messages will be extracted and highlighted, and ongoing discussion between coders will allow for further theorizing and making interconnections between research questions, coding categories, and raw data.[96]

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