UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN 03-03-11

1. PROJECT TITLE

Acceptance and Commitment Therapy to Address the Psychosocial Co-Morbidities of Chronic Pain in Aging People Living with HIV

2. PRINCIPAL INVESTIGATOR

Maile Karris, M.D.

3. FACILITIES

Training of Lay-personnel, performance of the intervention, assessments of study participants will be conducted at:

AntiViral Research Center (AVRC)
220 Dickinson Street, Suite A
Mail Code 8208
San Diego, CA 92103-8231

Based on space availability, performance of the intervention may also be conducted at:

Owen Clinic
Medical Offices South
4168 Front Street
San Diego, CA 92131

Due to concerns about COVID-19 the study procedures can be conducted remotely using Zoom teleconference services.

4. ESTIMATED DURATION OF THE STUDY

Training, enrollment and study procedures are projected to last 2 years. This study will be open with IRB for up to 7 years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS

Chronic pain affects a very high proportion of aging people living with HIV (aPLWH) and is thought to be related to both direct toxicity of HIV and antiretroviral therapy (ART) and by psychosocial factors that negatively affect pain (i.e. loneliness, HIV stigma). PLWH are also at increased risk for prescription opiate misuse. However as PLWH age, non-opiate medications used for pain can contribute to other negative outcomes such as falls, altered mental status and gastrointestinal bleeding. Thus there is a critical need for the development of novel interventions in the management of chronic pain in aPLWH that consider the psychological co-morbidities of aging with HIV and that can minimize the need for prescription medications. Acceptance and commitment therapy (ACT) has previously been evaluated in older persons with chronic pain and has demonstrated higher levels of satisfaction and efficacy when compared to cognitive behavioral therapy (CBT). ACT has never been evaluated in aPLWH for chronic pain, but has theoretical advantages over CBT for this population. Specifically several negatively modifying factors of CBT efficacy such as cognitive deficits are common in aPLWH.

6. SPECIFIC AIMS

Aim 1: To determine feasibility of training lay-personnel in the performance of ACT for aPLWH to inform future implementation. Many HIV clinics employ non-medical staff such as case managers and health educators who if trained to provide ACT would expand of ACT access to aPLWH. We will train a substance abuse counselor and case manager in ACT to inform the feasibility of future ACT scale-up efforts.

Aim 2: To conduct an uncontrolled study of group ACT for chronic pain in aPLWH to inform adaption of ACT for aPLWH. Ten aPLWH will participate in 6 weekly sessions of group-administered ACT. Informed by the Method for Program Adaption through Community Engagement (MPACE) Model, I will synthesize and present data from questionnaires, participant feedback and end of study focus group to a steering committee for adaption recommendations(1). These procedures can occur in person or remotely. We will statistically evaluate the process and compare group cohesion scores between persons who attend live and remotely.

Aim 3: To conduct a controlled, two-group, pilot randomized trial of adapted ACT for aPLWH as compared to group education. Forty aPLWH with chronic non-cancer pain will be randomized to 6 weeks of group ACT or group education. Participants will undergo evaluations of acceptability as the primary outcome as recommended by the ORBIT model(2). Additional evaluations will include self-reported pain severity and interference, outcomes of physical performance, and quality of life (3, 4).

The long-term goal of this research is to develop an effective non-pharmacologic intervention to improve chronic pain in aPLWH that can be feasibly implemented on a large scale in HIV clinics. This research, in conjunction with the activities proposed in the Professional Development Plan, will help launch my career as a future leader in aging-focused research.

In order to address these hypotheses and aims, human subjects are required.

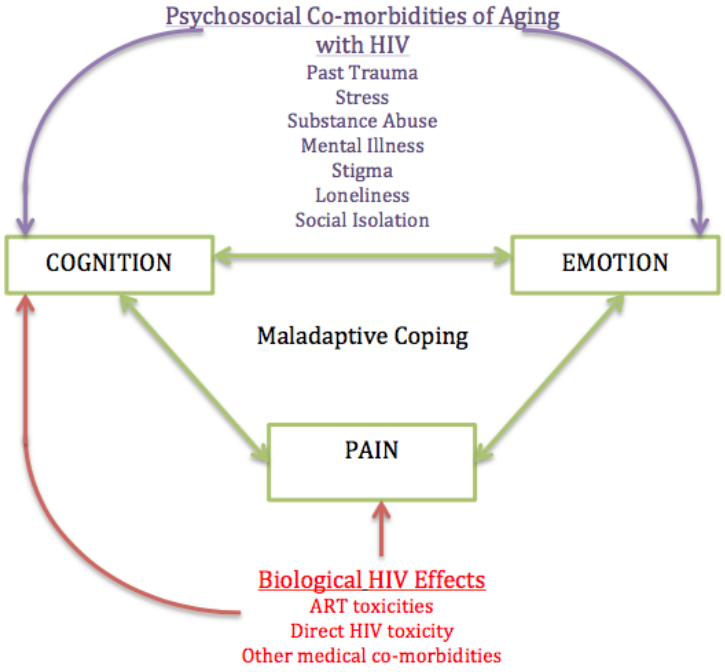
7. BACKGROUND AND SIGNIFICANCE

Chronic pain impacts up to 85% of people living with HIV (PLWH) (5-9). The high prevalence is due to direct and indirect effects of HIV (i.e., direct HIV toxicity and secondary toxicity of antiretroviral therapy on the central and peripheral nervous systems(10-13)) and magnified by co-occurring psychosocial factors such as depression (14), stress (15), past trauma (16), social isolation (17), and substance use (18-24). These co-occurring factors also contribute to increased risk for prescription opiate misuse and overdose mortality (25-27) and to maladaptive coping (avoidance, thought suppression, and catastrophizing)(28-32) that negatively modifies the pain experience. As this population ages, the medical management of pain increases in complexity as aging PLWH (aPLWH; $\geq$ 50 years in the literature) accumulate age-associated painful co-morbidities like osteoarthritis. Additionally, most non-opiate medications used for pain (i.e., skeletal muscle relaxants, NSAIDS) have side effects that increase risks for falls, delirium, and gastrointestinal bleeding that may further worsen the health of aPLWH (33-37). Thus, developing novel interventions that target pain relief and function, consider relevant psychosocial co-morbidities of aging with HIV, and minimize medication use remains a priority.

