Cover page

Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors

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PSILOCYBIN-ASSISTED GROUP THERAPY FOR DEMORALIZATION IN LONG-TERM AIDS SURVIVORS

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Principal Investigator (Sponsor-Investigator)

Brian Anderson, MD, MSc
University of California San Francisco
401 Parnassus Ave, Rm 309
San Francisco, CA 94143
E-mail: brian.anderson@ucsf.edu
Telephone: 415-476-7432

Co-Principal Investigator

Josh Woolley, MD, PhD
University of California San Francisco
401 Parnassus Ave
San Francisco, CA 94143
E-mail: josh.woolley@ucsf.edu
Telephone: 415-221-4810x24117 Fax: 415-379-5667

Co-Investigators

James Dilley, MD
Christopher Stauffer, MD

Statistician

Matthew Boden, PhD

Clinical Research Coordinator

Phillip Perl, MA
E-mail: phillip.perl@ucsf.edu
Telephone: 415-476-7432 Fax: 415-502-6361

Abstract

Title	Psilocybin-Assisted Group Therapy for Demoralization in Long-term AIDS Survivors
Patient population	HIV-positive people ≥50 years old who were diagnosed with HIV prior to the clinical availability of combination antiretroviral therapy (~1996).
Rationale for Study	Long-term AIDS Survivors (LTAS) are people living with HIV (PLH) who were diagnosed prior to the advent of combination antiretroviral therapy (ART) and, compared to their HIV seronegative peers, suffer higher rates of depression, anxiety, trauma exposure, substance use and risky sexual behaviors [1-6]. Prior to ART, people living with HIV were "end-of-life patients," then with advent of ART they became "chronically ill," and now many of them are re-approaching end-of-life status as their bodies age at an accelerated rate due to HIV infection, HIV therapies, HIV-associated non-AIDS conditions, or all of the above [7]. By 2014, 9,202 HIV-positive individuals living in San Francisco were older than 50 years old (58% of the city's HIV-positive population) [8]. Like "cancer survivors," AIDS survivors experience increased rates of psychological distress even long after their disease is controlled [9, 10]. LTAS are an emerging population whose mental health needs are under recognized and undertreated. Existential distress is a form of psychological suffering precipitated by the acute awareness of one's mortality [11]. Demoralization is one type of existential distress [12], and it is characterized by a sense of hopelessness, helplessness and a loss of meaning in life [13]. Demoralization is a well-characterized clinical syndrome that captures the form of psychological distress suffered by many LTAS [1, 14]. Demoralization is also a clinical construct well-suited for investigation as a hypothesized therapeutic benefit of psilocybin-assisted psychotherapy in a population with chronic existential distress, like LTAS. Because it is experienced as a loss of meaning, demoralization should theoretically be treatable with interventions that enhance meaning-making [15]. An investigational pharmacotherapy that is thought to potently enhance meaning-making is psilocybin [16, 17]. Recent trials of individual psilocybin-assisted psychotherapy for anxiety and depression in cancer patients have shown this intervention to be safe [18-20], and have found significant improvements in anxiety and depression lasting months after a single treatment [19, 20]. Such impressive results are thought to be mediated by two mechanisms: 1) Having a complete "mystical-type" experience under the influence of psilocybin [21], and 2) Subsequent enhanced social support in the weeks following the mystical experience [22]. It remains unknown how these impressive results may translate into other palliative care populations. Since the beginning of the HIV/AIDS epidemic, many psychotherapies for people living with HIV have been preferentially delivered as groups because of enhanced cost-effectiveness and the group format's unique clinical benefits with respect to the enhancement of social support in a population suffering high rates of isolation and loneliness [23]. This study will use the same standard psilocybin administration safety guidelines

Rationale for Study (continued)	as prior trials [24], but the psychotherapy sessions will employ a modified form of Supportive-Expressive Group Therapy (SEGT) [25]. SEGT is a widely used, manualized, evidence-based group intervention for existential distress in patients with life-threatening disease [26]. The current study will be the first modern study of psilocybin-assisted group psychotherapy. In the current study, the group psychotherapy format functions as a standardized context in which patients' experiences of social support can be objectively observed pre- and post-psilocybin. This is helpful because while prior trials of psilocybin-assisted psychotherapy evaluated clinical *outcomes*, they did not make use of validated measures of psychotherapeutic *process*. By administering psilocybin as an adjunct to SEGT, we will be able to explore quantitatively and qualitatively not only the intrapersonal, but also the interpersonal, therapeutic mechanisms catalyzed by psilocybin in LTAS suffering from demoralization.
Primary Objective	To demonstrate the safety and feasibility of Psilocybin-Assisted Supportive-Expressive Group Therapy (PA-SEGT) for demoralization in LTAS.
Exploratory Objectives	To explore the preliminary efficacy of PA-SEGT for improving demoralization, complicated grief, depression, anxiety, quality of life, functional social support, post-traumatic growth, openness to experience, mindfulness, social connection, nature relatedness and ART medication adherence in LTAS. To explore quantitatively and qualitatively the mechanisms through which PA-SEGT addresses existential distress in LTAS.
Study Design	Open-label mixed-methods pilot study of individual oral psilocybin drug sessions (with escalating dose) combined with an evidence-based, manualized brief group psychotherapy.
Number of patients	A maximum of 36 patients will receive the intervention and complete the study. A minimum of 8 patients will receive the intervention and complete the study.
Duration of Therapy	8 weeks after the initiation of the intervention.
Duration of Follow up	3 months after completion of the intervention.
Duration of study	2 years from the time the study opens to accrual.
Study Therapy	Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) will be administered once at a moderate-to-high dose of 0.3mg/kg (or 0.36mg/kg) po during an individual medication visit to be held after 4 group therapy visits have been completed. Patients will undergo a total of 10 group psychotherapy sessions.

Safety Assessments	Adverse events Vital signs Adverse Event Medication Session Form Columbia Suicide Severity Rating Scale Community Observer Rating Form
Feasibility Assessments	Rate of Patient Recruitment Rate of Patient Retention (Sessions Attended and Follow-ups Completed) Client Satisfaction Scale Individual Patient and Important Other/Caregiver Interviews Supportive-Expressive Group Therapy Topic Grid Focus Groups with Patients and Important Others/Caregivers
Primary Outcomes	Demoralization Scale-II Inventory of Complicated Grief
Secondary Outcomes	Antiretroviral Medication Adherence Scale Alcohol Use Disorders Identification Test Center for Epidemiologic Studies Depression Scale—Revised Challenging Experience Questionnaire Clinical Global Impressions Scale Credibility/Expectancy Questionnaire Duke/UNC Functional Social Support Questionnaire—5 Drug Use Disorders Identification Test Experiences in Close Relationships scale—Modified 16 Group Psychotherapy Intervention Rating Scale Group Questionnaire HIV and Abuse Related Shame Inventory Individual Group Member Interpersonal Process Scale International Personality Item Pool—Openness to Experience-20 Life Events Checklist - 5 McGill Quality of Life Questionnaire—Revised-Short Multidimensional Assessment of Interoceptive Awareness—Revised Mystical Experience Questionnaire—30 Nature Relatedness Scale, Short Form Post-traumatic Growth Inventory—Short Form PTSD Checklist-5 Schedule of Attitudes towards Hastened Death Social Connectedness Scale-Revised

	State-Trait Anxiety Inventory Qualitative analysis of therapy sessions, interviews & focus groups
Unique Aspects of this Study	This trial will be the first clinical trial of psilocybin-assisted psychotherapy for LTAS. It will also be the first modern trial of psilocybin-assisted *group* psychotherapy. It will be the first study of psilocybin-assisted psychotherapy for existential distress that will employ an evidence-based psychotherapy in the non-drug therapy sessions. The study will provide the first safety data for the use of this intervention in LTAS. It will not only yield preliminary data on the potential efficacy of this novel intervention, but it will also be the first study to employ both validated quantitative measures and qualitative methods in the analysis of the psychotherapeutic *processes* germane to psilocybin-assisted psychotherapy. It will also be the first clinical trial of psilocybin-assisted psychotherapy to assess the impact of the intervention on quality of life in partners/caregivers of LTAS. In anticipation of larger, better powered trials, clinical outcomes from this Phase I study will be used to produce the first estimates of effect size of this novel treatment for demoralization in palliative care patients.

Table of Contents

Abbreviations

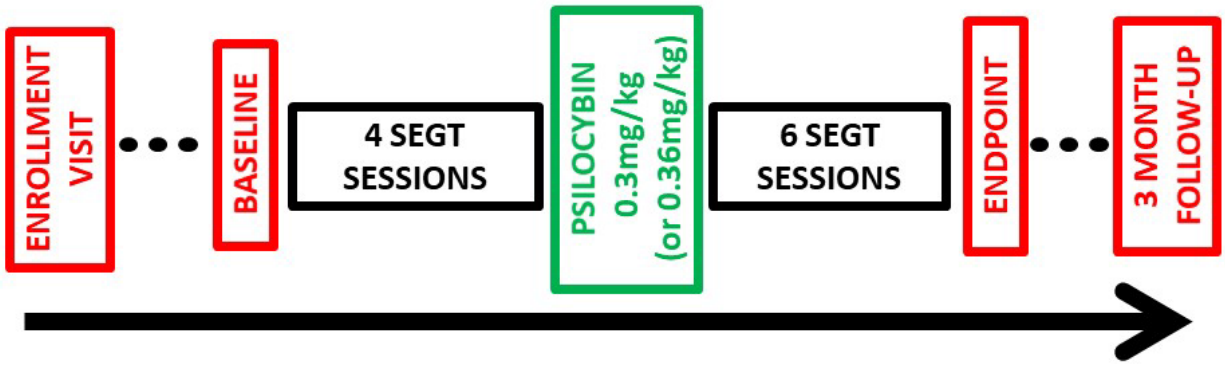
AGPA	American Group Psychotherapy Association
AHP	Alliance Health Project
AIDS	Acquired Immune Deficiency Syndrome
Albumin	Alb
AlkPhos	Alkaline phosphatase
Alt	Alanine aminotransferase
AMAS	Antiretroviral Medication Adherence Scale
AMAS	ART Medication Adherence Scale
ANOVA	Analysis of Variance
ART	combination Antiretroviral Therapy
Ast	Aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BUN	Blood Urine Nitrogen
CBC	Complete Blood Count
ChEQ	Challenging Experience Questionnaire
CrEQ	Credibility/Expectancy Questionnaire
CESD-R	Centers for Epidemiologic Studies Depression Scale—Revised
CHR	Committee on Human Research
CMP	Comprehensive Metabolic Panel
CORF	Community Observer Rating Form
Cr	Creatinine
CSS	Client Satisfaction Scale
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Concomitant Therapeutics Checklist
DEA	Drug Enforcement Agency
DS-II	Demoralization Scale—II
DSM	Data and Safety Monitor
DUDIT	Drug Use Disorders Identification Test
DUFSS-5	Duke UNC Functional Social Support Questionnaire-5
ECG	Electrocardiogram
ECR-M16	Experiences in Close Relationships scale—Modified 16
ES	Effect Size
FDA	Food and Drug Administration
FT4	Free thyroxine
Gluc	Glucose
GPIRS	Group Psychotherapy Intervention Rating Scale
GQ	Group Questionnaire
HAART	Highly Active Antiretroviral Therapy
HANA	HIV-Associated Non-AIDS
HARSI	HIV and Abuse Related Shame Inventory
Hct	Hematocrit
Hgb	Hemoglobin
HIM	Hill Interaction Matrix
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICC	Intraclass Correlation Coefficient
ICF	Informed Consent Form
ICG	Inventory of Complicated Grief
IND	Investigational New Drug
IPA	Interpretive Phenomenological Analysis
IPIP-OE-20	International Personality Item Pool—Openness to Experience-20
LEC-5	Life Events Checklist-5
LPPI	Langley Porter Psychiatric Institute
LSD	Lysergic acid diethylamide-25

LTAS	Long-term AIDS Survivor
MAIA	Multidimensional Assessment of Interoceptive Awareness
MAOI	Monoamine Oxidase Inhibitors
MEQ-30	Mystical Experience Questionnaire—30
MOCA	Montreal Cognitive Assessment
MQoL-RS	McGill Quality of Life Questionnaire—Revised-Short
NR	Nature Relatedness Scale, Short Form
NEO-PI-R	Revised NEO Personality Inventory
OPLH	Older People Living with HIV
PA-SEGT	Psilocybin-assisted Supportive-Expressive Group Therapy
PCL-5	PTSD Checklist
PEQ-S	Persisting Effects Questionnaire—Spirituality
PLH	People Living with HIV
Plt	Platelet
PPSv2	Palliative Performance Scale version 2
PTG	Post-Traumatic Growth
PTGI-SF	Post-Traumatic Growth Inventory—Short Form
PTSD	Post-Traumatic Stress Disorder
QoLLTI-Fv2	Quality of Life in Life-Threatening Illness—Family Carer Version 2
SAHD	Schedule of Attitudes towards Hastened Death
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SCID-5	Structured Clinical Interview for DSM-5
SCS-R	Social Connectedness Scale-Revised
SEGT	Supportive-Expressive Group Therapy
SEGT-TG	Supportive-Expressive Group Therapy Topic Grid
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SSRI	Serotonin Reuptake Inhibitors
STAI	State-Trait Anxiety Inventory
Tbili	Total bilirubin
TCA	Tricyclic Antidepressants
TProt	Total protein
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cell

1 Introduction

We propose to conduct a clinical trial of psilocybin-assisted psychotherapy for demoralization in Long-term AIDS Survivors (LTAS). This will be the first trial of psilocybin-assisted psychotherapy specifically for people living with HIV (PLH) and it will be the first modern trial of psilocybin-assisted *group* psychotherapy for any indication. The study will consist of up to six groups of six gay-identified HIV-seropositive people ≥50 years of age who were diagnosed with HIV prior to the clinical availability of combination antiretroviral therapy (~1996) and who have moderate-to- severe demoralization [13, 27]. Psychotherapy groups may be organized based on gender identity and sexual orientation to create homogenous groups. Each subject will undergo 10 sessions of a modified form of Supportive-Expressive Group Therapy [25] and one individual psilocybin treatment session [24] after group four of the intervention. Quantitative and qualitative measures of psychotherapeutic process will be used to explore the mechanisms by which this novel therapy seems to work, particularly on the interpersonal level. Quantitative and qualitative measures will assess changes in quality of life of the partners/caregivers of subjects undergoing the intervention. This study will contribute to the available data on the safety, feasibility and efficacy of psilocybin-assisted psychotherapy for existential distress in palliative care patients, and importantly will provide the first of such data on a palliative care population other than cancer patients [28].

