The Living Well Project: Early Palliative Care and Motivational Interviewing (MI) for Persons with AIDS

Protocol Dated July 11, 2016

NCT01848483

1. Background

a. Specific Aims

The overall goal of this project is to improve the health and quality of life of persons living with HIV/AIDS (PLWH). To this end, we will implement an innovative model of enhanced early integrative palliative care services (EPC) for persons newly diagnosed with AIDS. Patients will be recruited from either the inpatient service or outpatient infectious disease program (IDP) at the Grady Health System (GHS) in Atlanta, GA. The AIDS EPC Package includes use of motivational interviewing (MI) to facilitate adjustment to disease and advance care planning decision making. The project has three specific aims:

AIM 1. Conduct a RCT to examine the efficacy of the AIDS EPC Package intervention vs. standard HIV care (SOC) and compare outcomes at 12 months post baseline. Our hypothesis is that those in the AIDS EPC group will have:
i. Better clinical outcomes: a lower one year mortality, higher proportion who initiate antiretroviral therapy (ART), higher proportion with virologic suppression, higher CD4 gain, fewer opportunistic infections (OI), fewer hospitalizations, lower depression scores, and better symptom management (including cognitive dysfunction).
ii. Better psychosocial outcomes: Better coping skills, higher perceived social support, higher spirituality, higher levels of self-advocacy, lower proportion who report substance use.
iii. Better Quality of Life (QOL) and a higher proportion who report advance care planning activities: named a surrogate; set personal goals regarding life saving measures; and discussed these goals with a surrogate.

AIM 2. Evaluate the cost effectiveness and cost utility of the AIDS EPC Package compared to SOC where the outcomes are valued as survival and quality-adjusted life years (QALYs) respectively.

AIM 3. Promote engagement and retention in HIV care as evidenced by attending a greater proportion of scheduled appointments and reporting higher satisfaction with care compared to SOC.

b. Preliminary Studies

This project builds well on the collective work of the investigators related to palliative care and use of motivational interviewing in PLWH.

Need for palliative care. Based on preliminary data collected from 2001 to 2010, about 100 patients with HIV/AIDS per year were diagnosed on admission to GMH. These patients were quite ill, with median CD4 count of 50 cells/mm^3 and had an average hospital stay of 8 days. Data from admissions during 2004-2005 showed a 17% mortality rate in the 21 months following diagnosis, and only about a third began ART with17% of those achieving an undetectable viral load.[50] Factors associated with both death and readmission include substance use, psychiatric diagnosis, and homelessness.[51] Palliative care is a viable option for these patients where their comprehensive and multiple psychosocial issues can be addressed. These data led to the formation of the current HIV/AIDS PC program at GHS by co-investigator Dr. Marconi. It is modeled after the PC program developed by his colleague and our consultant, Dr. Sunpath, in South Africa.

Feasibility of palliative care. The HIV palliative care (PC) program at the GHS has two components: the inpatient and outpatient programs. The inpatient program began in May 2010 and focuses on individuals with new diagnoses of HIV/AIDS and patients with a previous diagnosis of HIV who have fallen out of care. The outpatient PC program at the IDP began in March 2011 and provides follow-up care to inpatients after discharge as well as patients who receive care at the IDP clinic who

have comprehensive physical, psychosocial, emotional and spiritual needs. Drs. Rachel Friedman, Rahwa Ghermay, and Vince Marconi conducted a feasibility study of the first 14 patients with AIDS who were seen in the inpatient and outpatient program since May 2011 through February 2012. All but 1 patient was male, the mean CD4 count was 29 cells/mm^3, indicating severe immune compromise. Six (43%) were newly diagnosed. Three persons died within one month of hospital admission (2 while in hospital). Of the remaining 11, 9 patients had an inpatient PC visit, 5 patients had follow-up PC appointments and kept them, and 6 patients kept their usual care (non-PC) outpatient HIV care follow-up appointments at the IDP. Of the 9 with an inpatient PC visit, 5 started ART (55.5%). Of the 2 who did not have an inpatient PC, 1 started ART (50%). Importantly, of the 4 patients who achieved an undectable VL, all had an inpatient PC and follow-up outpatient PC visit. None of the 14 patients had prior knowledge of palliative care, and all agreed that they would benefit from a clinic that specialized in palliative care. Though the numbers are small, these data provide preliminary support for the need for early integrated PC for patients with new AIDS diagnoses. The current PC program for PLWH is in its infancy; PC is not routinely integrated *early* in HIV/AIDS care, nor does it include consistent use of MI for disease adjustment and advance care planning. Our AIDS EPC Package would enhance and integrate PC into HIV care at both GMH and the IDP.