The biopsychosocial theoretical framework as first proposed in Melzack and Wall's "gate control theory of pain" and represented at the core of our conceptual model (in green in Figure 1) is a well-established, accepted model of pain(38, 39). This framework has influenced the development of several interventions including the self-regulatory approaches of biofeedback and mindfulness-based stress reduction and psychological approaches like cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT) (40). CBT, the longest standing psychological approach to pain management, can result in reduced pain, increased function, and decreased disability(41). However, success with CBT requires persons to 1) *understand* that thoughts and behaviors affect the pain experience, 2) *develop* cognitive and behavioral *skills to change* these thoughts and behaviors, and 3) *engage in ongoing work* to manage or reduce pain. Several pre-existing factors such as cognitive deficits or an inability to confront and control complex emotions impair CBT responses (42-44). ACT, on the other hand, recognizes that attempts to forcibly change negative thoughts and longstanding behaviors can be futile and result in increased suffering and distress (45, 46). ACT instead focuses on acceptance of negative feelings while concurrently taking steps towards outcomes that are valued and provide meaning to the individual (47-49). In chronic pain, ACT like CBT also improves pain related

factors such as emotional and physical function (50) and demonstrates higher levels of satisfaction as a pain intervention than CBT (51). Of note work by Dr. Wetherell ACT may also be more effective than CBT in older adults (52, 53), while younger persons appear to respond better to CBT. ACT is understudied in HIV and never evaluated for chronic pain, but exhibits a positive impact on HIV stigma(54) and life experiences (55, 56).This approach may be particularly effective in PLWH who demonstrate maladaptive coping such as thought suppression and avoidance due to underlying psychosocial co-morbidities of HIV including HIV stigma, substance use, and past trauma (57-60). Additionally, aPLWH demonstrate high rates of cognitive deficits and are limited in their capacity to change their circumstances (i.e. due to poverty, homelessness) (52, 53) (42-44) both factors that impair CBT response and favor ACT.

Figure 1 Biopsychosocial Conceptual Model of Chronic Pain adapted for aPLWH



Adapted with permission from Bushnell MC. Nat Rev Neurosci 2013

The scientific premise of this grant is that chronic pain in aPLWH is caused by the direct effects of HIV and modified by the psychological and social co-morbidities of aging with HIV (See Figure 1. Conceptual Model). Direct HIV effects on the brain (i.e. neurotoxicity of HIV and antiretroviral therapy) and the psychosocial co-morbidities of aging with HIV (past trauma, HIV stigma, perceived stress, loneliness, substance use, mental illness, and social isolation) lead to maladaptive coping (such as catastrophizing) that magnifies pain, impairs cognitive performance, and enhances pain perception. ACT has the potential to positively impact the chronic pain experience (pain, function, and quality of life) in aPLWH by addressing psychosocial co-morbidities and maladaptive coping and is less dependent than CBT on baseline cognitive function and the capacity to change personal circumstances.

Evaluation of new chronic pain strategies for aPLWH remains crucial because this is a steadily growing high need population[61] and chronic pain is a highly prevalent co-morbidity(5-9). Current CDC recommendations for the management of chronic pain are insufficient for aPLWH as these guidelines do not consider the serious side effects of non-opiate pain medications that PLWH are at risk for as they age(37) and the lack of access to non-pharmacologic therapies due to psychosocial circumstances of aPLWH.

ACT versus CBT for chronic pain in older adults: CBT and ACT are effective psychological interventions for chronic pain, and yet demonstrate small to moderate effect sizes(62-65)on pain outcomes. Key medical and psychosocial co-morbidities may influence treatment outcomes and effects, thus adaption of psychological approaches may enhance efficacy at the target population and individual level. In fact, CBT and ACT demonstrate differential effectiveness based on the population in which they are used. Dr. Wetherell, a Co-Investigator on this grant, performed an 8-week randomized clinical trial of CBT versus ACT for chronic pain in persons aged 18-89 years in San Diego, and although there were no differences in pain-specific outcomes, ACT participants reported higher levels of satisfaction(51). A

secondary analysis demonstrated that older participants were more responsive to ACT while younger participants responded better to CBT(52). This difference was present at completion of the intervention and at 6 month follow-up. Several characteristics of aPLWH suggest that ACT may be particularly effective for aPLWH, as previously discussed and represented in the Conceptual Model (Fig 1).

8. PRELIMINARY STUDIES/PROGRESS REPORT

n/a

9. RESEARCH DESIGN AND METHODS

This is a 6-week un-blinded, 2-arm randomized (1:1) controlled clinical pilot study. The overarching objective of this study is to determine the acceptability and feasibility of an acceptance and commitment therapy (ACT) intervention for the management of chronic pain adapted to aPLWH. To accomplish this objective this project will:

1) Train lay personnel to perform ACT to determine feasibility of this approach for future implementation,
2) Conduct audio recorded, uncontrolled group ACT in aPLWH to generate participant feedback and questionnaire data to inform ACT adaption with the assistance of a steering committee, and
3) Conduct an audio recorded, pilot randomized controlled trial (RCT) evaluating the acceptability of adapted ACT compared to pain education.