Fig. 1 INTERVENTION TIMELINE



1.1 Background on Indication

Existential Distress and Demoralization

Existential distress is a form of psychological suffering that occurs when one is confronted with one's own mortality [11]. Demoralization is a form of existential distress that is prevalent in the palliative care setting and is characterized by hopelessness and helplessness due to a loss of purpose and meaning in life [12, 13]. Demoralization is associated with, but distinct from, depression, anxiety, isolation, and the desire for hastened death [29]. In palliative care patients, demoralization has been shown to be more strongly associated with suicidal ideation than depression is [30]. In modern palliative care, the current standard is to address existential and spiritual issues in patients and their family members [31, 32]. Following the lead of innovators like Frankl [33] and Yalom [34], investigators have over the last two decades devised a number of existential psychotherapies [35-40] with varying impact on depression, anxiety and quality of life [26, 41]. Arguably, what these therapies have in common is what Cassel [42] long ago prescribed

for the relief of suffering—*transcendence*—an experience that is difficult to define medically and a challenge to provide consistently in clinical settings. Palliative care stands to benefit greatly from a time-limited intervention that enhances patients' capacity to forge meaning, to transcend suffering, and to overcome social isolation and the fear of the unknown in a safe, immediate and reliable manner. This need is pronounced among LTAS.

AIDS Survivors

By 2004, there had been an estimated 929,985 cases of AIDS in the US, and 524,060 of them had died [43]. With the advent of combination antiretroviral therapy (ART) in 1996, HIV seropositive individuals began to accomplish what once was thought to be impossible—living into old age. Because of the decreased lifespan and the apparently accelerated aging experienced by PLH, "older" in HIV is defined as ≥50 years of age [44]. Many LTAS are therefore also considered older people living with HIV (OPLH). Despite recent gains in mortality, many of today's LTAS are still grappling with having been, at one point, an "end-of-life" patient. Beyond being confronted by their own mortality at the time of diagnosis, LTAS frequently bore witness to the deaths of friends and loved-ones, and often served as informal caregivers to those dying of AIDS [45]. AIDS-related bereavement is associated with demoralization, depression, and problematic substance use [46]. Survivor's guilt is common among LTAS, as is loneliness [47]. Isolation and loneliness are highly prevalent among LTAS not only because affected communities were decimated by AIDS in the 1980s and '90s, but also because many OPLH often lack traditional family support structures due to several possible causes that include protective withdrawal from one's biological family, having been disowned by family or friends due to stigma, or not having children [1, 47]. Because of reduced social support networks, and therefore a relative lack of access to informal caregivers, OPLH are in general expected to be especially reliant on community-based services as they age [1].

Multimorbidities

Compared to HIV seronegative demographically- and behaviorally-matched peers, OPLH are at increased risk of multimorbidities known as HIV-associated non-AIDS (HANA) conditions, such as cardiac disease, with PLH having a 50% increased risk of acute myocardial infarction compared to HIV seronegative matched controls [48]. PLH are also at higher risk of some HANA malignancies, having three times the cumulative incidence of liver cancer and thirty times the cumulative incidence of anal cancer [49]. PLH are also at increased risk of serious bone, liver and kidney disease [44, 50]. As the health of OPLH declines, HANA and other conditions can serve as continual reminders of one's mortality. OPLH also suffer from high rates of mental health conditions such as depression (prevalence up to 50%), suicidal ideation, and anxiety (prevalence up to 20%) [1, 2]. AIDS patients have been found to have an increased desire for hastened death [51]. Among PLH (of all ages) PTSD has a prevalence that ranges 10-74% [3, 52]. Like PLH of other ages, OPLH have higher rates of substance use [4, 5, 53] and risky sexual behaviors [6] than the general population and these behaviors are associated with ART nonadherence and therefore disease progression and secondary HIV transmission [54]. The incidence of HIV in US adults over 50 years of age saw no improvement from 2010-2014 [55]. Comorbid depression, anxiety and PTSD are also associated with ART non-adherence in PLH [56-59]. Depression treatment has been shown to increase ART adherence in PLH [60], and possibly to decrease secondary transmission of HIV [61]. Data specific to OPLH and behavioral interventions that increase ART adherence, however, is limited to few studies that are wanting in methodological rigor [62].

Older People Living with HIV

The CDC projected that people over the age of 50 years would constitute the majority of the HIV-positive population in the US by 2015 [63]. OPLH became the majority of the HIV-positive population in San Francisco in 2012, and their proportion of the population continues to rise [8].

It is estimated that over 70% of the US HIV seropositive population will be ≥50 by 2020 [64]. The NIH Office of AIDS Research Working Group on HIV and Aging has highlighted as priority research areas, among others: Research on mental health in older adults with HIV and possible interventions; Research on substance use in older adults with HIV; Research on social networks and care giving of older adults with HIV [1]. The HIV community has responded to the demographic change by forming peer support groups and holding town halls on the issue across the country [65]. Organizational initiatives have sprung up around the issue, including patient advocacy groups like the Medius Institute and Let's Kick AIDS Survivor Syndrome (www.letskickass.org), with "AIDS Survivor Syndrome" being a patient-promoted syndrome characterized by traumatic exposure, complicated grief, depression, self-destructive behavior and hopelessness. Also, many local government and non-profit efforts have emerged over the last half decade, including the AIDS Community Research Institute of America's Center on HIV and Aging, the 50-Plus Program at San Francisco AIDS Foundation, and the San Francisco County Workgroup on HIV and Aging. Finally, the popular press has recently directed attention to the issue [66-68], and in 2016 the San Francisco Chronicle even made a feature-length documentary on the struggles of older HIV-positive gay men in San Francisco [69].

Treatment Needs

Much of the recent literature on the mental health treatment needs of OPLH has focused on depression [7]. Despite the well-established relationship between depression, grief and demoralization in PLH [46], grief and demoralization have been less frequently studied since the advent of ART. Preliminary analysis of outcomes from support groups for OPLH at UCSF's Alliance Health Project (AHP) indicates that depression and anxiety symptoms improve from participating in these groups, but trauma symptoms, particularly related to traumatic losses, tend to persist [70]. These AHP findings are supported by the literature that shows that coping/support groups for OPLH can improve depressive symptoms [71]. This is also supported by anecdotal evidence from the Director of the San Francisco AIDS Foundation's 50-Plus program, who reports that members of this community need more access to treatments for psychological trauma [65]. Current literature suggests that PLH have difficulty finding therapies that adequately address traumatic loss and grief [72]. More specifically, the Director of the San Francisco AIDS Foundation's 50-Plus program has stated "We need a treatment tailored to our community's needs; not just recycled therapies for other people," which again is supported by the literature which suggests that PLH respond better to therapies specifically targeted to grief and psychiatric distress (done in a group) than generic individual psychotherapy [73]. Whereas coping groups for bereavement in PLH have shown brief but unsustained improvements in grief, they have not proven to benefit general psychological distress or functioning [43]. Another recent study did demonstrate short-term reductions in traumatic stress from a coping group intervention in PLH, but no data are available on the durability of these benefits [74].

Group Therapy, Social Support, and Post-Traumatic Growth

Spiegel and Yalom's Supportive Expressive Group Therapy (SEGT) [34, 75] was originally designed as an intervention for advanced cancer patients, has since been modified to be used with a variety of palliative care patients, and has a robust evidence base for its efficacy [41]. SEGT emphasizes social support and increasing communication with caregivers. It also focuses on processing affect in the 'here and now' and 'detoxifying death and dying'; it includes exposure to a therapeutic altered state of consciousness (self-hypnosis); and it encourages emotional expression and openness [25]. Manuals exist for traditional (1 year) [75] and brief (12-week) [76] SEGT, and SEGT has been shown to be teachable [77]. SEGT has also already been modified for and used with success in patients with advanced HIV [78]. A recent study of tele-SEGT for depressed OPLH found that therapeutic alliance did not predict clinical response, but group cohesion and perceived member similarity did [79]. Social support in PLH is related to improved mood, well-being and medication adherence [44]. Enhanced social support in PLH is also associated with enhanced post-traumatic growth (PTG) [80]. Whereas much of the literature on

the mental health of PLH focuses on coping, the concept of PTG goes beyond coping with the problems associated with living with HIV and includes improvement in one's mental health. PTG comprises an increased appreciation for life, enhanced self-efficacy and ability to forge intimate relationships, and the increased expression of emotions and hope for the future [80]. PTG is associated with fewer depressive symptoms in PLH [81]. Currently, however, there is a dearth of literature specifically on PTG and HIV [3, 82], especially on interventions that enhance it. Of particular relevance to our study, PTG is associated with a heightened interest in spirituality [80].

Psychoneuroimmunology in HIV

It seems that HIV remains a rich field of investigation of the mind-body connection, and perhaps especially among OPLH who may have greater mental and physical health needs compared to younger PLH. Earlier literature on psychoneuroimmunology and HIV regularly found associations between depression, traumatic exposure and disease progression and mortality in PLH, both before and soon after the advent of ART [83, 84]. It is unclear whether such associations remain with the improved ART regimens available today. Nevertheless, recent data have shown that spiritual coping in PLH is associated with increased survival [85]. And after controlling for ART use, depression, hopelessness, and avoidant coping have predicted the progression of viral load and CD4 count longitudinally [86]. Recent data from the NIH indicate that PTSD is associated with differential immune activation in PLH, even in those who are virally suppressed [52]. While spirituality and religiosity have been positively associated with enhanced mental health in PLH, the personality traits of conscientiousness, openness and agreeableness (measured with the NEO-PI-R) are more strongly positively associated with mental health in this population [87]. Openness has also been inversely associated with disease progression over 4 years [88]. Finally, in PLH dispositional mindfulness has been inversely related to depression, stress appraisal and negative affect, while it is positively associated with positive affect [89].

1.2 Background on Psilocybin-assisted Psychotherapy

Psilocybin is a natural product found in many species of psychoactive fungi around the world [90]. Modern scientific research with psilocybin began when the chemist Albert Hoffman first isolated psilocybin from *Psilocybe mexicana* mushrooms in 1957 [91]. Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is the prodrug of psilocin (4-hydroxy-N,N-dimethyltryptamine), an indoleamine that acts as an agonist of serotonin 5HT 1A, 2A and 2C receptors [92]. In humans, psilocybin is rapidly metabolized to psilocin after oral ingestion, where it demonstrates linear pharmacokinetics over the 0.3-0.6 mg/kg dose range [93]. Psilocin has no known P450 interactions and is instead glucoronidated and renally excreted [91, 94, 95]; less than 2% of plasma psilocin is excreted in the urine in that form, suggesting no need for dose adjustment in patients with mild-moderate renal impairment [93]. Relative to other psychedelics (e.g., lysergic acid diethylamide-25, a.k.a. LSD), psilocybin has a simpler neurotransmitter receptor profile (it is known to act only at serotonin receptors) and a shorter duration of acute effects (4-5 hours) [91, 96]. Psilocybin is one of the "classic hallucinogens" (a.k.a. "classic psychedelics") that were investigated in the mid-20th century for their potential as pharmacologic adjuncts to psychotherapy. By the mid-1960s, over 1,000 clinical reports were published on the experiences of over 40,000 treatment sessions in which psychedelics had been legally administered to patients in clinical settings [97] such as at Harvard [98], UCLA [99], and UCSF [100].