Motivational interviewing (MI). Dr. Holstad has conducted several studies using MI. She was a co-investigator on a nursing intervention study funded by NINR (NR01 NR04857, C. DiIorio, PI), the Get Busy Living (GBL) project. This project examined the effects of a nurse-delivered 5 session one-to-one MI intervention compared with the usual nurse education program on ART adherence in 247 HIV+ men and women. Adherence was measured by Medication Event Monitoring System (MEMS) and participants were assessed at baseline, and 3, 6, and 12 months post baseline. We found a significant group by time improvement in adherence at the 8th month, which was sustained to the 12th and final follow-up.[52] As PI of the KHARMA Project (NIH/NINR R01 NR008094-01-A1), Dr. Holstad designed and implemented a group motivational intervention (based in MI) focused on dual outcomes of adherence to ART and risk reduction behaviors in HIV infected women. Women who attended 7 of 8 group motivational sessions had better adherence and reported practicing abstinence and using condoms more frequently than the control group.[53] Dr. Holstad trained health workers in Lagos, Nigeria in MI and piloted the KHARMA intervention there. She found significantly higher rates of self-reported adherence and more frequent safer sex practices in the intervention group. We believe it is the first time MI has been used in Nigeria.[54] Dr. Holstad has also used MI techniques in a recently developed music program (LIVE Network) to promote ART adherence and self-management of symptoms and side effects (R21 NR010862). MI was used in the simulated DJ talk show portion of the program where health experts responded to questions of callers about HIV medications and issues.[55] After 12 weeks, VL of those in the LN showed a significant decline (desired) while that of the SOC control increased (p=0.02).

c. Significance

HIV/AIDS in the Southern U.S. and Georgia The southeast is now the most HIV affected region in the US: Half of all new HIV diagnoses in the US occurred in the South where the combined population represents only 37% of the US population; 46% of new AIDS diagnoses (indicating advanced disease); and 90% of states with the highest HIV related death rates are Southern. Georgia is one of those disproportionately affected southern states and was 6th overall in the US for AIDS diagnoses per 100,000 in 2009. Georgia also has significant racial disparities in HIV/AIDS: African Americans represent 30% of the state's population, but 74% of its HIV/AIDS cases.[6] Atlanta, the capital of Georgia, ranks 8th among US cities in its ratio of HIV infections to overall population and concentrates 60% of all cases in the state. Located in the Deep South, where high rates of HIV infection and mortality from HIV/AIDS

prevail, Grady Health System (GHS) is a large public hospital system with both inpatient (Grady Memorial Hospital [GMH]) and comprehensive outpatient services. GHS serves some of the most vulnerable persons in the metro-Atlanta area and is home to one of the largest Ryan White funded HIV care clinics in the US, the Infectious Disease Program (IDP). Each year over 750 newly diagnosed PLWH are seen in GHS and IDP. The GHS provides care to the majority of Atlanta's HIV infected population. With over 5,000 unique patients in the case load and over 100 newly diagnosed patients at GMH each year, the burden of disease in the GHS is large. Among those newly diagnosed during a hospital stay, the median CD4 count in 2008 was 50 cells/mm^3 and the average length of hospital stay was 8 days. The GHS HIV/AIDS population is among the most vulnerable: low income, uninsured or on Medicaid, Medicare and predominately African American. In 2011 over 650 new PLWH were seen at the IDP and of these 398 were newly diagnosed with AIDS. These data provide compelling evidence for the need for early and comprehensive interventions in this group.