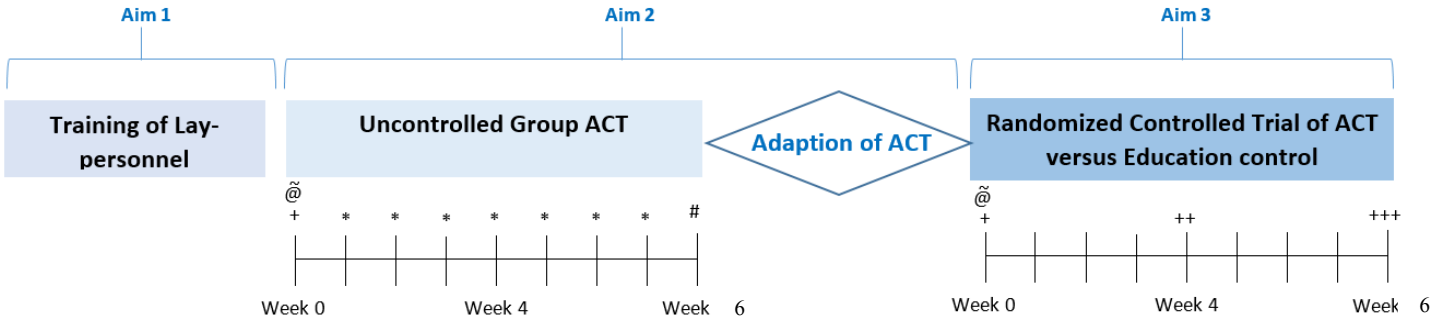
Due to concerns about COVID-19 the study procedures can be conducted remotely using Zoom teleconference services.

At completion of this project we expect to have successfully trained lay personnel to perform group ACT, adapted ACT from quantitative and qualitative data collected from an uncontrolled study of group ACT, and determined whether ACT is acceptable and feasible as an intervention in aPLWH. These expected outcomes may benefit other aging populations with chronic pain that are enriched for psychosocial co-morbidities such as persons who inject drugs, the socioeconomically disadvantaged, and racial or gender minorities. This proposal is aligned with the Office of AIDS Research High Priorities to better understand “HIV-associated comorbidities” which includes pain and to “Reduce Health Disparities in treatment outcomes of those living with HIV/AIDS” and with the National Pain Strategy to “expand investment … in the development of safe and effective pain treatments.”

Research Design and Procedures:

For AIM 1 *Training of Lay-personnel in ACT:* Dr. Wetherell will train Mr. Seefried (a retired nurse) and Ms. Justice-Royster (a substance abuse counselor) in the performance of ACT based on procedures in which non mental health providers have been taught to perform psychological interventions (66-71). Training will use Dr. Wetherell's previously developed therapist and client manuals of ACT for chronic pain. This will include an initial 8-hour introduction to ACT followed by weekly 1 hour meetings using the manual to guide case-based scenario training. This amount of preparation is well within the range provided to non-mental health professionals in previous studies of manualized psychotherapy. The final phase of ACT therapist training will take place in the field during Aim 2. Dr. Wetherell will listen to audio recordings of 20% of ACT sessions and meet weekly with ACT counselors to assist with

Figure 2. Study Schema



Legend
~ Study participant informed consent @ Baseline demographics + Pain and Psychosocial Co-morbidity Assessments
*Short telephone or in-person interview about ACT experience
#Focus group
++Acceptability and Pain Assessments
+++Acceptability, Pain and Psychosocial Co-morbidity Assessments

troubleshooting, provide expertise, and ensure fidelity. I will be present through training and at 20% of ACT and education sessions to experientially learn these processes. The ACT therapist trainer and ACT trainees will be complete recorded guided interviews after completion of training.

For AIM 2*: Uncontrolled group ACT for Chronic Pain in aPLWH:* Ten aPLWH will be recruited for 6 weeks of 2-hour group ACT using previously developed ACT for chronic pain manuals developed for therapists and clients by Dr. Wetherell (Table 2). All sessions will be audio recorded for future analysis. Following each session participants will undergo recorded 10 minute short interview on aspects of the class they liked most and least. These surveys will employ open-ended questions about program content. Participants will undergo baseline demographics and questionnaires about pain and psychosocial co-morbidities (see assessments) to inform generation of open-ended questions and development of a focus group guide. Data from participant feedback and questionnaires will be presented to the steering committee to assist with development of the focus group guide. Participants will complete follow up questionnaires and guided interview questions 3, 6, and 12 months after completion of the group sessions to assess long-term use of ACT.

Table 2: Session Intervention Content

Session	ACT	Take Charge of Your Pain
1	Letting Go	Things to Know about Pain
2	Values	Relaxation
3	Cognitive Defusion	Imagery
4	Mindfulness	Activity Pacing
5	Commitment	Sleep Tips
6	Moving Forward	Dealing with Pain Flare-Ups
7	Practice/review	Review
8	Practice/review	Review

For AIM 2 *Adaption of ACT:* Following the final group session, a 1-3 hour long focus group will be performed to obtain suggestions for program modification. The focus group will be audiotaped and responses transcribed, categorized and summarized and distributed to members of the study's steering committee which will then meet to review and adjudicate suggested ACT adaptations. Adaptions will

be incorporated into new therapist and client manuals and further training will be provided to ACT therapists for the performance of adapted ACT.

For AIM 3 *Acceptability and Feasibility of Adapted ACT Intervention:* Forty persons will be randomized to either group adapted ACT or group education. In anticipation of ~15% early discontinuation or lost to follow up, we plan to recruit 50 participants overall. All sessions will be audio recorded for future analysis. Adapted ACT will be provided by ACT therapists in weekly 2-hour group (8-10 persons per group) sessions for the 6 weeks of the intervention and will include brief review of at-home practice assignments, introduction of new material and end with assigned at-home practice exercises. Participants randomized to control will also participate in 2-hour 6 weeks group sessions (8-10 persons) using the "Take Charge of Your Pain" handbook developed by Investigators at the Weill-Cornell Translational Research Institute for Pain in Later Life (Table 2). All sessions will be audio recorded for future analysis. Study participants will complete assessments at baseline, week 3 (midpoint) and week 6 (endpoint). Following completion of study we will assess for persistence of ACT activities and practices by a short telephone follow up. Participants may come to the AVRC for an in person discussion but this will not receive monetary compensation.