This early research suggested that one of the most promising indications for psychedelic-assisted psychotherapy was the treatment of existential distress in patients with advanced disease, particularly cancer. This was first reported by Kast, an internist who administered LSD (without psychotherapy) to terminally-ill patients as an experimental analgesic. He found that a single dose of LSD decreased physical discomfort and improved mood, and that these effects lasted for about 10 days [101]. More systematic work later occurred at Spring Grove Hospital

near Baltimore, Maryland where a team developed a protocol for psychedelic-assisted psychotherapy for the terminally ill. Their protocol included several non-drug preparatory sessions designed to build trust and rapport between the participant and the therapists. Then, during the drug session itself, the therapists (usually a team of two) would sit beside the patient and mostly provided non-directive verbal reassurance. Afterward, several non-drug psychotherapy follow-up sessions took place over the next few weeks to psychologically "integrate" the drug experience into the patient's life. One legacy of this work is the safety protocol recently developed at Johns Hopkins [24] for psychedelic drug administration, which has been adapted for this proposed study.

In the 1970s, before rigorous and well-controlled trials of the Spring Grove protocol could be undertaken, clinical research with psychedelics in the US was abandoned due to increased regulatory requirements and an unfavorable political climate. Nevertheless, pharmacology and neuroscience studies continued, producing a clear understanding of psilocybin's effects on neurotransmitter receptors and human physiology [91, 92, 102]. Unlike many other Schedule I controlled substances, the "classic psychedelics" are physiologically safe over a wide range of doses and have a low potential risk of addiction [92, 103]. The published case series of mid-Century psychedelic-assisted psychotherapy reveal an overall low rate of adverse events when administered in controlled clinical settings [104]. (For more clinical safety data, see Section 4.1.1 below.) And while clinical research ceased in the US in the 1970s, psilocybin-assisted individual and group psychotherapy continued to be practiced legally in Germany and Switzerland into the 1990s [105].

Clinical research with psychedelics in the US reemerged in the 1990s when Strassman investigated the pharmacology of dimethyltryptamine in healthy volunteers [106]. He was followed by Griffiths et al who conducted a double-blinded RCT in which healthy volunteers were administered a single high dose of psilocybin (0.43mg/kg) vs active placebo (methylphenidate) and found that a significantly higher proportion of volunteers receiving psilocybin had "complete mystical experiences" [17]. Seventy-four percent of subjects rated the psilocybin experience as one of the five most spiritually significant experiences of their lives (compared to 8% of controls) [17]. Remarkably, subjects who received psilocybin also demonstrated significant increases in the personality trait of Openness on the NEO-Personality Inventory (e.g., aesthetic appreciation and sensitivity, imagination and fantasy, and tolerance of others' views and values) 12 months after drug administration. No other discrete clinical intervention has ever been shown to cause significant and enduring changes in an adult's personality structure [107].

This was followed by three double-blind, cross-over RCT studies investigating psilocybin-assisted psychotherapy for cancer patients with DSM-IV diagnoses that included symptoms of anxiety and/or depression. First, in 2011, Grob et al [18] demonstrated the safety and feasibility of psilocybin-assisted psychotherapy in 12 advanced cancer patients with a DSM–IV anxiety diagnosis deemed to be secondary to their cancer diagnosis. This study utilized a single moderate dose of oral psilocybin (0.2mg/kg), and found positive trends toward improvements in anxiety and depression in the months following the intervention [18]. Next, in 2016, Ross et al. compared an active placebo (niacin) to a single high dose of oral psilocybin (0.3mg/kg), both paired with psychotherapy, in 29 cancer patients with moderate-to-severe anxiety and whose cancer was either active or in remission with a chance of recurrence. They found significant within- and between-group reductions in anxiety and depression measured at three different time points and persisting for up to eight months. They also found significant reductions in demoralization and hopelessness [19]. Also in 2016, Griffiths et al compared a placebo-like dose (0.014 or 0.043mg/kg) to a high dose (0.314 or 0.429mg/kg) of oral psilocybin in 51 cancer patients with depression and anxiety [108]. They found significant within- and between-group reductions in anxiety and depression at 5 weeks; the within-group improvement persisted at the 6 month follow-up [20].

Both Ross et al. and Griffiths et al. found rates of clinical response to a single dose of psilocybin at the long-term follow-up (>=6 months) to be approximately 60-80% for measures

of anxiety and depression [108, 109]. These studies were followed by Carhart-Harris et al., an open-label feasibility study in which 20 patients with unipolar treatment-resistant major depression received two doses of oral psilocybin (10 and 25 mg) along with psychological support [110]. They found significant reductions in depression at all six time points measured after the drug sessions, persisting out to 6 months. Notably, the patients in this study had more severe baseline depression on average than those in the Ross et al. and Griffiths et al. studies, and they had all previously failed to respond to at least two pharmacologically distinct antidepressant drugs. While only suggestive because of the open-label design, these data are promising given the treatment-resistant group.

Over the past 20 years psilocybin has been shown to be safe and preliminarily effective in the treatment of not only anxiety and depression in cancer patients [18-20], but also treatment-resistant alcohol use disorder [111], treatment-resistant tobacco use disorder [112, 113], and obsessive- compulsive disorder [114].

1.3 Rationale for the Proposed Study

Rationale for Psilocybin-Assisted Psychotherapy for Demoralization in LTAS
Per Section 1.1, above, there is a large unmet need for the treatment of existential distress in LTAS. Compared to classic examples of acute existential distress in end-of-life patients (e.g., cancer patients or advanced AIDS patients), the existential distress of LTAS is a more chronic condition complicated by severe grief and traumatic exposure. Like “cancer survivors,” AIDS survivors often experience increased rates of psychological distress long after their disease is controlled [9, 10]. While the existential distress of LTAS is multifaceted and complex, the well-characterized clinical syndrome of demoralization appears to capture the type of psychological distress suffered by many LTAS [6, 7]. The concept of demoralization is predicated on the loss of one’s meaning-making ability in the face of distress. Enhancing meaning-making to address existential distress and complicated grief is a strategy that has been embraced not only by palliative specialists [36] and thanatologists [15], but also by the HIV community itself [65]. In general, the mental health needs of LTAS —an emerging, medically and psychosocially complex, and stigmatized population—remain under-recognized and undertreated, but in particular it seems LTAS could benefit from a brief intervention that would enhance meaning-making in order to better cope with, and transcend, years of loss and suffering.

Modern studies of psilocybin-assisted psychotherapy for cancer patients and cancer survivors with existential distress provide promising preliminary evidence of this intervention in treating demoralization in palliative care patients [18-20]. These clinical improvements are thought to be mediated by having a complete “mystical-type” experience [21], which leads to an enhanced sense of meaning in one’s life [115], and an enhanced ability to engage with one’s social supports [22]. Moreover, psilocybin may also help improve patients’ relationships with love-ones who have already died: According to the most experienced clinician in the field of psilocybin-assisted psychotherapy, Dr. William Richards (who began treating palliative care patients with this method in the 1970s), psilocybin-assisted psychotherapy can be highly effective at treating protracted grief [116]—a rather difficult to treat symptom in LTAS (see above, Section 1.1 Treatment Needs).

LTAS – An Ideal Model for Studying Chronic Existential Distress in Palliative Care Patients
Clinical trials in palliative care are fraught with many methodological challenges, especially subject recruitment given patients’ lack of interest in spending their limited time in research studies, or inability to comply with the physical demands of attending study visits and research protocols [117]. Attrition rates of up to 50% are not uncommon among psychotherapy trials with palliative care patients [36, 77, 118]. Recent trials of psilocybin-assisted psychotherapy for existential distress in cancer patients have struggled with recruitment [28]. The current proposed study of psilocybin-assisted psychotherapy in LTAS is unlikely to be hindered by these same recruitment challenges because the form of existential distress to be examined, demoralization,

is thought to occur at high rates [65] among a largely ambulatory population that is known to avidly volunteer for medical research [119] and is desperately in search of treatment options [65]. Despite the fact that HIV is now considered a "chronic illness" and not an acutely life-threatening condition for most patients, PLH potentially face their mortality on a daily basis when they choose, or choose not, to adhere with their ART regimen, thus likely enhancing existential distress chronically.

Rationale for using Psilocybin as a Psychotherapy Adjunct, and eschewing Psilocybin Monotherapy

This trial does not include a control arm of psilocybin without psychotherapy. When psilocybin and other psychedelics were investigated as pharmacologic adjuncts to psychotherapy in the 1950s and 60s, clinical experience led to the principle of "drug, set and setting," [120] which states that the clinical safety and outcomes of a psychedelic drug experience are highly influenced by the non-pharmacological variables of the patient's mental state prior to drug administration ("set") and their environment during the experience ("setting"). Unlike other modalities of drug-assisted psychotherapy (e.g., D-cycloserine-assisted cognitive behavioral therapy), in psychedelic-assisted psychotherapy, not only is the drug experience thought to deeply influence the content of the psychotherapy, but the content of the psychotherapy is likewise understood to intimately shape the drug experience itself. This consideration has led to the consensus that it is unethical for psychedelics to be administered to patients absent a supportive and therapeutic context. This context has typically been individual psychotherapy, but group therapy modalities have also been used. [97, 121]

Rationale for Group Therapy

Since the beginning of the HIV/AIDS epidemic, many psychotherapies for PLH have been preferentially delivered as groups because of enhanced cost-effectiveness and the group format's unique clinical benefits with respect to the enhancement of social support in a population suffering high rates of isolation and loneliness [23].

The theoretical basis of the original Spring Grove approach to treating existential distress in palliative care patients was that patients suffer extreme *isolation* because of their disease, and that psychedelic-assisted psychotherapy could help relieve this isolation by facilitating: 1) living meaningfully in the present moment, and 2) reaching out and authentically connecting with loved ones [22]. Various clinical benefits were reported from their uncontrolled experimental sessions, including improvements in mood and anxiety, and increased openness to communication with loved ones [122]. These older findings are consistent with more recent social psychology findings that psilocybin decreases the subjective feeling of social exclusion [123] and another classic psychedelic, LSD, enhances emotional empathy and prosocial behavior [124].

The Spring Grove team concluded that optimal clinical outcomes were dependent upon attaining a "psychedelic peak experience," which was conceived of as akin to William James' "conversion experience," [125] or Abraham Maslow's "peak experience," [126]—a transcendent state of unity, intense positive emotions, and ineffability that was experienced as deeply meaningful. [22] To describe this mental state, the current psilocybin literature has adopted the terminology of the "complete mystical experience," which is defined by standard criteria using a validated psychometric measure, the Mystical Experience Questionnaire—30 item [127]. Because the Spring Grove team believed that the "transcendental nature of the experience [could] neutralize a sense of alienation…" they sought to facilitate such experiences in order "to maximize patients' opportunities for living by lessening their sense of isolation and alienation, and in so doing, assist in their reaching out to those around them" [128]. One aspect of this model that has received little mention in the recent literature is that the original Spring Grove protocol included non-drug *family therapy sessions* conducted both before and after drug sessions [22]. The purpose of these sessions was to prepare the family to better help the patients integrate their psychedelic experience after the drug sessions, as well as to aid the

family in their imminent grieving process.

Spontaneous feedback from several subjects in the recent NYU psilocybin-assisted psychotherapy trial for existential distress in cancer patients included the request to be introduced to the other study subjects [19], apparently to share, process and integrate their experiences in a setting of mutual aid and understanding. Subjects from recent MDMA-assisted psychotherapy trials for PTSD have also spontaneously made this request, leading the study sponsors to create a web forum for the patients to be in touch with each other after completing the trials [129]. It appears to be helpful to patients treated with psychedelic-assisted psychotherapy to spend time with peers in their attempt to integrate the “peak” experiences, the phenomenology of which can be rather uncanny and perhaps difficult for psychedelic-naïve family or friends to comprehend [130].

Conducting non-drug psychotherapy sessions in groups may shed light on possible key mechanisms of psilocybin-assisted psychotherapy for existential distress. Whereas *therapeutic alliance* is thought to be the most important mediator of clinical outcomes in individual psychotherapy, *group cohesion* is widely recognized as the analogous mechanism in group psychotherapy [131, 132]. Examining the change of group cohesion pre- and post-psilocybin with validated self-report [133] and observer-rated instruments [134] will provide a novel and standardized means of observing how psilocybin drug sessions may affect the interpersonal functioning of distressed palliative care patients.