HIV/AIDS and Palliative Care (PC) A diagnosis of AIDS typically occurs after a person has been HIV infected for a very long time (e.g. 10 years or longer). However, about 20% of HIV infected persons in the US do not know their HIV status and thus are at risk for late diagnosis and AIDS.[7] Despite recent initiatives from CDC and other organizations to promote HIV testing, a large percentage of persons infected with HIV are diagnosed late. CDC estimated that nearly 40% of persons diagnosed with HIV in the US had an AIDS diagnosis within 1 year.[8] AIDS frequently is associated with a higher level of morbidity from OI, pain, depression, ART related symptoms, and often results in a consequent higher use of health care resources. PC is an approach delivered by a multidisciplinary team that improves quality of life of patients through optimization of physical, spiritual, psychological, and social aspects of care.[9] Palliative care can be employed at any time during the illness and is an approach that includes all therapies that are of benefit to a patient.[9] Only when patients have a prognosis of 6 months or less are they eligible for hospice care. Patients with late stage lung cancer who received early palliative care had improved quality of life, improved survival and with less aggressive interventions at the end of life.[10,11] Inpatient palliative care consultation has been shown to not only add to quality of care but have significant cost-savings particularly in underserved populations.[11,12] Currently the Ministry of Health in Vietnam mandates PC for PLWH and has achieved successful outcomes for both providers and patients.[13] PC is also used successfully for PLWH by our consultant, Dr. Henry Sunpath at McCord Hospital in Durban, So Africa.[14]

Mental health needs have been identified as one of the greatest areas of suffering to target in palliative care models for PLWH.[15-17] Trends suggest that palliative care, when initiated early, can improve outcomes in PLWH particularly in the domains of pain and symptom control, anxiety, insight, and spiritual wellbeing.[18-22] Clinicians must also be skilled beyond HIV/AIDS care given that more than half of patients that die with HIV die with non-AIDS related illness though look to their HIV/AIDS care providers for support.[23] Outpatient palliative care models in HIV/AIDS have been shown to improve quality of care and can be an integral part of a patient's care plan.[13,24-26] Clinicians have identified caring for the AIDS patient, particularly those who fail to adhere to therapy at the end of life, as challenging to care but enhanced communication and continued patient-clinician communication has been shown to deliver benefit. [27,28]

Cost effectiveness Although the costs and quality of care for people with life-limiting conditions has been an area of concern for some time, the literature on outpatient palliative care and costs is limited. When addressed, most of the focus has been on the inpatient setting and reducing the costs of care for people while in the hospital. For example, in an observational study of Veterans, direct hospital costs were $464 a day lower for those receiving PC compared to those with similar conditions who did not receive PC; PC patients were also less likely to be admitted to an ICU.[29] One study reports cost

analysis is underway on an outpatient PC intervention for PLWH in Vietnam,[13] and only one study known to the authors has been reported thus far on the cost effectiveness of providing outpatient PC to PLWH. The authors note that outreach PC cost 50% less than the average inpatient visit [30] The proposed project will address a gap and a need for such data. Conducting a cost effectiveness analysis will allow us to evaluate the additional costs, if any, associated with the additional benefit of palliative care over standard care. By using survival and quality-adjusted life years as outcome measures, we can also benchmark our intervention compared to that of other interventions for a variety of conditions.[31]