Remote Engagement of Study Participants

To ensure safety of participants (who are all older adults with the co-morbidity of HIV) during COVID-19 and respect the "shelter at home" state-wide order this aim will be performed 100% virtually. The protocol specifically has been adapted to include

1) over the phone consent. This is a minimal risk study and with COVID-19 the risk of an in-person evaluation greatly outweighs the potential benefit.
2) Questionnaires to be completed via a) online through REDCAP mechanism that provides a link and password to allow participants to securely complete questionnaires or b) complete paper questionnaire mailed to participant with stamped envelope for return with only the study ID on papers to protect participant privacy
3) Online group meetings using Zoom with password to prevent hackers.
4) Compensation provided either using an electronic gift card or a script mailed to the study participant.

Aim 3 substudy: An additional substudy involving two to ten participants will also be performed with the intent in better understanding the relationship between older age, HIV, San Diego as a border town and access to prescribed and non-prescribed medications used for pain. This was originally designed as a focus group, but will now be performed using individual interviews in response to COVID-19.

Assessments: *P*articipants will complete surveys asking about demographic (age, gender, race/ethnicity, education, etc.) and HIV (risk factor, duration of HIV infection, CD4 T cell counts both current and nadir, HIV viral loads, and self-reported ART adherence) factors and montreal cognitive assessment test. Chronic pain diagnoses, medications and non-pharmacologic methods used for pain and the duration of pain will also be collected from participants. Treatment satisfaction will be determined as measured by the Client Satisfaction Questionnaire (CSQ)(72, 73) and The Group Questionnaire at midpoint and intervention end. Treatment expectations will be determined as measured by the Treatment Expectations Questionnaire at week 0 and intervention end. Pain assessments will include change in the Brief Pain Inventory (BPI) Interference subscale and Pain Self Efficacy Questionnaire (PSEQ) from week 0 to 8(74) , the Patient Reported Outcomes Measurement Information System (PROMIS) pain behavior and pain interference questionnaires, measures of physical function using the Short Physical Performance Battery (SPPB) (75) and quality of life using

EuroQol(76). Lastly co-morbidities proposed to impact the pain experience in HIV will be evaluated: stress (Perceived Stress Questionnaire(77)), loneliness (UCLA Loneliness Scale(78)), depression and anxiety (Patient Health Questionnaire-9 and GAD-7(79, 80)), past trauma (Stressful Life Events Screening Questionnaire (81)), social isolation (Friendship scale(82)) stigma (HIV-Stigma scale(83)). Acceptance and action questionnaire, depression and anxiety (Patient Health Questionaire-8(79) to avoid positive questions about active suicidality given insufficient capacity to immediately address that in the research setting), profile of mood states questionnaire, wisdom questionnaire and substance use (Alcohol, Smoking, and Substance Involvement Screening Test(84)).

Table 1: Step 1 Unadapted ACT Schedule of Events

	Pre study	Wk 0	ACT Intervention								End of Step 1
			1	2	3	4	5	6	7	8	
Training of lay personnel in ACT	X										
Informed Consent	X										
Refusal Survey	X	X									
Demographics/Medical History		X									
Pain Assessments		X									
Psychosocial Co-morbidities		X									
Telephone call about ACT experience			X	X	X	X	X	X	X	X	
Focus group											X
*IC-informed consent, Wk - week											

Table 2: Step 2 Adapted ACT Schedule of Events

	Pre-study	Wk 0	ACT Intervention						End of Step 2	Follow up	
			1	2	3	4	5	6		3 mo	6 mo
Study Steering Committee	X										
Adapt ACT to HIV	X										
Informed Consent	X										
Refusal Survey	X										
Demographics/Medical History		X						X			
Pain Assessments		X						X			
Psychosocial Co-morbidities		X						X			
Acceptability Assessments						X		X			
Pain Assessments						X		X			
Telephone call about ACT persistence										X	X
Selected Treatment Survey						X					

Step 1 (Un-adapted ACT)

Screening Assessment (Week 0)

A PID will be assigned to each patient screened for the study. PID's should not be reassigned even if patient fails to enter the study. The PID must be included on every CRF and patient blood sample. Each site must maintain a master list of PID's in a central location. The patient registration and inclusion/exclusion CRF must be completed on the online system.

Screening will be conducted by Dr. Karris, or another trained member of the study team and will include medical history, confirmation of HIV test results, evaluation of inclusion/exclusion criteria, and signing of study consent form.

Patients who meet the study eligibility but decline to participate will be offered participation in a brief refusal survey. Patients who verbally consent to participate in the refusal survey will be administered the questionnaire in written or verbal format.

Entry Evaluations

At study entry baseline surveys will be collected using paper CRF or web-based computer assisted system (to view baseline survey see Appendix III). The computer assisted system will allow private completion of questionnaires without concern that clinic or study personnel can view the subjects responses in order to encourage candor. Participants will undergo baseline demographics and questionnaires about pain and psychosocial co-morbidities to inform generation of open-ended questions and development of a focus group guide.

Data Abstraction

It is expected that subjects will not remember exactly their recent medical history. We will abstract HIV VL, CD4, CD4 nadir, estimated date of diagnosis. ART history, and Veterans Aging Score.

Telephone or in Person Feedback from Each Session

Within 48 hours of the session each participant will be contacted by Dr. Karris or another trained member of the study team and will inquire about the experience of each individual. This will include aspects of the class they liked most and least. These surveys will also employ open-ended questions about program content.