A significant limitation of group therapy clinical trials is that large sample sizes are required to demonstrate efficacy because of the likely interdependence of outcomes of members of the same group [135]. For this reason, qualitative (e.g. Interpretive Phenomenological Analysis) and/or sequential (e.g. the Hill Interaction Matrix) measures of psychotherapeutic *process* are often used to make inductive inferences about clinical change from group therapy over time [136]. Process is understood as the conglomeration of intrapersonal functions, interpersonal dynamics and group environment that leads to therapeutic change [137]. To improve the evidence base for group psychotherapy, the American Group Psychotherapy Association (AGPA) has developed clinical practice guidelines [138] and a standard set of measures and tools for creating and managing psychotherapy groups for clinical practice and research [139]. In developing the protocol for this proposed study, we have drawn not only from the literatures on psilocybin-assisted psychotherapy and palliative care, but also from these AGPA clinical and research guidelines, as well as on the consultation of local group psychotherapy experts [140].

Rationale for Dosing Regimen
Griffiths et al [141] have characterized the dose-response relationship of oral psilocybin in healthy volunteers. They found that when considering the odds of attaining a complete mystical experience versus having a temporary anxiety reaction during the drug experience (lasting on the order of minutes), the optimal dose likely falls between 0.29mg/kg and 0.43mg/kg [141]. This dose range has been successfully used in studies of psilocybin-assisted psychotherapy for existential distress in cancer patients [19, 20], severe alcohol use disorder [111] and tobacco use disorder [112]. The current study will employ a dose of 0.3mg/kg po in the first group, and if this is well tolerated will then escalate to 0.36mg/kg po in subsequent groups.

The dosing of the psychotherapy—10 sessions occurring at a frequency of 1-2 times per week—was chosen on the basis of comparison with similar group psychotherapies for existential distress in palliative care patients. The group psychotherapy with the best evidence-base for treating existential distress in palliative care patients, Meaning-Centered Group Psychotherapy, employs 8 sessions [142]. The group psychotherapy with the best evidence-based for treating complicated grief has 16 weekly sessions [143]. Our protocol uses a modified course of Brief Supportive-Expressive Group Therapy, which was designed and tested as a 12-week course of treatment [76]. Empirical data suggest that group therapies lasting at least 12 sessions are shown to have greater correlations between group cohesion and clinical outcomes

[132]. We hypothesize that psilocybin will catalyze group cohesion in a shorter period of time, thus making 12-16 weeks of group therapy unnecessary for detecting comparable results with regards to cohesion and clinical outcomes.

Rationale for Supportive-Expressive Group Therapy

While prior trials of psilocybin-assisted psychotherapy for existential distress in palliative care patients have followed a standard drug administration safety protocol, they have not used manualized psychotherapies in the non-drug therapy sessions; our study will be the first to do this, which should enhance generalizability of the results. The format and content of SEGT are appropriately flexible for incorporating individual psilocybin sessions during the course of therapy, and including psychoeducation on psilocybin in the preparatory sessions. The focus of SEGT on expressing emotions and enhancing communication with caregivers is expected to be helpful in integrating psilocybin experiences [121]. Psilocybin has been shown to enhance access to positive emotional memories [144] and to increase the personality trait of openness [107], and this should support SEGT's aim of increasing awareness of one's emotions and openness to new experiences. Because the primary aim of this pilot trial is to assess safety and feasibility of this modality—and assessing efficacy is a secondary aim—no control group of traditional SEGT will be included in the study. For the rationale on why psilocybin monotherapy (without an adjunctive psychotherapy) will not be offered as control condition, see above.

1.4 Study Hypotheses

Primary

1. The study will recruit, consent and enroll 18 subjects (in 3 groups of 6 members) over 18 months; these subjects will complete all treatment and evaluation sessions and they will experience no treatment-emergent serious adverse events.

Secondary

1. The difference in pre- and post-treatment mean scores of demoralization, complicated grief, depression, PTSD, shame, anxiety, quality of life, functional social support, post-traumatic growth, openness to experience, attachment security, mindfulness, global clinical impressions and ART medication adherence will trend toward significant improvement. These improvements will be sustained at 3-month follow-up.
2. The difference in pre- and post-psilocybin rates of change of group cohesion and group process will trend toward significant improvement.
3. Qualitative analyses of subject behavior and caregiver/important other reports will lead to greater understanding of the interpersonal mechanisms of action of psilocybin-assisted psychotherapy.

2 Objectives of the Study

2.1 Objectives

2.1.1 Primary Objective

- To demonstrate the safety and feasibility of Psilocybin-Assisted Supportive-Expressive Group Psychotherapy (PA-SEGT) for demoralization in long-term AIDS survivors (LTAS).

2.1.2 Exploratory Objectives

- To explore the preliminary efficacy of PA-SEGT for improving demoralization, complicated grief, depression, PTSD, shame, anxiety, post-traumatic growth, quality of life, functional social support, openness to experience, attachment security, social connection, nature relatedness and ART medication adherence in LTAS.
- To explore quantitatively and qualitatively the mechanisms (e.g. group cohesion) through which PA-SEGT addresses demoralization and other mental health outcomes in LTAS.

2.2 Endpoints

2.2.1 Primary Endpoints

- Safety will be defined based on the rate of adverse reactions (defined by the NIH Division of AIDS Table of Grading of Severity of Adult and Pediatric Adverse Events V2.0) (see Section 5 below). The safety of acute drug effects will be assessed by monitoring vital signs for tachycardia (HR>100bpm), bradycardia (HR<60bpm), hypertension (SBP>140mmHg or DBP>90mmHg) and hypotension (SBP<100mmHg or DBP<60mmHg). Drug-induced mental status changes will be assessed using the Adverse Event Medication Session Rating Form during drug sessions, pre and post measures with the Montreal Cognitive Assessment, and the Persisting Effects Questionnaire—Spirituality at study follow up. Suicidality will be assessed with the Columbia Suicide Severity Rating Scale. Follow-up safety data will be gathered for 3 months.

- Feasibility will partially be assessed in terms of the rates of patient recruitment and retention. Feedback on acceptability will also be gathered from subjects and caregivers/important others using the Client Satisfaction Scale. Patients and caregivers will also be invited to provide feedback during a focus group and patients will be invited to participate in individual interviews after the intervention. A SEGT Topic Grid will be used to evaluate video recordings of group therapy sessions in order to assess therapist adherence to the PA-SEGT model.

2.2.2 Exploratory Endpoints

Preliminary efficacy will be assessed with the primary clinical outcome measures:

- Change in demoralization will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up scores of the Demoralization Scale-II.

- Change in complicated grief will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Inventory of Complicated Grief.

Preliminary efficacy will also be explored with the following secondary endpoints (See Section 5 for details on individual measures):

- Change in ART medication adherence will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the ART Medication Adherence Scale.

- Change in depression will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Center for Epidemiologic Studies Depression Scale—Revised.

- Change in subject quality of life will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the McGill Quality of Life Questionnaire—Revised.

- Change in desire for hastened death will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of Schedule of Attitudes towards Hastened Death.

- Change in anxiety will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the State-Trait Anxiety Inventory.

- Change in social support will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Duke/UNC Functional Social Support Questionnaire-5.

- Post-traumatic growth due to the intervention will be defined by post-treatment and 3-month follow-up mean scores of Post-Traumatic Growth Inventory—Short Form.

- Change in PTSD symptoms will be defined as the difference in pre-treatment, post- treatment, and 3-month follow-up mean scores of the PTSD Checklist-5.

- Change in global clinical status will be defined as the difference in pre-treatment and post- treatment mean scores of the Clinical Global Impressions Scale completed by a clinical rater.

- Change in openness to experience will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the International Personality Item Pool—Openness to Experience-20 scale.

- Change in mindfulness will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of subscales of the Multidimensional Assessment of Interoceptive Awareness.

- Change in social connectedness will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Social Connectedness Scale—Revised.

- Change in Nature Relatedness will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Nature Relatedness Scale, Short Form Version.

- Change in alcohol and drug use will be defined by different in the baseline and 3-month follow-up AUDIT and DUDIT scores

Psychotherapeutic process and mechanisms will be explored with the following endpoints:

- Change in group cohesion will be defined as the difference in rate of Group Questionnaire score change pre- and post-psilocybin.

- Change in group process will be assessed as the difference in rate of progression of the Hill Interaction Matrix score pre- and post-psilocybin.

- Change in group process will be assessed as the change in the Individual Group Member Interpersonal Process Scale over time.

- Expectancy effects will be estimated based on the pre-psilocybin total score of the Credibility/Expectancy Questionnaire.

- Subjective experience of a psilocybin treatment session will be evaluated with the Mystical Experience Questionnaire—30 and the Challenging Experience Questionnaire.

- Change in attachment security will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Experiences in Close Relationships scale—Modified 16.

- Qualitative analysis of therapy session video footage, semi-structured patient interviews, focus groups and process notes written by study staff.

- Change in inclusion of other in self will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up results of the Inclusion of Other in Self measure.

3 Study Design

3.1 Characteristics

This is a Phase I open-label pilot mixed-methods study of the safety and feasibility of an 8-week group psychotherapy intervention that includes one individual drug session with oral synthetic psilocybin. This intervention is designed to treat demoralization in LTAS. Groups of 6 subjects will be run in sequence. Safety data will be gathered before, during, immediately after, and for 3 months after the intervention. Subjects will complete self-report measures and semi-structured interviews related to acceptability and subjective experience. Exploratory analyses will be conducted of clinical outcomes. Exploratory analyses will also include quantitative and qualitative assessments of psychotherapeutic process mechanisms.

3.2 Number of Subjects

We estimate that a total of 72 patients will be consented and screened in-person for the study in order to enroll 6 therapy groups of 6 members each. Patients who have been assigned to a group will be replaced only if they drop out prior to the first group therapy session. (See Section 8.2.1 Sample Size and Power Estimate.)

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first group therapy session and must satisfy all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. HIV-positive persons (laboratory-confirmed) ≥50 years old who are able to understand a written informed consent document and who are willing to sign it.
2. Participant-reported diagnosis of HIV or AIDS prior to the clinical availability of protease inhibitors (mid-1996).[1]
3. Moderate-to-severe demoralization, determined by a score of 8 or higher on the Demoralization Scale-II [27].

3.3.2 Exclusion Criteria

1. Life expectancy <6 months (determined by the patient's non-study PMD)
2. Current pregnancy, or the intention of becoming pregnant within 3 months of enrollment
3. Being of childbearing potential, and refraining from dual-method contraception
4. Poor functional status (Palliative Performance Scale-v2 <60%).
5. Major cognitive impairment (Montreal Cognitive Assessment <23).
6. The regular use of psychotropic medications within 2 weeks of study participation, including antidepressants (such as serotonin-reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors),[2] antipsychotics, and mood

[1] This includes participants who at a later timepoint had laboratory-confirmed HIV but prior to mid-1996 had refused or not accessed testing, yet they believed themselves to be HIV+ and by clinical reasoning were likely to have seroconverted by this timepoint.

[2] Individuals taking antidepressants will be presented with the option of tapering off, and remaining off, of their medication for the duration of the study, if their prescribing physician agrees with this course of treatment.

stabilizers. Low dose (≤50mg) TCAs prescribed for neuropathic pain are not considered psychotropic; participants are prohibited from using these medications during the study, but do not need to demonstrate a period of psychiatric stability for 2 weeks prior to enrollment. Patients will be asked to refrain from consuming alcohol, prescription analgesics, PRN anxiolytics and PRN stimulants the day before and of a psilocybin session.

7. History of a psychotic disorder or Bipolar disorder I or II (determined by SCID-5).
8. Family history of primary psychotic disorder or primary bipolar disorder (first or second degree relative).
9. Current, severe Major Depressive Episode (These individuals will be referred to standard-of-care treatment in the community).
10. History of active suicidal ideation with intent in the last 3 months (Suicidal ideation score >3 and Reason for ideation >1 on C-SSRS); or a history of suicide attempt in the last 2 years with Actual lethality/Medical damage >0 or Potential lethality >0 (on C-SSRS).
11. Narcissistic personality disorder, moderate-to-severe (determined by SCID-5-PD).
12. History of Hallucinogen Use Disorder (Moderate or Severe) or Hallucinogen Persisting Perception Disorder (determined by SCID-5).
13. History of a seizure disorder in adulthood.
14. CNS metastases or symptomatic CNS infection.
15. Clinically significant cardiovascular disease (CAD, CHF, arrhythmia); or baseline QT/QTc>500msec; or baseline QT/QTc 451-500msec with repeat QT/QTc >500msec.
16. Uncontrolled hypertension (SBP>139mmHG or DBP>89mmHG if over 65 years old) or tachycardia (average HR>90bpm if over 65 years old) averaged over at least two measurements.
17. Supplemental oxygen requirement.
18. Poorly controlled diabetes mellitus (e.g., history of an episode of hypoglycemia or hospitalization for hyperglycemia on the current diabetes regimen).
19. Inadequate hepatic function (Total bilirubin >2mg/dL, OR AST >6 upper institutional upper limit of normal, OR AST >6 upper institutional upper limit of normal), as determined by most recent laboratory tests.
20. Inadequate renal function as determined by eGFR < 30 mL/min/1.73 m2 (based on the MDRD equation) or CrCl < 30 mL/min (based on the C-G equation).
21. Concomitant dosing of psilocybin with known UGT1A10 and UGT1A9 inhibitors (e.g., diclofenac and probenecid) will be avoided. There is *no* exclusion criterion based on the use of medications or substances that are inhibitors or inducers of CYP450 enzymes.
22. The use of efavirenz (a.k.a, Sustiva or Atripla).
23. If deemed by clinical judgment of the study investigators to be unsafe for undergoing the intervention and/or inappropriate for participating in a therapy group.