Engagement and Retention The "*Test and Treat*" paradigm has recently emerged as a major part of the new National HIV/AIDS Strategy in the United States. This strategy posits that identifying HIV-infected individuals through testing and linking them to care to receive prevention services and antiretroviral therapy will both improve health outcomes and reduce HIV transmission at an individual and at a population level. To date, much of the activity and discussion surrounding this new paradigm has focused on strategies for identifying new cases through enhanced HIV testing and linking newly diagnosed patients to HIV care. Considerably less attention has been paid to retention in care, the critical "fourth component" of successful engagement in care. Consequently, there is a great need to develop intervention strategies, such as EPC to promote engagement and retention in HIV care among individuals who are aware of their diagnosis. *Linkage and retention in care is the top priority for the Office of AIDS Research.* Poor retention in care is associated with both poor ART persistence[32] and poor adherence. Persons newly diagnosed with AIDS are at risk for both, particularly in the first year of care. Engagement and retention in care is a multi-factorial process that includes variables related to the individual, relationships, the community, health care system, and health policy. The supportive and caring nature of our AIDS EPC Package intervention will provide a mechanism to address several of the barriers encountered on the individual level (social welfare barriers, social support, spirituality, coping, mental health, self-efficacy, self-advocacy) relationship level (with partners, loved ones, providers, and other members of the health care system), and community level (stigma, structural violence, and social capital).[33]

Motivational interviewing (MI) is a client centered directive counseling method that helps clients resolve ambivalence and resistance toward and build motivation for behavior change.[34] MI counseling has been successful in changing many health behaviors including substance use, fruit and vegetable intake, and physical activity[35-38]. More recently MI has been used with PLWH to address substance use, [39,40] medication adherence,[39,41,42] and safer sex preventive behaviors[40,43-47]. MI has been successfully used to improve mood and reduce mortality when used soon after a stroke. In these stroke patients, MI was used to help adjustment to the physical, functional, and social support issues associated with stroke, and set realistic personal goals for recovery.[2,3] Similarly, MI can be used in palliative care communications;[5] however the directive approach may be re-focused toward making choices based on the client's own personal values and goals, rather than a pre-determined healthy behavior (i.e., weight loss). Focus on the spirit of MI is key: collaborative partnerships, supporting autonomy in decision making, evoking and eliciting information about one's motivations. The five principles underlying MI are: 1) Express empathy: demonstrate acceptance and understanding of the client through reflective listening; 2) Develop discrepancy: an awareness of the incongruity of behavioral consequences and one's important life goals will motivate change; 3) Avoid argumentation: defense of one's position is counterproductive and produces resistance to change; 4) Roll with resistance: the client is not the opponent but a partner; 5) Support self-efficacy: provide positive feedback and encouragement for success.[34] Persons newly diagnosed with AIDS experience issues such as depression, denial, stigma, similar to those with stroke. They also have numerous symptoms and social issues that need attention. Challenging conversations related to advance care planning, starting ART, changing risky

behaviors, and need for social support balanced with the fears of disclosure and stigma are common. The empowering and non-confrontational nature of MI lends itself well to these types of communications and helps to create a therapeutic alliance. Newly diagnosed persons with AIDS could benefit from an EPC package such as ours that includes MI in order to facilitate adjustment to their diagnosis on many levels.

Innovation In the AIDS EPC Package, we are combining two cutting-edge strategies that show promise for improving QOL, mortality, and mood for persons with chronic fatal conditions. The seminal article by Temel and colleagues[10] supports the innovation of early integration of PC with regular medical care to improve QOL, mood, and survival for those with a fatal chronic illness (non-small cell lung cancer). Emerging work from our consultant Dr. Sunpath in South Africa[14] and that of Green and colleagues[13] in Vietnam provide evidence that early outpatient PC in PLWH is feasible and effective even in low resource settings. And the work of Watkins,[2,3] our consultant, provides rationale for early use of MI to facilitate disease adjustment and improvement in mortality and mood in a potentially fatal chronic disease (stroke). Combining these two strategies is novel and the first time this approach will be tested in a controlled manner.

Potential Impact The challenge for HIV providers is to comprehensively address the many physical, social, and psychological symptoms and issues associated with a new AIDS diagnosis. The AIDS EPC Package is a highly innovative and creative way to enhance quality of life and facilitate engagement and retention in care for these individuals. It addresses gaps noted in the few existing HIV PC studies due to poor experimental methods and non-standardized measures.[18] It is also cost-effective in that persons who begin and maintain ART are more likely to achieve viral suppression, will have fewer costly OI and hospitalizations, and will be less likely to transmit HIV to others. Thus, there are important implications for the both the individual and the public's health. Should the AIDS EPC Package show promising results, this innovative strategy, could serve as a model to address the comprehensive needs of newly diagnosed PLWH nationwide and enhance the national priority of engagement and retention in HIV care.