Long-Term Follow Up

Each participant will be contacted via telephone 3, and 6 months after completion of the group ACT sessions by Dr. Karris or another trained member of the study team and will inquire about persistence of ACT practices and strategies participants recommend for ongoing use of ACT. Specifically we will ask if they are continuing ACT practices.

Step 2 Adapted ACT RCT

Screening Assessment (Week 0)

Screening will be identical to Step 1.

Entry Evaluations and Randomization

Subjects will be randomized (1:1) to ACT versus education control. A total of 20 subjects (10 per arm) will be randomized and followed for the duration of the six weeks of the intervention and control. Once ten participants are enrolled into one group that will start that adapted ACT intervention will start. At study entry baseline surveys will be collected using paper CRF or web-based computer assisted system (to view baseline survey see Appendix III) similar to Step 1.

On-Study Evaluations

Study specific follow-up visits for each subject will be kept to a minimum in order not to bias the outcome of lost to follow up. Participants will undergo pain and acceptability questionnaires at week 3 (Appendix VI). These will be repeated along with psychosocial co-morbidity questionnaires at week 8. Participants

will be provided $20 for completion of baseline assessments, $30 for midpoint and $50 for endpoint assessments.

Instructions for of Evaluations

Documentation of HIV

Documentation of HIV-1 infection will be confirmed by reviewing a positive test from any licensed screening antibody test, such as ELISA, and confirmed by a second antibody test, such as Western blot, or detectable plasma HIV-1 RNA at any time prior to study entry. If an ELISA or Western Blot is not available, HIV infection may be documented by two HIV RNA values ≥ 2000 copies/mL, drawn at least 24 hours apart. The RNA assays should have been run at CLIA approved laboratory or equivalent.

Medical and Laboratory History

At screening, a medical history will be obtained and must be recorded in the source documents. The medical history should include any previous HIV-related diagnoses, pain, malignancies, and AIDS-defining events which will be recorded on the electronic CRF. History will include date of HIV diagnosis, date of last HIV clinic visit (for those returning to care), antiretroviral (ARV) history (if any), concomitant medical conditions, substance use history.

Medication History

At screening, a medication history (only of those taken within the last 30 days prior to entry) with actual or estimated start and stop dates should be obtained and recorded in the source documents and the concomitant medication CRF, including:

- All prescription medications, including medications taken for the treatment or prophylaxis of opportunistic infections.

Non-prescription medications.

Alternative therapies and/or dietary supplements.

Allergies to any medications and their formulations must be documented.

Concomitant Medications

At baseline concomitant medications of interest taken since the last visit will be recorded in the source documentation and entered into the concomitant medication log CRF.

Antiretroviral and Pain Medication Modifications

All modifications of antiretroviral and pain medications will be recorded on the CRF's at the baseline, week 3 and 6 data extractions for Step 2: including initial doses, patient-initiated interruptions, modifications, and permanent discontinuations. These medications will also be reviewed and confirmed at the annual study visits.

Clinical Assessments

Height and Weight

Height and weight should be documented at study entry and weight documented at annual visits.

Immunologic and Virologic Studies

Nadir CD4+ T-Cell Count

The subject's prior nadir CD4+ cell count (absolute value and date) should be documented during screening and, when possible, a copy of nadir CD4+ cell count report should be included in the source

document. If this documentation is not available, then subject recollection will suffice. For Subjects who do not know the exact nadir value and for whom there is no source documentation, then recall of the categorical nadir (e.g., < 50, < 100, < 200 cells/mm^3) will suffice.

CD4/CD8 and HIV-1 RNA

At baseline, the past 12 months of CD4/CD8 count and percentage and HIV-1 RNA will be recorded. The results will be obtained via chart extraction.

Antiretroviral resistance testing

If patients have had an antiretroviral resistance test during routine care, that data will be collected via chart abstraction.

Clinical Management Issues

This is a minimal risk study. No toxicities are anticipated a no treatment or invasive procedures are being performed as part of the study. However possible risks include:

Emotional distress

This behavioral intervention bring up past trauma or experiences that cause emotional distress. A highly experienced psychologist with post traumatic stress disorder experience is the Co-investigator of this study and will assist in triage as needed. In addition, the Owen Clinic has embedded psychiatrists that are available daily for emergency evaluations and will be utilized if any study personnel raise concerns about the state of participants. Emergency room evaluations will be encouraged if distress occurs after hours. Of note the AntiViral Research Center has a 24 hour physician on call to assist with triage of participants in various studies.

Selected Pain Interview

Participants will be asked to complete a short survey concerning their pain and pain treatment methods. These surveys will take place during the second (2^{nd}) Arm 2 study visit.

Criteria for Discontinuation

- Subject requests to withdraw participation
- Primary care provider requests for subject withdrawal based on the provider's belief that study participation is no longer in subject's best interest
- Medical provider belief that the patient has life threatening clinical condition
- By the discretion of the site IRB, NIH or investigator

Statistical Considerations

This section briefly describes the planned statistical analysis. The statistical Analysis Plan (SAP) provides details. If the language in this section differs from the language in the SAP, the SAP takes precedence.

Analytic Plan: Dr. Jain and her team will lead all statistical analyses for this study. For the RCT we will obtain descriptive statistics to compare baseline characteristics between study arms (ACT versus pain education). Categorical variables will be analyzed using Fisher's Exact Test and continuous variables using Wilcoxon Rank Sum Test. To determine acceptability of group ACT, we will use the CSQ at endpoint of the intervention as the primary outcome. This is a pilot study, but we will utilize a superiority

study design, and incorporate an intent-to-treat (ITT) approach to analyze the outcome data. We will employ multivariable logistic regression analysis to study the association between clinical (duration of HIV infection, nadir CD4, BPI), demographic (i.e., age, sex, duration of HIV infection, nadir CD4), and psychosocial factors (i.e., substance use, loneliness) and intervention arm adjusting for baseline demographic and clinical characteristics. Variables significantly associated with treatment groups and outcome ($p<0.10$) including appropriate interaction terms, will be included in the final multivariable logistic regression model as covariates. CSQ at midpoint and proportion of sessions attended will be evaluated in sensitivity analyses. The study procedures can occur in person or remotely. We will statistically evaluate this process and compare group cohesion scores between persons who attend live (if feasible) and remotely.