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 8 weeks or until:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Patients will be followed for 3 months after completion of treatment or removal from study, or

until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events.

3.6 Randomization Procedures

Patients will not be randomized; this is an open-label pilot trial with one treatment arm.

3.7 Study Timeline

3.7.1 Primary Completion

The study will reach primary completion 36 months from the time the study opens to accrual.

3.7.2 Study Completion

The study will reach study completion 48 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug: Psilocybin

Psilocybin is available as a powder that can be encapsulated for oral administration.

Classification

Psilocybin is an indoleamine psychedelic and is one of the "classic psychedelics." It has a chemical structure similar to that of the neurotransmitter serotonin.

Mechanism of Action

Psilocybin is an agonist of serotonin 5HT2A, 2C and 1A receptors [92, 102].

Metabolism

After ingestion, psilocybin is rapidly dephosphorylated to psilocin, which is metabolized via oxidation and glucuronidation in the small intestine and the liver, and subsequently excreted renally [91, 94, 95].

Contraindications

Current safety standards for experimental psilocybin administration [24, 145] include providing a comfortable environment, the presence of supportive and non-directive therapists or research staff, and strict exclusion criteria. Beyond this basic principle, psilocybin should generally not be administered to individuals with a personal or family history of psychosis or bipolar disease, or individuals who are acutely suicidal. It should also not be administered to individuals with severe cardiovascular disease. Co-administration with medications associated with the serotonin syndrome [146] should be avoided.

There have been no rigorous studies of the effects of psilocybin on pregnancy. We are aware of only one published care report from a research study in which a woman consumed pure psilocybin about every 2 weeks throughout her pregnancy to no apparent detriment to the child, who was followed for 1 year postnatally [120]. It is recommended that women who are pregnant avoid using psilocybin. Non-clinical and clinical data describing the effects of oral psilocybin on lactation, sperm, and teratogenicity are not available.

Availability

Psilocybin is a Schedule I compound, and so requires a DEA Schedule I license to handle. For the purposes of this study, psilocybin is available from the laboratory of Dr. Roland Griffiths at Johns Hopkins University (IND#133202) and from Usona Institute (Madison, WI).

Storage and handling

Psilocybin is stored at 15-30°C. Each subject's dose will be, to the nearest milligram, as close as possible to that indicated by their actual bodyweight (e.g., 0.30mg/kg or 0.36mg/kg), with a maximum dose not to exceed that calculated for a BMI of 35 at that participant's height. The psilocybin will be provided to UCSF in powder form, and the UCSF Investigational Drug Service of the UCSF Department of Pharmacy Services will encapsulate the drug. The study drug will be stored in a secure vault in the Investigational Drug Service in the Inpatient Pharmacy in Moffitt-Long Hospital (505 Parnassus Ave, San Francisco).

Side Effects

Psilocybin is known to be physiologically safe at the doses proposed for this study, and is not addictive [92, 103]. Safe administration is dependent on using a supportive and structured administration protocol [24]. Psilocybin is known to possibly cause the following transient side effects: Anxiety, thought disorder, nausea, emesis, increase or decrease in heart rate, increase or

decrease in blood pressure, and headache [18, 24, 91, 96, 147, 148]. Anxiety and thought disorder reactions appear to be dose-dependent, with higher doses associated with greater frequency of temporary anxiety and thought disorder reactions [141].

Clinical Safety Data

Psilocybin, in the form of psilocybe mushrooms, has been consumed by humans for ritual and healing purposes for at least hundreds of years [149]. The most extensive review of mid-Century reports of the safety of the controlled, clinical uses of psychedelics, including psilocybin, found an overall low incidence of adverse events [104]. After clinical research with psilocybin in North America stopped in the 1970s, psilocybin continued to be used legally as a psychotherapy adjunct in Germany and Switzerland in the 1980s and 90s, but no comprehensive safety data are available from this period [105, 150].

Since the 1990s, hundreds of doses of psilocybin have been administered to humans in clinical trials and research laboratories across North America and Europe. Gouzoulis-Mayfrank et al found negligible acute effects on vital signs (heart rate, blood pressure, temperature) and neuroendocrine levels (cortisol, prolactin, growth hormone), but did find significant transient mental status changes in eight healthy volunteers administered a moderate dose (0.2mg/kg, with total dose <15mg) of oral psilocybin [151]. A review of results from the Vollenweider laboratory in Zurich, Switzerland found that in 110 subjects administered 1-4 low-to-high doses of oral psilocybin there were no detectable persisting adverse effects, and all acute adverse reactions (e.g., dysphoria or anxiety) were controlled with interpersonal support alone, meaning no pharmacologic or other medical interventions were necessary [145]. Moreover, several subjects who did report acutely distressful experiences later claimed in long-term follow up that these experiences had been “enriching”. [145] A subsequent review from that laboratory found that among 261 subjects who received low-to-high doses of oral psilocybin, both mystical-type experiences and acute anxious reactions were strongly positively correlated with drug dose [152]. Importantly, anxious reactions were also strongly correlated with the experimental setting (more anxiety was reported if the subject underwent a PET scan during the experiment), which argues in favor of the idea that the risk of adverse events can be mitigated by providing a comfortable and supportive setting for drug administration. This laboratory’s recent findings from 50 subjects [153], and another 25 subjects [154] receiving a moderate oral dose of psilocybin (0.16mg/kg po or 0.215mg/kg po) reported no adverse events, and found improvement in mood. In contrast to the PET study above, another laboratory in London found no adverse events when they administered moderate dose iv psilocybin to 15 healthy subjects with prior psychedelic experience while undergoing brain fMRI; these subjects reported improved well-being on 2-week follow up [144].

Grob et al conducted the first modern study on the use of psilocybin in subjects with advanced-stage cancer [18]. Subjects received a single moderate dose (0.2mg/kg) of oral psilocybin with pre- and post-drug supportive psychotherapy. This was well-tolerated with subjects showing only mild transient increases in blood pressure and heart rate compared to active placebo; no subjects experienced acute anxiety during the experience; and subjects spontaneously requested that a second dosing session be added to the protocol. Since the Grob et al. study, two larger double-blind RCTs of psilocybin-assisted psychotherapy in cancer patients with anxiety or depression, conducted at NYU and Johns Hopkins, were published; they both reported no adverse reactions (e.g., headache, anxiety or psychosis-like symptoms) lasting longer than 24 hours [19, 20]. Separately, the Johns Hopkins laboratory has reported zero persisting psychological problems among the 54 subjects to whom they had administered high dose (>25mg po) oral psilocybin to by 2008 [24]. By October 2016, the Johns Hopkins team has had no significant adverse events after administering psilocybin to approximately 270 subjects over 560 drug treatment sessions, and emergent medications have never been needed to maintain the safety of the subjects nor the study therapists [155].

Oral psilocybin has also been administered to other clinical populations in modern controlled clinical settings with good safety outcomes. Of 9 subjects with OCD who were administered

low-to-high doses of oral psilocybin, the only adverse event reported was transient hypertension [114]. Of 15 nicotine-dependent smokers receiving moderate-to-high doses of oral psilocybin, adverse events included acute anxiety, mild transient increases in hypertension and heart rate, and mild headaches [112]. Of 10 subjects with alcohol dependence administered moderate-to-high doses of oral psilocybin, the only adverse event reported was mild transient hypertension [111]. A recent open-label pilot study of 12 subjects with treatment-resistant depression, each receiving a low oral dose (10mg) followed one week later by a high dose (25mg) found transient anxiety, thought disorder, nausea and headache, but no severe or unexpected adverse events when followed for up to 3 months after the high dose session [156]. Finally, recent epidemiological data argue for a positive correlation between lifetime classic psychedelic use (including psilocybin) in the US population and reduced rates of past month psychological distress, past year suicidal ideation and past year suicidal attempt [157].

4.2 Drug Accountability

Each UCSF campus investigator using Schedule I substances in research must obtain their own Schedule I registration with the DEA and is responsible for the ordering, security, accountability and disposition of all product ordered under their registration. Psilocybin will be obtained from a DEA-approved Schedule I researcher or distributor (e.g., Dr. Roland Griffiths at Johns Hopkins University, or the Usona Institute, or Beckley Labs), and the drug will be shipped to the Investigational Drug Service of the Department of Pharmaceutical Services at UCSF Medical Center (505 Parnasssus Ave, Room M39C, San Francisco, CA 94143; Phone 415.353.1798). The pharmacy has been used for the storage and preparation of Schedule I controlled substances for individual campus Schedule I registrants for many years.

Storage: Schedule I substances will be stored in one of two large combination lock safes located in the investigational drug storage room of the UCSF Inpatient Pharmacy. The investigational drug storage room is a limited access storage room located in the basement of Moffitt Hospital on the UCSF Parnassus Campus (505 Parnassus Avenue). The room bears a security lock, accessible to the investigational pharmacy staff. The combination of the safe is known only to the investigational drug pharmacy staff.

Upon receipt of a medication order from the investigator, the drug supply will be accessed by the investigational pharmacy staff. The ordered dose will be obtained, placed in appropriate pharmacy dispensing container and labeled for the research subject. The dose contained will be sealed with a tamper evident seal. Research staff will escort the patient to the Inpatient Pharmacy on the day of dosing. Drug will be dispensed directly to the research subject by the pharmacy staff after confirming patient identification and acquiring the patient's signature on the pharmacy's chain of custody documentation. The subject will then be escorted by study staff from the Inpatient Pharmacy through indoor hallways that connect the Moffitt Hospital (where the pharmacy is located) to the Langley Porter Psychiatric Institute (where the drug administration will take place).

Dispensing: Psilocybin will be shipped in powder form and will need to be allocated into gelcaps by the UCSF Investigational Drug Service. Subjects will be dispensed one gelcap with their dose based on weight, as measured prior to the drug treatment day by study staff. Psilocybin will be ingested by study subjects in the testing area (LP-A312) of the third floor annex of Langley Porter Psychiatric Institute.

Records: Record keeping will be in accordance with federal and state regulations for Schedule I controlled substances. Inventory will be taken at least every two years at end of the business day and maintained in a printed form.

4.3 Drug Ordering

UCSF will obtain psilocybin directly from a licensed Schedule I distributor (e.g. Usona Institute) or from another Schedule I registered investigator (e.g., Dr. Roland Griffiths at Johns Hopkins University).

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

Table 5.1 Regimen Description

Study Drug	Premedication / precautions	Dose	Route	Schedule
Psilocybin	Avoid all other psychotropic agents within 48hr of each dose	0.3mg/kg or 0.36mg/kg (moderate-to-high)	Oral	After 4 group therapy visits

Psilocybin is not physiologically toxic at the doses being used in this study. No human data exists that suggest what a toxic dose of psilocybin might be, but experiments in animals suggest that the LD50 of psilocybin in humans may be in the range of grams [91], which is two orders of magnitude higher than the highest dose to be used in this study. Patients could have short-term (<24hr) challenging psychological reactions. Patients who have a serious adverse event consisting of a negative psychological reaction that lasts >24hr will be followed by a study physician until the resolution of the event and, at the discretion of the PI, may be removed from the study. There is reason to believe that participating in the integration group therapy sessions after a negative psychological reaction may help in recovering from such an event, and so participants will not automatically be removed from the study merely for having a prolonged negative psychological reaction to the psilocybin session (See Section 7.3 for definitions of Adverse Event.)

5.1.1 Other Modalities

Patients will participate in group therapy sessions following a modified form of Brief Supportive-Expressive Group Therapy (SEGT) [76]. SEGT emphasizes therapeutic goals that include enhancing mutual support, openness and emotional expression, improved social and family support, and detoxifying death and dying. The weekly sessions will last 90 minutes and be conducted by 2 co-facilitators with experience leading psychotherapy groups.

5.2 Monitoring and Toxicity Management

Of the hundreds of subjects administered psilocybin in clinical or research settings over the last two decades, none have required emergent psychiatric medications or emergency department care [24, 145, 157]. Each subject receiving psilocybin will be evaluable for safety. The safety parameters include physical findings and spontaneous reports of adverse events reported to the investigator by subjects and primary caregivers. Each subject will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NIH Division of AIDS Table of Grading of Severity of Adult and Pediatric Adverse Events V2.0 (http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf)

. We will monitor specifically for hypertension, hypotension, tachycardia, nausea, emesis, headache, anxiety, dysphoria, mania, suicidality and psychosis during drug sessions using the Adverse Event Medication Session Rating Form (see Appendix). Acute physical adverse events (e.g., nausea or hypertension) will trigger increased frequency of monitoring. Acute psychological adverse events will be managed by supportive reassurance and, if needed, medications such as lorazepam or olanzapine. Further management of physical or psychiatric adverse events will depend upon the judgment of the on-call study physician and may include, if necessary, transportation to the UCSF Parnassus Emergency Department, which is located immediately adjacent to the Langley Porter Psychiatric Institute.