2. Design

a. Sample and b. Setting

We propose a 2-arm RCT[49] comparing the efficacy of the AIDS EPC Package vs. SOC in approximately 128 persons with diagnosed AIDS within the Grady Health System inpatient and outpatient settings (Ponce Center IDP). We plan to recruit up to 350 persons to account for screen failures and attrition.

Eligibility criteria include: 1) Diagnosis of AIDS (using current CDC criteria); 2) Detectable viral load[1] (> 1.6 log or > 40 copies per ml); 3) Not currently on ART; 4) Age ≥18 years; 5) Able to speak and write English; 6) Able to give and understand consent; 7) Willing to participate in study activities.
Exclusion criteria: Participants who have a Karnofsky score of 30 or less and are impaired in 5 activities of daily living (ADL) from this list: Bathing, dressing, transferring from bed or chair, walking, eating, toilet use, grooming will be excluded because these criteria are predictive of mortality in about 4 months. Also excluded are those not HIV infected, are a minor under 18 years of age and therefore unable to give independent informed consent, are unable to read or understand English since all of the questionnaires and study activities will be conducted in English, cognitive impairment (inability to comprehend the

[1]Viral load has been deemed the most important measure of response to HIV treatment by the CDC[87]. Optimal viral load is defined as <1.6 log or < 40 copies per ml by the Ponce Center IDP laboratory protocol.

informed consent document), are actively psychotic, severely depressed/suicidal, or pose a risk of harm to themselves or others (Brief Symptom Inventory; BSI), since these persons may not be capable of completing the assessments or study activities. Depending on the severity, these persons will be walked to or referred to the mental health counselor; once the mental health issues have been addressed, they may be re-screened for eligibility. Substance users will not be excluded from the study, except if they display the above mentioned mental health characteristics or pose a risk of harm to themselves or others.

It is expected that a small percentage of women who meet the eligibility criteria could enter the study pregnant or become pregnant during the study. Since the intervention will not harm and may benefit pregnant women, they will not be excluded from the study.

c. Recruitment and Enrollment

In the *inpatient hospital setting*, trained recruiters will review inpatient medical records of all patients diagnosed with AIDS for eligibility (IRB and HIPAA compliant procedures), then consult with social workers, charge nurses and other healthcare providers to identify medically stable patients slated to receive outpatient care at the IDP clinic. Once eligible patients are stable, alert, and oriented, they will be approached.

- If a patient is interested, the study will be described and, if possible, the study informed consent will be reviewed and signed, and a Screening Visit conducted.
- If further information is needed to determine eligibility, staff will: 1) conduct a Screening Consent, 2) ask screening questions and record the answers in a database, 3) review the medical record, then 4) schedule the candidate for an in-person Screening Visit.
- If the patient is not able to be screened or enrolled at that time, study staff will give the patient written study information and ask if study staff can follow-up with him/her at a later time. If the patient agrees, contact information will be collected.

In the *outpatient IDP setting*, recruiters will work with the Education Department, where all new patients are first seen prior to clinic enrollment, as well as healthcare providers, nurse educators and other clinical staff to identify eligible patients. Study staff will review medical records to identify potential candidates, then ask appropriate clinic staff to introduce the study to those patients; if this discussion is confirmed, study staff will contact the patient to see if s/he is interested.

In addition, flyers will be used to advertise as follows: posted in the clinic; given to providers; handed out in clinic waiting rooms (non-targeted); handed out to eligible patients (those previously identified by record review) in clinic after their appointments; distributed at appropriate patient meetings. In most cases, patients will call the study phone number if they are interested.