10. HUMAN SUBJECTS

Inclusion criteria are HIV-seropositive, age ≥ 50 years, diagnosis of chronic non-cancer pain, English speaking and consents to study participation.

Exclusion criteria are cancer-associated pain, unwillingness to participate in audio recorded sessions, and enrollment in hospice.

Upon signing informed consent, the participant is considered enrolled in the study.

The exclusion criteria noted above was developed to prevent the confounding nature of cancer associated pain. We will be excluding monolingual Spanish speaking individuals as this will likely impact group dynamics of therapy. Monolingual Spanish speaking individuals aging with HIV in chronic pain is a group we will consider evaluating in future studies if our intervention demonstrates efficacy.

We will recruit persons who receive medical care at the Owen Clinic with chronic non-cancer pain (i.e. pain > 3 months that is not cancer-related) who are ≥ 50 years old. Common co-morbidities include mental illness (24% with anxiety disorders, 12% with mood disorders, 3% with schizophrenia and 5% with other psychiatric disorders), substance use disorders including tobacco and alcohol (75% have a current or past history) and poverty (43% of the population is on Medicaid, 26% is on Medicare and 8.9% is on a healthcare plan for low income PLWH or Ryan White) which enhances the real-world translatability of this intervention. Of note 8% of all Owen clinic attendees prefer Spanish, but it is unknown what proportion are monolingual Spanish only. Demographics of PLWH ≥ 50 years on > 3 months of opiate prescriptions (and thus underestimate the chronic pain population) are presented (Table 1).

Table 1. aPLWH on > 3 months of opiates for chronic pain at Owen Clinic (January 5, 2017)

	N = 355
Age years mean (range)	56 (50-70)
Sex	
Male	255 (71.8%)
Female	100 (28.2%)
Race/Ethnicity	
White	235 (66.1%)
Black	76 (18.5%)
Asian	2 (0.6%)
Native American	2 (0.6%)
Other	40 (11.3%)
Hispanic	52 (15%)
HIV Outcomes mean (range)	
CD4 T cells/mL[2]	608 (1439)
HIV Viral load <20	363 (80.3%)

Psychosocial co-morbidities and coping strategies in PLWH differ between men and women, and sex may be a modifying variable(85-87). To address sex as a biological variable, I will recruit at least 20% women and if needed rely on the Center For AIDS Research Disparities Core to achieve this (Stockman Letter of Support).

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Study Recruitment and Retention: Previously successful recruitment strategies will be employed including using CNICS infrastructure to identify eligible participants at Owen Clinic for provider-based referrals, self-referral through flyers placed in each exam room, and presentations to relevant community organizations. For pre-screening recruitment purposes ONLY, we are requesting for a partial waiver of informed consent to interrogate the EPIC database and identify potential prospective research participants who meet the eligibility criteria for enrollment as listed in Item 10 Human Subjects.

The investigator believes the pre-screening to be used for recruitment meets the following requirements for this request per 46 CFR 46.116:

1. The (pre-screening) procedure is considered no more than minimal risk to the potential subjects, since we will not perform any procedure and the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life.
2. The waiver or alternation will not adversely affect the rights and welfare of the subjects.
3. The (pre-screening) research could not practicably be carried out without the waiver or alternation; and.
4. Once the potential participants are identified, we will contact their PCP and ask them to distribute one of our IRB-approved flyers. If interested, study participants will contact the study team and schedule a screening visit (per IRB-approved study protocol). Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Recruitment procedures will also involve the review of subject records by designated study personnel (e.g., investigators and/or study coordinators) in order to identify potentially eligible subjects. Since Protected Health Information (PHI) will be accessed via the hospital's medical record database prior to contacting the potential subject about the research study, we are requesting a partial waiver of HIPAA authorization for access to PHI for purposes of prescreening only.

For HIV-infected participants recruited through the Owen Clinic, we request a partial waiver of consent to screen the Owen Clinic database for eligible participants. A list of potential eligible participants will be printed and will include the name and contact information of the responsible primary care physician. Study personnel will contact primary care providers via phone or in person and ask them to distribute study flyers. Potential participants will be contacted only through their primary care providers. Study personnel will not contact any potential participant directly. The list of name will be destroyed as soon as the providers are informed. If interested, potential study participants can contact the AVRC and schedule a screening visit.

If additional participants are needed to fulfill our recruitment needs we will seek IRB approval before distributing any recruitment materials and will implement our standard AVRC recruitment plan as described below.

Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent.

A brief subset of preliminary eligibility criteria such as age, gender, and sexually transmitted disease diagnosis in the past 12 months, will be reviewed by study personnel to determine subjects' preliminary eligibility for the research study. There will be no direct contact of the potential research subject by the pre-screener (i.e., study staff). The pre-screener will ask the subject's treating physician to approach the subject. The treating physician will further discuss the research study with the potential subject and ask whether they would like to be contacted by study staff to discuss the trial (i.e., counseling) and/or provide the potential subject with the study staff's contact information. Eligibility may be formally

determined at the time of counseling, but any research-specific screening procedures will only be performed after informed consent is obtained and a standard, stand-alone HIPAA authorization form is signed.