5.3 Pregnancy

Subjects of childbearing potential must have a negative pregnancy test at enrollment and prior to the drug treatment session, and must agree to use adequate birth control through 10 days after the drug treatment session. Adequate birth control methods include intrauterine device (IUD), injected or implanted hormonal methods, abstinence, oral hormones plus a barrier contraception, or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e. condom plus diaphragm, condom or diaphragm plus spermicide, oral hormonal contraceptives plus spermicide or condom). Not of childbearing potential is defined as permanent sterilization, postmenopausal, or assigned male at birth.
Any pregnancy occurring after the drug treatment session and before the final group session will be followed until an outcome is known. (i.e., spontaneous miscarriage, elective termination, normal birth). All live births must be followed for a minimum of 30 days or to the first well-baby visit.

6 Study Procedures and Observations

See* Appendix A *for a timeline of all assessments

6.1 Study Site

All in-person pre-treatment and treatment patient contact will occur at the Langley Porter Psychiatric Institute (LPPI) at 401 Parnassus Ave, San Francisco. LPPI is a psychiatric hospital within the UCSF Medical Center Parnassus Campus and is immediately adjacent to the UCSF Parnassus Emergency Department.

6.2 Selection of Measures

Antiretroviral Medication Adherence Scale (AMAS)—A single item 11-point Likert scale (0%-100%) of ART medication adherence percentage over the past week. This scale was invented for this study.

Alcohol Use Disorders Identification Test (AUDIT) – A 10-item screening tool developed by the World Health Organization to assess alcohol consumption, drinking behaviors, and alcohol-related problems.

Center for Epidemiologic Studies Depression Scale-Revised (CES-D-R)—A 20-item validated 5-point Likert scale self-report scale for the detection of depression [158] that has been shown to be sensitive to change in symptoms in palliative care patients. [159].

Client Satisfaction Scale (CSS)—A 4-item 10-point Likert scale (“very dissatisfied” to “very satisfied”) designed for this study assessing satisfaction with the intervention.

Clinical Global Impressions scale (CGI)—A widely-used 3-item clinician-administered assessment developed by the NIMH to assess change in patients in psychopharmacology trials [160].

Challenging Experiences Questionnaire (ChEQ)—A validated 26-item 6-point Likert scale of the extent to which subjects experienced challenging experiences during a psychedelic drug treatment session [161]. The scale has 7 factors: fear, grief, physical distress, insanity, isolation, death and paranoia.

Columbia Suicide Severity Rating Scale (C-SSRS)—A validated 17-item scale that assesses suicidal ideation and behavior (www.cssrs.columbia.edu) according to the Columbia Classification Algorithm for Suicide Assessment (C-CASA), which the FDA Division of Psychiatric Products requires be used in clinical trials it oversees.

Community Observer Rating Form (CORF)—A 13-item 10-point Likert scale developed by Griffiths et al to triangulate behavioral observations of individuals administered psilocybin [17].

Concomitant Therapeutics Checklist (CTC)—A checklist designed for this study to assess the following categories of mental health therapies used over the last week: Prescription medications, non-prescription medications, psychotherapy, mutual aid groups, self-help

techniques, integrative medicine modalities, other.

Credibility/Expectancy Questionnaire (CrEQ)—A 6-item self-report measure of cognitive and affective assessments of a mental health therapy with high internal consistency and good test-retest reliability [162] that we have adapted for psychological distress.

Demoralization Scale-II (DS-II)—An abbreviated, 16-item and 3-point version of the well-validated original 24-item Demoralization Scale [163], which is the most widely used self-report measure of demoralization in palliative care patients [29]. The DS-II has two subscales: Meaning and Purpose, and Distress and Coping Ability, and shows both good internal and external validity in palliative care patients [27, 164].

Drug Use Disorders Identification Test (DUDIT) – An 11-item screening tool developed as a parallel to the AUDIT to assess drug consumption, drug use behaviors, and drug-related problems.

Duke UNC Functional Social Support Questionnaire-5 (DUFSS-5)—A 5-item, 3-point Likert, self-report measure of perceived functional social support. The abbreviated 5-item scale has been validated in patients with severe medical illness (advanced cancer or AIDS) [165].

Experiences in Close Relationships scale—Modified 16 (ECR-M16)—A 16-item, 7-point Likert self-report measure of attachment security. The abbreviated 16-item version is reliable and has been validated in patients with severe medical illness (metastatic cancer) [166].

Group Questionnaire (GQ)—A validated self-report 30-item 7-point Likert questionnaire of therapeutic relationships in group therapy [133]. GQ has a three-factor model of group cohesion: Positive Bonding, Positive Working, Negative Relationships, all of which manifest in both member-member and member-leader relationships [167]. GQ was empirically-derived from measures in the AGPA CORE-R Battery [139] that assess therapeutic alliance and cohesion—the two factors known to best predict clinical outcomes of group psychotherapy trials [132].

Group Psychotherapy Intervention Rating Scale (GPIRS)—An empirically-derived observer-rated 48-item instrument that assesses group therapist behaviors that help create and maintain group cohesion [168].

HIV and Abuse Related Shame Inventory (HARSI)—A validated 22-item 5-point Likert scale (“Not at All” to “Very Much”) [169].

Hill Interaction Matrix (HIM)—The gold standard in group therapy process measures [170], the HIM is an observer-rated instrument that assesses group therapy sessions using a 4x4 matrix of style categories (conventional, assertive, speculative and confrontational) and content categories (general, group, personal, relationship). The HIM has been used since the 1960s and there exists an extensive database of normative data against which to compare outcomes [134].

International Personality Item Pool-Openness to Experience-20 (IPIP-OE-20)—A 20-item self-report measure that uses items in the public domain to evaluate a construct approximately equivalent to Openness, which is evaluated by the NEO-PI-R [171].

Inventory of Complicated Grief (ICG)—A well-validated 19-item 5-point Likert scale (“never” to “always”) that is the gold standard self-report instrument for measuring complicated grief [172, 173].

Life Event Checklist—5 (LEC5)—A 17-item self-report screening measure of different categories of potentially traumatic events that have occurred over the respondent’s

lifetime.[174]

McGill Quality of Life Questionnaire-Revised-Short (MQoL-RS)—A well-validated 15-item 11-point Likert scale that assess quality of life in palliative care patients by assessing the following domains: Overall quality of life, Physical well-being, Psychological well-being, Social support and Existential well-being. We will only use 4 items, which are Parts A (Overall quality of life) and B (Physical symptoms).

Multidimensional Assessment of Interoceptive Awareness-Revised (MAIA-R)—A well-validated 32-item 6-point Likert scale of bodily and mental awareness that measures the following 8 domains: Noticing, Not-distracting, Not-worrying, Attention regulation, Emotional awareness, Self-regulation, Body listening and Trusting [175]. If this study, we will use the Emotional awareness (5-tiems), Self-regulation (4-items) and Trusting (3-items) subscales.

Mystical Experience Questionnaire-30 (MEQ-30)—A well-validated 30-item 6-point Likert scale ("none; not at all" to "extreme [more than any other time in my life]") self-report measure of mystical-type experiences [127], derived from the earlier work of Pahnke et al. [122].

Nature Relatedness Scale, Short-Form Version (NR-6)—A 6-item version of a well-validated 5-point Likert scale self-report measure of environmental connectedness [176].

Palliative Performance Scale version 2 (PPSv2)—A validated clinician-administered tool based on the Karnovsky Performance Scale but adapted for a palliative care population [117, 177].

Persisting Effects Questionnaire—Spirituality (PEQ-S)—An instrument developed by Griffiths et al for subjects who have been administered psilocybin to assess enduring changes in attitudes about life, attitudes about self, mood changes, relationships, behavioral changes, and spirituality [141]. The measure also includes 4 questions about the drug experience itself concerning personal meaningfulness, spiritual significance, how psychologically challenging it was, and personal psychological insights gained. We will only use the Spirituality subscale (59-item, 6 point Likert scale ["none; not at all" to "extreme"]), and the four questions about the psilocybin experience.

Post-traumatic Growth Inventory-Short Form (PTGI-SF)—A validated 10-item 6-point Likert scale meant to assess the following psychological factors in populations that have suffered a traumatic event or major crisis: quality of relationships with others, openness to new possibilities, personal strengths, spiritual change, and appreciation of life [178].

PTSD Checklist (PCL-5): A validated 20-item, 5-point Likert scale (from "Not at All" to "Extremely") to measure symptom criteria for PTSD from the DSM-5. [179]

Schedule of Attitudes towards Hastened Death (SAHD)—A 20-item True/False self- report measure of the desire for hastened death validated in patients with HIV/AIDS and other palliative care conditions [180].

Social Connectedness Scale-Revised (SCS-R)—A well-validated 8-item 6-point Likert scale (negatively-worded items rated from "strongly agree" to "strongly disagree") self-report measure which has shown strong construct, convergent and discriminant validity as well as reliability ($\alpha >$ .92) for assessing the degree to which subjects feel connected to their social environment [181]

State-Trait Anxiety Inventory (STAI)—A 40-item 4-point Likert scale that is the gold standard in self-report measures for state and trait anxiety [182, 183].

Supportive-Expressive Group Therapy Topic Grid (SEGT-TG)—A measure developed by Spiegel and Spira for the original studies of SEGT [75]. Independent raters watch video of

therapy sessions and document the number of minutes in which particular target discussion topics are handled in the session.

Structured Clinical Interview for DSM-5 (SCID-5)—The gold standard structured clinical interview for DSM-5 criteria for major psychopathology. We will use portions of the SCID to screen for lifetime Depressive, Psychotic, Bipolar and Hallucinogen-related disorders.

Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD)—A self-report questionnaire based on DSM-5 criteria for personality disorders. We will use this to screen for Cluster B personality disorders.

6.3 Qualitative Analyses

Qualitative analyses be grounded in Interpretive Phenomenological Analysis (IPA) [184]. Data for qualitative analysis will include transcripts from a convenience sample of group therapy sessions and psilocybin drug sessions, therapist process notes, patients' written accounts of their psilocybin experiences, verbal feedback elicited from patients throughout the study, transcripts from focus groups conducted after the study endpoint, and transcripts from 30-to-60-minute semi-structured interviews conducted with selected patients after the 3-month follow-up. IPA is widely used in studies of psychological interventions to better understand a patient's experience of their treatment, and is typically used to elicit convergent and divergent themes in studies with small sample sizes [184]. Two investigators with experience in qualitative analysis will at first independently code the same transcripts for prominent themes, followed by comparison of their codes until a consensus is reached on an appropriate coding scheme. A code book will be established which will be used to code further sources. Consensus will be re-established on an iterative basis according to the criteria of the coders and the PI.

6.4 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6 Schedule of Study Procedures and Assessments. Screening assessments will be performed on enrollment. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 7 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

6.4.1 Phone Screening

Potential subjects will be screened over the phone to assure that they understand the time requirements of the study, they are at least 50 years old, they were diagnosed with HIV prior to the clinical availability of combination antiretroviral therapy (~1996), they report experiencing moderate-to-severe symptoms of demoralization on the DS-II, and that they do not meet any major exclusion criteria (e.g., history of psychosis or bipolar disorder; recent active suicidal ideation). They will also be screened for complicated grief on the ICG to better characterize their clinical appropriateness for the study. A brief orientation to the study protocol, including psychoeducation on psilocybin, will be provided to patients who are not excluded. The patient will then be scheduled for an in-person screening and enrollment visit.