Once initial contact is made, pre-screening will be conducted:

- Study staff will read a script which describes the study, including eligibility criteria, and (if in person) give candidates a study flyer.
- If an interested candidate states that s/he meets the eligibility criteria, s/he will be scheduled for an in-person Screening Visit.
- If further information is needed to determine eligibility, staff will: 1) conduct an Oral Consent for Study Screening (if discussion occurs via phone) or a Screening Consent (if in-person), 2) ask screening questions and record the answers in a database, 3) review the medical record, then 4) schedule the candidate for an in-person Screening Visit.
- If at any point in the process an individual is not eligible, the pre-screening process will stop and all personal identifiers will be scrubbed from the screening database.

The study informed consent form will be discussed at the in-person Screening Visit. Since this population is at risk for cognitive impairment that may, in some cases, limit their capacity to provide consent, a consent post-test will be administered after the informed consent discussion to evaluate understanding of study procedures, risk/benefits, etc. Those who obtain a score of <100% after 3 attempts will be excluded. Those who pass will sign the informed consent form and proceed to screening for psychopathology. Select items from the Brief Symptom Inventory (BSI) will be used to assess for psychopathology.[59] Eleven key items from this 53 item self-report inventory will be used to assess for suicidal ideations and severe depression [9, 16, 17, 18, 35, 50], and psychotic behaviors [3, 14, 34, 44, 53]. Potential participants will be excluded if they have suicidal ideations, or if either total subscale score exceeds 18. (Potential participants with serious problems will be referred immediately to a mental health professional. Once they have been evaluated, participants may return after approximately 2 – 8 weeks for BSI re-screening. This procedure has worked well in our previous projects.) Potential participants who pass the BSI will be enrolled.

Once fully consented and screened, a baseline assessment (via ACASI) will be obtained that day or scheduled for another day/time, depending on patient preference. After completion of their baseline assessment, participants will be randomized in a 1:1 treatment:control ratio using stratified block randomization. Block sizes of 4 are used to minimize deviation and ensure efficient deployment of clinic resources, and blocks are stratified by recruitment site (inpatient vs. outpatient) to ensure balance across the groups by recruitment site. (That is, the first subject recruited as an inpatient will receive the first assignment from inpatient randomization block 1, the second subject recruited as an inpatient will receive the second assignment from inpatient randomization block 1, the first subject recruited as an outpatient will receive the first assignment from outpatient randomization block 1, and so on.) Randomization within blocks is achieved via the use of a computerized (pseudo) random number generator.

After randomization, participants will be told their study group assignment and the appropriate appointments will be scheduled:

- Randomized study *inpatients* will receive an EPC visit in the hospital. They will then have to register as an IDP outpatient before further study procedures can occur. When they are registered at IDP, those randomized to:
    - The AIDS EPC Package group will have an outpatient (IDP) EPC clinic appointment and four ½-hour motivational interviewing sessions scheduled, in addition to a usual care IDP HIV-care clinic appointment. The motivational interviewing sessions will be scheduled to begin within 1 – 4 weeks of Baseline. The PC clinic appointment will optimally be scheduled by the PC clinic team within 3 months of Baseline.
    - The SOC group will have a usual care IDP HIV-care clinic appointment scheduled per usual clinic procedures.
- Study *outpatients* (enrolled from IDP) who are randomized to:
    - The AIDS EPC Package group will have an outpatient (IDP) EPC clinic appointment and four ½-hour motivational interviewing sessions scheduled, in addition to a usual care IDP HIV-care clinic appointment. The motivational interviewing sessions will be scheduled to begin within 1 – 4 weeks of Baseline. The PC clinic appointment will optimally be scheduled by the PC clinic team within 3 months of Baseline.
    - The SOC group will have a usual care IDP HIV-care clinic appointment scheduled per usual clinic procedures.
- For all AIDS EPC Package participants, per IDP PC clinic standard of care, additional (follow-up) PC clinic appointments will be scheduled as needed as determined by the PC clinic provider and

team. Therefore, some patients will have one PC clinic visit and others will have more. These will be tracked.

- For all SOC participants, if they are referred to the PC clinic as part of their usual care, they will not be excluded and will be considered in the SOC for the intent-to-treat analysis.