For the partial waiver of individual authorization for pre-screening recruitment purposes ONLY of individual HIPPA/Protected Health Information. The following conditions apply:

1. The (pre-screening) research involves no more than minimal risk, since we will not perform any procedure and the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life.
2. Granting of waiver for recruitment purposes only will not adversely affect privacy rights and welfare of the individuals whose records will be used.
3. The pre-screening could not practicably be conducted without a waiver.
4. The pre-screening could not practicably be conducted without use of PHI.
5. The privacy risks are reasonable relative to the anticipated benefits of research.
6. An adequate plan to protect identifiers from improper use and disclosure is included in Item 16.
7. Participant identifiers/sensitive information shall be removed/destroyed as soon as they are no longer needed and in accordance with AVRC policy. The investigators have procedures in place to periodically review collected participant identifiers/sensitive information to ensure it is still required to satisfy a particular purpose or carry out a function.
8. The participants' PHI will not be re-used or disclosed for other purposes.

The standard AVRC step-by-step recruitment plan is delineated by the following four steps: 1) Educate potential participants and promote study enrollment using flyers and media in waiting rooms and in treatment rooms at UCSD clinics and other likely recruitment sites throughout the community, e.g., local hospital psychiatry services, community based organizations, local pharmacies, etc.; 2) Station recruitment staff in clinics (e.g., UCSD's Owen Clinic) to work with providers in identifying individuals potentially eligible for the research study; where appropriate and with IRB consent, these activities may include reviews of clinical charts; 3) Conduct outreach and informative presentations to staff and potential participants at identified recruitment sites; 4) List the study on AVRC website for potential participants. This website is known throughout the San Diego HIV community to be a resource for HIV-related information; 4) Ask identified study participants to recruit others who may be eligible for inclusion using established sampling techniques (e.g., snowball sampling, respondent driven sampling).

However, now that a majority of outpatient visits are being performed using video visits – potential participants are no longer being exposed to study flyers in clinic. We request Owen clinic providers be allowed to recommend this study using mychart communications. We also propose to utilize social media – such as facebook, Instagram and twitter to recruit potential participants. Only approved wording (as indicated in the study flyer) will be included.

Philosophy of recruitment

Working with a population experiencing the complex issues of HIV disease, we have found that it is especially important to have flexibility in the assessment schedule. Thus, the assessment schedule designed for this project has the necessary flexibility to adapt to the real-life complexities of working with this clinical population. For example, visits can be scheduled Monday – Saturday and can be completed in one visit or split over multiple visits. Procedures are also in place to overcome barriers such as lack of transportation, need for childcare or dependent care, and other factors. Reminder calls

are also provided. Participants who miss a visit are contacted and the reasons that contributed to the missed visit are examined. Planned future visits take this information into account and make accommodations whenever possible.

12. INFORMED CONSENT

Providing Informed Consent: Individuals who are interested in participating in the study will complete a screening informed consent. If we determine that they meet criteria for the study they will complete the informed consent process conducted by trained study personnel and will be provided with copies of the informed consent document, HIPPA consent document, and the "Experimental Subject's Bill of Rights." Potential participants will be fully informed of the risks of participating in this research study. During the informed consent procedure, patients will be informed that all data obtained during the study is strictly confidential, and that no information will be shared with others without the participant's express written approval. Potential participants are encouraged to ask questions throughout this process. Documentation of informed consent will be obtained at the time of a subject's enrollment in the study.

Due to the COVID-19 pandemic, a telephone and/or video teleconference consent process will occur. Study staff will document consent to participate on the telephone consent form. Since we will obtain consent via phone or by videoconference, we request a waiver of documented consent. We will obtain oral consent from all participants. This waiver is justified as the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to participating in this study is not participating. Not participating will not impact the participation in other on-going care or other AVRC or Owen clinic studies.

14. POTENTIAL RISKS

The focus groups, questionnaires, and physical function assessment all pose minimal risk, but may cause increased stress, anxiety, and fatigue in some individuals as they ask participants to relay information regarding sometimes sensitive psychological states.

There is a risk of audio recording. One potential risk is that of breach of confidentiality could occur when interviewed, audiotaped or participating in a focus group, wherein a person's sexual behaviors, drug use history, or other sensitive information might be disclosed, resulting in embarrassment or even prejudicial treatment by others.

To minimize this risk, we will adhere to the standard risk management protocol, including use of participant identification numbers, locked data cabinets, and password protected computer databases and address all group participants by a pseudonym.

This behavioral intervention bring up past trauma or experiences that cause emotional distress. A highly experienced psychologist with post traumatic stress disorder experience is the Co-investigator of this study and will assist in triage as needed. In addition the Owen Clinic has embedded psychiatrists that are available daily for emergency evaluations and will be utilized if any study personnel raise concerns about the state of participants. Emergency room evaluations will be encouraged if distress occurs after hours. Of note the AntiViral Research Center has a 24 hour physician on call to assist with triage of participants in various studies.

Lastly Because we are using Zoom conference there is the potential for frustration with the technology. However we will provide training in person prior to the groups and troubleshooting in groups. To prevent risk of hacking we will also be using password protection.

Since this is a research study, these assessments and procedures may also involve other risks that are currently unforeseeable.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Decreasing participant burden: To reduce the risk of anxiety and fatigue, the time needed to complete interviews will be minimized by thoroughly familiarizing staff with all data collection materials and questionnaires. Staff are also trained to recognize the symptoms of anxiety and frustration and do not press participants to answer questions that appear unduly distressing. Interviews, exams and assessments are rescheduled or omitted if a participant displays symptoms of becoming overly distressed, fatigued, or frustrated by their efforts. Individuals with clinically significant depression symptoms are offered referral for appropriate psychiatric care (e.g., counseling and/or medication management). We will offer participants the option of assessment over multiple days.

Participants can elect to withdraw from the study at any point, and they will be reminded that they do not have to answer any questions that they do not wish to. Participants may also elect to take breaks during assessments or reschedule appointments on other days in case of fatigue. As the study assessments will involve discussion of emotional distress, HIV status, and substance abuse, we will mitigate against negative effects of the assessment by reminding participants that they may elect not to answer questions about sensitive topics.