6.4.2 In-person Screening and Enrollment

Screening procedures and assessments to be completed on day of Enrollment (prior laboratory results may be considered instead of performing labs at enrollment if the results are less than 1 month old):

- Informed Consent Form and HIPPA form. Participants will be provided with a printed version of the study brochure.
- Demographics questionnaire (Age, ethnicity/race, civil status, years of education, income)
- Vital signs; Physical examination; Mental Status Exam; Complete medical and psychiatric history, including current medication list; Performance status (PPSv2); Cognitive Status (Montreal Cognitive Assessment)
- Complete blood count (WBC, Hgb, Hct, Plt)
- Comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Cr, Gluc, Tbili, Ast, Alt, AlkPhos, TProt, Alb)
- TSH, FT4
- CRP
- Urinalysis
- Urine beta-hCG, when applicable (must be completed on day of Enrollment)
- Urine toxicology (must be completed on day of Enrollment)
- HIV viral load, CD4 count, CD8 count
- RPR or Treponemal Antibody
- Electrocardiogram (ECG)
- Selected screening portions of Structured Clinical Interview for DSM-5 Clinical Trials Version (SCID-5); sections on current Depressive disorders; lifetime Psychotic disorders, Bipolar disorders and Hallucinogen-related disorders), Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD) section on Cluster B disorders.
- Columbia Suicide Severity Rating Scale (C-SSRS): Baseline/Screening (last 12 months)
- ART Medication Adherence Scale (AMAS), Centers for Epidemiologic Studies Depression Scale—Revised (CESD-R), Demoralization Scale—II (DS-II), Inventory of Complicated Grief (ICG), McGill Quality of Life Questionnaire-Revised-Short (MQoL-RS), Life Event Checklist—5 (LEC5), PTSD Checklist-5 (PCL-5), Schedule of Attitudes towards Hastened Death (SAHD), State-Trait Anxiety Inventory (STAI).
- Clinical interview of about 45 minutes duration to discuss details about the subject's personal life, such as past and current relationships, family dynamics, and concerns about their disease.
- Eligible subjects will be placed on the waitlist until 6 subjects are available to start a group.
- Subjects who score high on the SCID-5-PD dimensional scale for Borderline Personality Disorder and are enrolled in the study will be monitored closely during the trial and study clinicians will consider offering them an individual therapy visit around the time that the subacute beneficial effects of psilocybin are expected to wear off (about 10 days post exposure) if the subjects appear unusually distressed at that time.

6.4.3 Baseline Assessments (Week 0)

6.4.3.1 Baseline Subject Assessments

Baseline assessments will be filled out during an individual therapy session wherein the subject will meet one or both of the group therapists in the week prior to the first group therapy session. Separately, the subject's caregiver/important other will be invited to meet with study staff for a brief interview on their relationship with the subject [see Appendix C for interview guides]. The individual session for the study subject is meant to build trust and rapport with the group therapists, to learn more about the subject's life history and struggles with his/her health, to elicit the subject's preferences and intentions for the treatment sessions, and to orient the subject further to the intervention protocol. If screening/enrollment measures were completed within 1 week of the baseline assessment, those measures will not need to be repeated.

- AMAS, AUDIT, CESD-R, CTC, DS-II, DUDIT, DUFSS-5, ECR-M16, ICG, IPIP-OE-20, MAIA-R, MQoL- RS, NR-6, PCL-5, PTGI-SF, SAHD, SCS-R, and STAI. A clinical rater will perform a CGI and C-SSRS(Interval) for each subject.

6.4.3.2 Baseline Caregiver/Important Other Assessments

- CORF

6.4.4 Treatment Period

6.4.4.1 Group Therapy Sessions #1-4 (Weeks 1-2)

Patients will undergo four 90-minute group therapy preparatory sessions (2 per week) that will be audio and video recorded. Video footage of a random sampling of sessions will be analyzed with the HIM, SEGT-TG and the GPIRS. Patients will fill out the GQ after the sessions in Week 2 and 4. Women of child-bearing potential will provide a urine sample for a urine beta-hCG at Group Therapy visit #4. A clinical rater will administer the C- SSRS(Interval) to each subject at each weekly study visit.

6.4.4.2 Individual Drug Sessions (Week 3)

Patients will undergo individual drug sessions in which they are administered psilocybin 0.30mg/kg (or 0.36mg/kg) po, with a maximum dose not to exceed that calculated for a BMI of 35 at their height. The drug will be administered following the safety guidelines outlined by Johnson et al [24].

The day prior to the session, patients will be screened over the phone for contraindicated medications and reminded about procedures for the medication visit. ***Specifically, participants will be reminded that they cannot drive an automobile for the rest of the day after their medication visit, and they will be advised that if they will take the BART, they should not drive their car to the BART station.***

On the day of the medication visit, patients will arrive at the Langley Porter Psychiatric Institute around 08:00 and be oriented to the drug session room, which will contain a couch for the patient to lie on and aesthetically pleasing décor. Before the medication session starts, participants will complete a urine drug screen and the CrEQ. Patients will also undergo a blood draw at the Clinical Research Service for the following tests: CBC, CMP, and CRP. Participants will then return to the study room and hand over their shoes, keys, wallet and phones to the study therapists for safe keeping; these will all be returned to the patient upon completion of the treatment session.

The entire session will be audio and video recorded for subsequent behavioral analysis and

rating of therapist adherence to the therapy protocol. Participants have the option of requesting that AV recording be turned off momentarily if they will to discuss material they feel is too personal to be recorded.

During the drug session, vital signs (heart rate and blood pressure) will be recorded at 10 minutes prior to drug ingestion ("Minute -10"), and then 30, 60, 90, 120, 180, 240, 300, and 360 minutes after drug ingestion. If at 360 minutes blood pressure is elevated compared to Minute -10, blood pressure will continue to be repeatedly assessed until it has returned to its Minute -10 measurement.

If the Minute -10 assessment (the mean of at least two readings separated by at least 2 minutes) of baseline blood pressure exceeds either 140 systolic or 90 diastolic, periodic blood pressure readings will be obtained (e.g. at 5 minute intervals) to determine if the elevation may be temporary (e.g. due to anticipatory anxiety). If blood pressure decreases to (or below) 140 systolic and 90 diastolic within 20 minutes, capsule administration will proceed. If baseline blood pressure continues to exceed either 140 systolic or 90 diastolic, periodic blood pressure readings will be continued and the study physician will be contacted. The study physician can authorize drug administration if the study physician believes that it is safe to proceed and if the last two blood pressure readings do not exceed 155 systolic or 95 diastolic.

The patient will ingest the psilocybin capsules with about 4 ounces of water and then be instructed to lie down on the couch wearing eyeshades and listening to a preselected music soundtrack via headphones. The subject will be instructed to focus their attention internally and to attempt to interact minimally with the two therapists who will be present in the room throughout the drug session, but will be as non- directive as possible in their interactions with the patient. In the event of a psychologically challenging experience such as significant anxiety or confusion, the therapists will provide verbal reassurance. Patients will have been instructed in the preparatory therapy session to notify the study therapists if during the treatment they feel anxiety or fear.

In the event of a psychiatric emergency, verbal de-escalation and physical and/or chemical restraint will be used to maintain the safety of the subject and the therapists, according to the clinical judgment of the on-call study physician. All possible efforts will be made to avoid using restraints of any kind. Subjects will not be allowed to leave the premises until the drug effects have worn off.

In the event of a medical emergency, subjects will be evaluated by the on-call study physician who will be on-site for all drug administrations. At least one ACLS-certified study clinician will be on-site for all drug administrations. While expected to be rare, the most likely serious adverse event to occur would be a hypertensive crisis. If a subject's blood pressure becomes grossly elevated (SBP >180mmHg, DBP >110mmHG) or unsafe (BP elevations with associated symptoms such as chest pain or shortness of breath), blood pressure will be rechecked immediately in both arms and the on-call physician will be notified if s/he is not already in the treatment room. If the subject is clinically suspected of being in ***hypertensive emergency*** (with signs of end-organ damage), then the subject will be transported to the UCSF Emergency Department for further evaluation and treatment. The Emergency Department's door is less than a 1 minute walk from the Langley Porter Psychiatric Institute. If the patient if determined to be in ***hypertensive urgency*** (without clinical signs of end-organ damage), then blood pressure will be re-assessed with greater frequency while the study physician continues to her/his evaluation for signs of clinical instability, and the study physician may attempt to calm the subject with verbal de-escalation or an anxiolytic (e.g. lorazepam) as transient hypertension is most likely to be due to a challenging psychological experience. If after 20 minutes the hypertensive urgency has not improved, the study physician will evaluate the need for transporting the subject to the Emergency Department for further evaluation and treatment. In the case of ***acute chest pain***, the on-call study physician will have available sublingual nitroglycerin to administer to the subject and an electrocardiogram machine. A crash cart is located in the building, but the goal will be to transport a decompensating patient to the Emergency Department prior to the crash cart becoming imminently necessary. In the event of a suspected ***hypoglycemic episode in a***

subject with diabetes mellitus, a finger stick blood glucose will be checked on an as needed basis, and fruit or oral glucose tablets will be available.

As the drug effects begin to wear off at the 5-6 hour mark, the therapists will engage the patient in a therapeutic interview to explore the experience (see Appendix C for interview guide); this discussion will also be videotaped. A clinical rater will administer the C-SSRS(Interval). Only once patients are deemed to be free of the acute effects of the drug, and after at least 7 hours have passed since ingestion of the drug, will the participant be allowed to leave the premise in the company of a caregiver who has been instructed on how best to support the patient over the coming days.

The patient and caregiver will be given a study clinician's pager or work cell phone number in case of any clinical event off-site that needs further assessment. Patients must agree not to drive themselves home, nor to drive later that same day after they arrive home. Patients will be instructed to write a detailed account of their experience during the drug session at some point over the next week.

In the event that a participant did not arrange a friend/family member to accompany them home, the participant will be required to stay with the study clinicians longer, will be encouraged to eat, and then the participant will be escorted to the curb by study staff and seen into a taxi/Lyft/Uber that will be instructed to take them home. The participant will also be instructed to call the study MD when they arrive home. All efforts will be made to avoid this situation. In the weeks prior to the medication session, participants will be regularly reminded to arrange for someone to accompany them home.

The following day patients will return to the study site to meet with a study therapist and engage in a therapeutic discussion of their experience for 90 minutes. Before the session patients will present to the Clinical Research Service for a blood draw for these studies: CBC, CMP, CRP. Patients will complete the MEQ-30, ChEQ, STAI, SAHD, MQoL, and the C-SSRS(Interval) at this visit. Patients may again meet with study staff in person prior to the next group therapy session if they request this or if study clinicians deem it clinically warranted.

6.4.4.3 Group Therapy Sessions #5-10 (Weeks 4-6)

Patients will undergo six group therapy sessions each 90-minutes long. Video footage of a random sampling of sessions will be analyzed with the HIM, SEGT-TG, IGMIPS and the GPIRS. Prior to each session, patients will be screened for adverse events and evaluated with the CSSR-S. Prior to sessions 5, 7 and 9, participants will fill out the CTC. After sessions 6, 8 and 10, participants will fill out the GQ. At the end of session 5, participants will fill out these questionnaires: CESD-R, DS-II, ICG, PCL-5, HARSI. After session 7 participants will fill out the DS-II and ICG.

6.4.5 Endpoint Assessments

6.4.5.1 Endpoint (Week 6) Study Measures for Subjects

Immediately after the last group therapy session (Week 8), patients will complete the AMAS, CESD-R, DS-II, DUFSS-5, ECR-M16, ICG, MQoL-RS, NR-6, PCL-5 SAHD, SCS-R, STAI, PTGI-SF, IPIP-OE-20, MAIA-R, HARSI, CTC, and CSS. A clinical rater will perform a MoCA and CGI for each subject.

6.4.5.2 Endpoint (Week 6) Study Measures for Caregivers/Important Others

Patients' primary caregivers/important others will complete the CORF and CSS.

6.4.6 Post-treatment/Follow Up Assessments

6.4.6.1 Focus Group (Week 8)

Two weeks after the last group therapy session, subjects and their caregivers/important others will be invited to participate in a focus group wherein they will be asked to give feedback regarding their experiences in the study. Effort will be made to get both responders and non-responders to attend the focus groups. A clinical rater will administer the C-SSRS(Interval) to each subject. Prior to the focus group each participant will fill out the DS-II and ICG. This will be audio-recorded for subsequent qualitative analysis. See Appendix C for focus group guide.

6.4.6.2 3-Month Follow-up for Subjects

At 3 Months, patients will be emailed a link to the following measures to be completed in REDCap: AMAS, AUDIT, CESD-R, DS-II, DUDIT, DUFSS-5, ECR-M16, HARSI, ICG, MQoL-RS, NR-6, PCL-5, SAHD, SCS-R, STAI, PTGI-SF, IPIP-OE-20, MAIA-R, CTC, and the CSS. They will be called and encouraged to complete the measures. If they have difficulty with email or filling out the forms electronically, paper-and-pen measures will be sent to them with a self-addressed envelope for returning the measures.

6.4.6.3 3-Month Patients for Caregivers/Important Others

At 3 Months, primary caregivers/important others will be emailed a link with the following measures to be completed in REDCap: CORF and CSS. They will be called and encouraged to complete the packet.

6.4.6.4 3-Month Qualitative Interviews

Between the Focus Group and the 3-month follow-up, subjects and caregivers/important others will be invited to participate in a semi-structured interview of their experience in the study. These interviews will be analyzed to detect potential mechanisms of the intervention as well as outcomes not addressed by the study measures. See Appendix C for interview guide.

6.5 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interest. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

6.6 Dietary Restrictions

No dietary restrictions are included in the protocol.