Inpatients may not be well enough, or may not have time due to their clinical needs, to proceed to baseline & randomization prior to hospital discharge. These patients will be scheduled for a baseline visit after they enroll at, or return to care at, IDP.

Monitoring recruitment. We anticipate recruiting approximately 5 persons a month over 24 months. Current GHS data show that about 100 patients with AIDS are admitted to GMH and 650 new PLWH (>350 new AIDS) with are seen annually at the IDP. Thus we will be able to meet our sample size within the recruitment period even after accounting for screen failures and variable interest.

Recruitment materials will be uploaded.

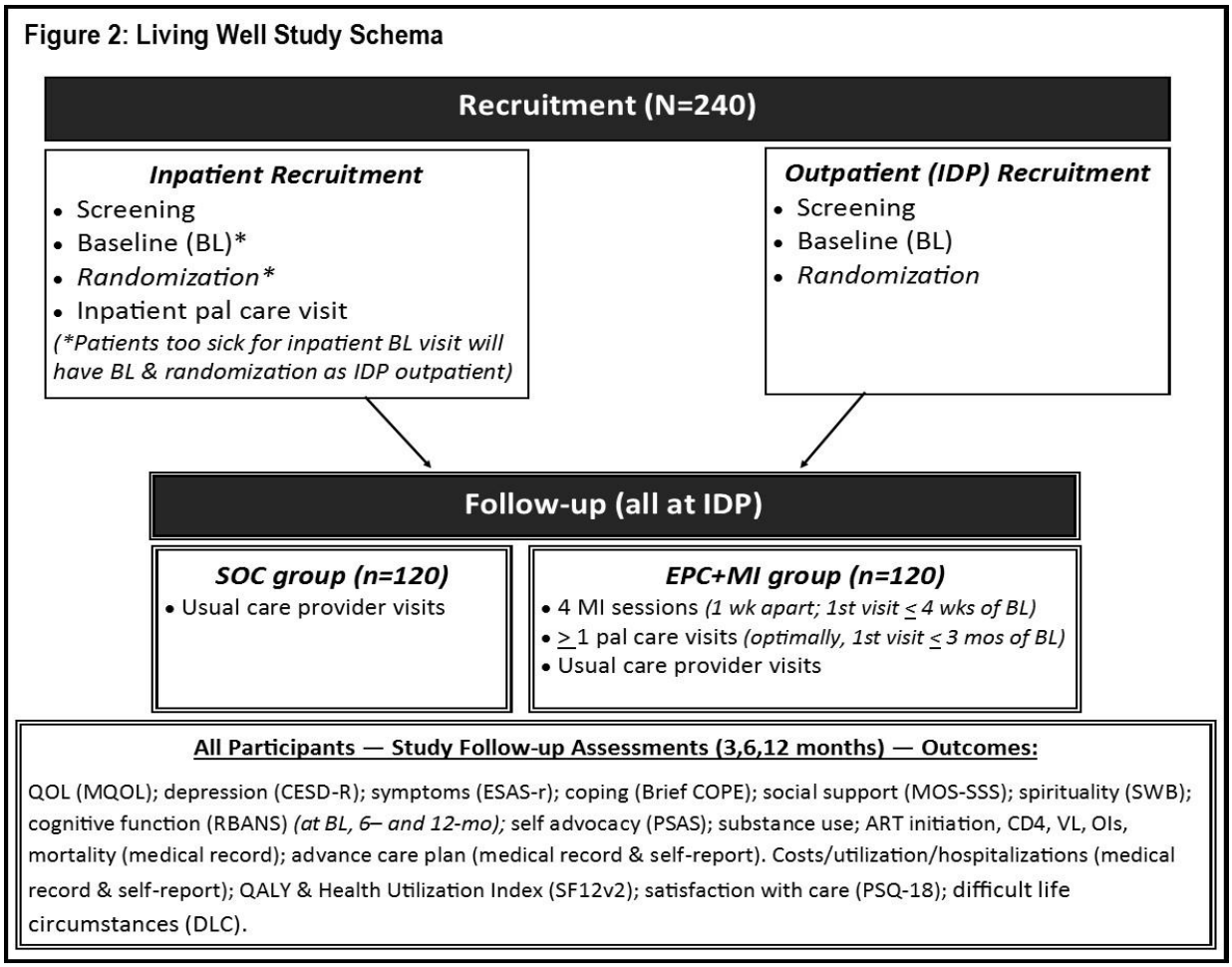
d. Procedures

d.1 Study design is a 2-arm RCT.[49] See Figure 2, page 10.