Collected data (transcribed focus group recordings) will be stripped of any participant identifiers (e.g., name) and only identified by the coded ID's in order to maintain participant confidentiality. Fake names can be used in place of subjects legal names to protect identity. Once the interview has been transcribed the audio recording will be destroyed. All records will be kept locked in a cabinet in a secure office at the study sites available only to the site investigators. All computer entry and networking programs will be done with coded numbers only and analyzed centrally without any possibility of linking subject identity with subject data.

The ACT intervention is planned for a duration of two hours for six weeks. ACT providers will be specifically trained to be aware of participant fatigue, and participant triggering and to stop the intervention as deemed necessary to address these issues. Five to ten minute breaks will be allowed as needed and participants will be free to come and go during the intervention if necessary. Participants will also be instructed to communicate their personal needs to the group and request a break, or more intensive psychiatric assistance as needed.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Security of data: Participant records are maintained in a confidential and secure manner. All staff are trained to maintain participant confidentially. Data collection forms carry only study identification numbers. All records are stored securely in locked rooms and/or locking file cabinets. Standard measures exist for all computerized records, which limit data access to selected research project personnel. The electronic data are protected by four separate levels of password access, specifically: 1) to an individual machine, 2) to the server machine, 3) to the central database, and 4) within the database to each data table assigned by the database administrator to an individual user. Collected data (transcribed focus group recordings) will be stripped of any participant identifiers (e.g., name) and only identified by the coded ID's in order to maintain participant confidentiality. . Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB and governmental agencies.

The AVRC research staff has undergone the CITI Biomedical Human Research, and Good Clinical Practice (GCP) training along with the HIPAA training.

The research staff will protect Patient Protected Health Information (PHI) or other Personal Identification Information (PII) of any individual in general, obtained from as part of the University or Healthcare or other work-related records, for whatever purpose, as private and confidential, and will make every effort to safeguard such information from unauthorized access or dissemination. Steps in place to protect this information are outlined below (Data Security).

Data Security: Any data collected as part of this study that is stored at the AVRC and/or is transferred via the internet will follow our data security process as outlined below.

With the fast-developing technology, dependable and comprehensive data security measures are key components to defy the perceived threats of Internet hackers and accidental disclosure of confidential information. In the following we provide a summary of the key features pertinent to this project.

- An anonymous participant identification number is used for all data collection, recording, and submission to the project database.
- Data that contain any participant identifiers (e.g., name or contact information) other than the unique identifier are password protected and accessible only to staff members whose job requires knowledge of such data.

Data transfer and all Web-based utilities use secure access (user and server authentication, 128-bit SSL encryption). This type of encryption is the same as is used for Web-based transactions that involve credit cards or Web banking.

17. POTENTIAL BENEFITS

There are no direct benefits of taking part in this study.

18. RISK/BENEFIT RATIO

It is the opinion of the investigators that because the risks of participation are minimal and anticipated knowledge to be gained is significant, the benefits outweigh the risks.

19. EXPENSE TO PARTICIPANT

There is no expense to the participant.

20. COMPENSATION FOR PARTICIPATION

Participants will be compensated $20 for completion of baseline questionnaires. For persons in the RCT arm compensation will be $30 for mid-study questionnaires and $50 for the final questionnaire. An additional $20 will also be provided if participants choose to participate in an individual interview. To ensure safety of participants during COVID-19 and respect the “shelter at home” state-wide order compensation will be provided either by an electronic gift card OR by mailing of a script.. Participants will not receive compensation for their involvement in the follow up questions. (occur via phone).

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

This is not a VA Study.

Maile Young Karris, MD is an Associate Professor of Medicine in the Division of Infectious Diseases is an active clinical researcher who will serve as PI for this project and will be primarily responsible for completion of all planned activities. She is well trained in the Responsible Conduct of Research and up to date on all other required training.

Julie Wetherell PhD, ABPP, is a certified geropsychologist at the Veterans Affairs San Diego Healthcare System where she directs behavioral medicine services and a Professor of Psychiatry at UCSD. She will lead training of ACT and co-develop adapted ACT protocols for RCT. of Dr. Wetherell is also an active researcher and up to date on required training.

Alison Moore MD, MPH, FACP is a Professor of Medicine and the Division Chair of Geriatrics. She is an expert in the performance of clinical and behavioral interventions in minority populations including a mixed behavioral intervention on chronic pain in people with HIV and substance use. She is up to date in the responsible conduct of research.

Dilip Jeste, M.D., is a faculty member in the Department of Psychiatry at UCSD will serve on the steering committee for this project. He will assist in synthesizing data from focus groups and feedback and determining adaptions to ACT for the RCT.

Sonia Jain PhD, is the lead statistician for the study and will assist with data monitoring, tracking reports and statistical analyses of qualitative and quantitative data.

Edward Seefried, is a retired nurse who will undergo training in ACT and perform adapted ACT in RCT.

Velma Justice-Royster is a substance abuse counselor who will undergo training in ACT and perform adapted ACT in RCT.

Zachary Smith will assist with data management.

M. Carrington Reid is a faculty member in the Department of Psychiatry will serve on the steering committee for this project. He is part of the steering committee and will assist in synthesizing data from focus groups and feedback and determining adaptions to ACT for the RCT.

Helene Le and **Joseph Lencioni** will serve as the regulatory contacts.

22. BIBLIOGRAPHY

19. FUNDING SUPPORT FOR THIS STUDY

We have received a Just in Time notification for this project from the NIH. The award number is R03 AG060183

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable

26. IMPACT ON STAFF

There will be minimal impact on other staff.

27. CONFLICT OF INTEREST

There is no conflict of interest for the investigators or key personnel of this study.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

The subjects enrolling/participating in this study will have the ability to:

- Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, as well as the risks and benefits of participating versus not participating;
- Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for their own situation and condition;

- Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternative, and
- The ability to express a choice about whether or not to participate.