6.7 Prohibited Medications

Patients are prohibited from using medications from the following classes while enrolled in the study:

- Serotonin Reuptake Inhibitors (SSRIs and SNRIs)
- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Atypical antidepressants (e.g., mirtazapine, nefazodone, buspar)
- Antipsychotics/Neuroleptics (typical and atypical)
- Anti-epileptics or mood stabilizers (e.g., lithium, valproate)

- Efavirenz (Sustiva, in Atripla)
- OTC supplements intended to affect mood or anxiety (e.g., 5HT-P or St. John's Wort).

Conditional medication restrictions

- Trazodone
  - Trazodone ≤50mg/24hr for insomnia is allowed, but not within 48hr of psilocybin session
- Benzodiazepines
  - PRNs are not allowed 24hr prior to the psilocybin session
  - "z-drugs" (e.g., zolpidem) are not allowed 24hr prior to the psilocybin session

Individuals who at screening would be excluded for taking contraindicated antidepressants, anxiolytics, stimulants or herbal supplements can be considered for the study if—under the guidance of their usual physician—they successfully taper off these medications and demonstrate a period of psychiatric stability lasting at least 2 weeks. One exception to the required 2-week period is for individuals taking low dose TCAs (≤50mg imipramine equivalent) for reasons other than depression or anxiety (e.g., peripheral neuropathy or insomnia). These individuals may, under the guidance of their usual physician, taper off these medications and then be enrolled in the study once they are no longer taking the TCA.

6.8 Study Clinicians

Study clinicians (group therapists and treatment session guides) will be approved by a panel consisting of: Dr. Josh Woolley (PI), Dr. Alicia Danforth (UCLA psilocybin team, and lead clinical supervisor for UCSF the team), Dr. Brian Anderson (UCSF psilocybin team), and Robert Jesse (Johns Hopkins psilocybin team). Group therapists and treatment session guides will all be licensed clinicians (MD, RN, NP, MFT, LCSW, PhD, PsyD, Chaplain, etc) in the state of California; an exception will be made if the person is unlicensed but currently enrolled in a clinical training program and has had sufficient clinical exposure, according to the judgment of the above-mentioned panel. The selection of therapists/guides will give preference to those who have: 1) prior clinical experience working with the study population; 2) have demographic similarities to the study population (age, gender, sexual orientation); 3) prior experience conducting group therapy; 4) prior experience working with individuals under the influence of psychedelics either in research settings or harm-reduction settings (such as the Zendo Project); 5) have completed the CIIS certificate program in Psychedelic-assisted Psychotherapy and research.

Group therapist pairs will consist of one lead and one secondary therapist. The lead must have had significant experience as a group therapy leader; the secondary must have some experience as a group therapy leader. Group therapists will undergo at least 16 hours of training in Supportive-Expressive Group Therapy (SEGT) by studying SEGT training videos, the SEGT adherence rating scales that will be used in the study, and the 3 following SEGT manuals: the original manual for metastatic breast cancer patients [75], the manual for brief SEGT in newly diagnosed breast cancer patients [76], and the adaptation by Maldonado et al for patients with AIDS [78]. All group therapists will undergo at least one 'dry run' session of the SEGT method prior to starting a group.

Each subject will have 2 guides working with them in their drug treatment day (not necessarily one male and one female). At least one of the treatment session guides will be one of the subject's group therapy co-therapists. Treatment session guides will undergo instruction by Dr. Alicia Danforth and/or Dr. Anderson. Overall clinical supervision will be a responsibility shared by Dr. Josh Woolley (Co-PI), Dr. Brian Anderson (PI) and Dr. Danforth (lead psychotherapy supervisor). Clinical consultation will be available from others involved in the study, such as Dr. Jim Dilley, Co-Investigator of this study and founder and of the UCSF Alliance Health Project, as well as Dr. Rob Daroff, a study clinician who is a staff psychiatrist at the SFVA with many years experiencing running psychotherapy groups for gay men in San Francisco.

Clinical supervision specifically related to psilocybin, and SEGT, will happen in the form of debriefing sessions after every study visit. Dr. Anderson will be an in-the-room observer of the group therapy sessions to take notes and later discuss with the group therapists their adherence to the SEGT method and its current adaptation to the psilocybin trial. Dr. Anderson and Dr. Danforth will review video of treatment sessions and discuss the technique observed with the individual session guides on an as needed basis. Video segments of group therapy sessions and psilocybin treatment sessions will be used for discussion in a periodic supervision workshop to be held after the completion of each group therapy cohort and which all study clinicians will be highly encouraged to attend. The number of supervision sessions a study clinician is required to attend to maintain eligibility to work on the study will be up to the discretion of the clinical supervisors.

7 Reporting and Documentation of Results

7.1 Evaluation of Safety and Feasibility

The assessment of safety and feasibility will be informed by surveillance of adverse events in all patients who enroll in the study. The study will use the NIH Division of AIDS Table of Grading of Severity of Adult and Pediatric Adverse Events V2.0 for reporting of adverse events. Analyses of feasibility and acceptability will also be informed by rates of patient recruitment and retention, therapist protocol adherence, self-report measures (CrEQ and CSS), and spontaneous feedback from subjects, caregivers/important others, and study therapists.

7.2 Evaluation of Efficacy

We will evaluate for trends in changes of group mean measures of demoralization, complicated grief, depression, anxiety, and other constructs mentioned above. These evaluations will consist of self-report measures (e.g., DS-II) and observations from caregivers/important others and clinical raters (e.g., CORF and CGI).

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or

as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All adverse events will be entered into UCSF REDCap, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NIH Division of AIDS Table of Grading of Severity of Adult and Pediatric Adverse Events V2.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into UCSF REDCap using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator. When specific adverse events are not listed in the above NIH DAIDS Table of Grading of Severity, they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild: Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
Grade 2	Moderate: Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
Grade 3	Severe: Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
Grade 4	Potentially life-threatening: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into UCSF REDCap, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the Data and Safety Monitor (DSM) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

In addition, all adverse events and suspected adverse reactions considered "serious," entered into UCSF REDCap will be reviewed and monitored by the Data and Safety Monitor on an

ongoing basis, discussed at DSM meetings which take place after each therapy group completes the 8-week intervention.

7.7 Expedited Reporting

Reporting to the Data and Safety Monitor

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSM within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 7.3.2.1)
- Unexpected (as defined in 7.3.2.2)
- Serious (as defined in 7.2.3.3)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Pharmaceutical Companies providing Study Drug

Serious adverse reactions will be reported to the Heffter Research Institute and the Usona Institute, which are consultants for this study.

8 Statistical Considerations and Evaluation of Results

8.1 Study Design

This open-label single-arm mixed-methods pilot study will use descriptive statistics and qualitative methods to evaluate safety and feasibility in terms of rates of adverse events, patient recruitment and retention, and feedback on the intervention's utility, content and duration. Given the small sample size of this study, small-to-medium effect sizes will likely be undetectable; and so descriptive statistics will be used to report changes in mean measures at baseline compared to the endpoint, and again at the 3-month follow-up. Exploratory ANOVAs will also be done to model changes in therapeutic process values (e.g., group cohesion) over time. Qualitative thematic analysis will also be used to evaluate verbal and written reports of patient and caregiver/important other experiences with the study in order to optimize implementation of the intervention in larger, future trials.

8.1.1 Randomization

No randomization procedures will be used.

8.1.2 Stratification Factors

No stratification procedures will be used.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

This pilot study of the safety and feasibility of psilocybin-assisted group therapy aims to enroll at least 18 subjects, and will have a maximum total sample size of 36. We estimate needing to enroll 18 subjects given attrition rates of up to 45% reported in trials of other group therapies for existential distress in palliative care patients [118]. For comparison, four different safety and feasibility pilot studies of psilocybin-assisted psychotherapy have been conducted over the last two decades, and have included 9, 10, 12 and 15 patients each [18, 111, 112, 114]. Four recently published feasibility pilot studies of meaning-focused group psychotherapies for palliative care patients have included 5, 11, 11, and 16 patients each [40, 185-187].

Group therapy studies should include at least 2 groups of at least 4-6 members [138], so we plan to have at least 8 subjects complete the intervention. We expect to be able to enroll at least 6 subjects every 6 months.

Because the proposed study is a pilot focused on investigating safety and feasibility, power calculations for efficacy measures are not indicated. Pilot studies are often used to estimate values that are then utilized in power calculations for full-scale trials. Indeed, we will estimate effect size (ES) and the intraclass correlation coefficient (ICC) [135] for the intervention based on our preliminary efficacy results. Group psychotherapy trials generally require large sample sizes to demonstrate statistical significance in change in efficacy measures given the likely interdependence of clinical outcomes when interventions are delivered in groups [135, 136]. Thus, future full-scale trials can utilize our estimates to derive adequate, and likely large, sample sizes.

8.2.2 Replacement Policy

Study subjects who have been assigned to a group and drop out prior to the first group session can be replaced by a new subject who will be assigned to the same group. Subjects who drop out after the first group therapy session will not be replaced.

8.2.3 Accrual estimates

The annual number of eligible patients is high given the size of the population of HIV-seropositive people in the San Francisco Bay Area. In 2014, San Francisco reported 15,979 people living with HIV, of whom 9,202 were at least 50 years old [8]. If accrual falls short of expectations, advertising and recruitment efforts will be expanded.

8.3 Interim Analyses and Stopping Rules

After the occurrence of one Adverse Event judged to be Severe and potentially related to the drug/intervention, enrollment will be stopped until a Safety Review has been completed and the appropriate protocol amendments implemented.

8.4 Analyses Plans

The study's biostatistician is Matthew Boden, Ph.D. Alongside the PI, Dr. Boden will be co-responsible for assuring that clinical data are correctly collected, stored and analyzed. He will work directly with the PI to assure that interpretations of these data are coherent and justified. Dr. Boden's professional interests are rooted in the research, evaluation and implementation of evidence-based treatments for complex and severe mental disorders. As a Health Science Specialist at the Center for Innovation to Implementation (Ci2i), Veterans Affairs (VA) Palo Alto Health Care System, Dr. Boden investigates the clinical effects and implementation of evidence-based psychosocial treatments for psychotic, anxiety, and substance use disorders. His research utilizes a variety of assessment (e.g., structured clinical interviews, biological assays) and statistical (e.g., linear mixed models, exploratory structural equation modeling) techniques. As a Senior Evaluator at the Program Evaluation and Resource Center (PERC), VA Office of Mental Health Operations (OMHO), Dr. Boden supports OMHO's nationwide program evaluation and quality improvement efforts.

8.4.1 Analysis Population

All patients who enroll in the study will be included in analyses of safety and tolerability.

All patients who make any contact at all with the study (including those who are screened out over the phone) will be included in analyses of feasibility.

All patients who enroll in the trial will be included in analyses of efficacy. Repeated efficacy measures will be gathered and trended, regardless of missing data or protocol non-adherence.

All patients who participate in at least one group therapy session will be included in analyses of psychotherapeutic process.

8.5 Primary Analysis

Safety analyses will be performed for all patients who enroll in the study. The study will use the NIH Division of AIDS Table of Grading of Severity of Adult and Pediatric Adverse Events V2.0 to

classify adverse events. Descriptive statistics (percentages) will be reported for the incidence of any Adverse Events reported, including suicidality as measured by the C-SSRS. Median scores will also be calculated for total scores of the feasibility measures: CSS, CrEQ, and PEQ-S. The differences of mean pre- and post-treatment scores on the CORF will be calculated. Differences in individual pre- and post-treatment MoCA scores will be assessed for each individual. Therapist protocol adherence will be reported as a rate of discussion topic deviations from the protocol.

8.5.1 Exploratory Analyses

Change in efficacy measures from pre-treatment to post-treatment to 3-month follow-up will be analyzed with descriptive statistics to represent trends in mean levels. Recognizing that the calculations will likely be underpowered, we will also perform ANOVAs of the secondary outcome measures. To assist in gauging the clinical relevance of these data relative to measurement error, and to overcome some of the limitations of the study's small sample size, Reliable Change Indices (RCI) will be calculated [188]. Data from efficacy measures will also be used to estimate effect sizes and intraclass correlation coefficients for use in larger, future studies.

Change in process measures (e.g., the HIM, QPIRS and GQ) over time will be analyzed with ANOVAs to assess the slopes of individual participants and of the whole sample.

Qualitative thematic analyses will be conducted according to the methods outlined in Section 6.3. Iterative inductive analyses will be performed with the aid of NVivo analytical software.

8.6 Study Results

Study results will be reported following the guidelines of the TREND Statement for reporting of results from non-randomized interventions [189]. The study biostatistician will oversee or review the interpretation of all the above analyses and descriptive statistics.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

During enrollment, patients will be consented for participation in the study, including having the various aspects of their participation video-recorded. They will also sign a Release of Information for study staff to speak to the patients' primary caregivers and primary physicians. Primary caregivers/important others will also be consented during enrollment.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into UCSF REDCap via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

9.7 Oversight and Monitoring Plan

The DSM will routinely review all adverse events and suspected adverse reactions considered "serious". The DSM will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSM audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix for Data and Safety Monitoring Plan for additional information.

9.8 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

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