d.2 Data collection procedures

Sources of information will include baseline, 3, 6, and 12-month follow-up assessments conducted solely for the purpose of this research. Assessments will include quality of life indicators, measures of symptoms, depression, self-advocacy, coping, social support, spirituality, cognitive functioning, substance use, demographic information, difficult life circumstances, advance care planning, and health care visits. We will obtain several measures from electronic medical records: Lab results for CD4 and viral load, advance care planning information, mortality, and health care utilization (emergency room use, hospitalizations, diagnoses of opportunistic infections). We will also obtain cost information for participants through the clinic and hospital billing systems. Study interview assessments will be conducted using ACASI and the tests for cognitive function will be conducted in person. The combined assessments will last about 2 hours total with a break offered half way through the visit. We will also record all MI sessions (with permission of the participant). If participants move away during study participation, study interviews and motivational interviewing sessions may be conducted via phone. For the phone interviews, the ACASI questions will be read out loud by study staff, rather than the computer. The cognitive functioning assessment will not occur, since that must be conducted face-to-face.

Participants will be assigned to one of two conditions: an AIDS EPC intervention package or SOC. All participants will receive the usual care at the site. Identifiable private information about study participants will be stored in a password-protected REDCap database accessible only by approved study staff members who deal directly with participants. Minimal paper-based forms will be used; those that contain private data with identifiers will either have the identifiers redacted before being stored with research data, or will be kept separate from research data, and both will be kept in locked cabinets.



d.3 Total Respondent burden is about 2 hours.

e. Study instruments are uploaded into the e-IRB

f. Risks

There is a risk of breach of confidentiality associated with this research project. Identifiers and confidential information about participants could inadvertently or accidently be revealed. Completion of the assessments and participation in the interventions are free of risks for physical harm. However, both the assessments and the intervention may raise psychological concerns, such as discussions about coping with an AIDS diagnosis, spirituality, and advance care planning, which may be troublesome to some of the participants. Some participants may feel anxious as a result of dealing with these issues. These risks will be explained in the consent form. There are mental health professionals who will see the participants as part of the EPC and are fully trained to discuss and deal with emotional issues specific to AIDS. All study staff will be trained in the mental health aspects of HIV/AIDS, how to recognize and deal with emotional or behavioral problems, including anxiety, as they arise, and will be asked to report all adverse events to the principal investigator.

Protections Against Risks

In order to maintain confidentiality, a Certificate of Confidentiality has been obtained from the National Institutes of Health. Study staff will rely on the Certificate to refuse to give out study information that identifies participants. In addition, all study staff and investigators will be required to sign a confidentiality statement.

After candidates give oral consent, they will be asked basic eligibility questions, and their answers will be documented in a REDCap database. This information is needed in order to compare their answers to their medical record and definitively determine eligibility. If a candidate is not eligible for the study, however, all PHI will immediately be deleted from REDCap.

Using a coding system for tracking assessments will minimize threats to confidentiality. All confidential information including code numbers and data will be kept in a locked office in locked file cabinets with limited access. Names will never be linked with data, except in one form in the REDCap database; however, this database is password-protected and contains built-in protections that prohibit identifiers from being exported or printed. All study data will be kept on a secure password protected, HIPAA-compliant server at Emory University. Any text messages sent as study reminders will not contain private information or terms that may disclose status. Code words will be used when needed to send reminders for study activities. When calling participants, we will always ask if they can talk privately and if not, set a time to call back.

Digital audio recordings used for monitoring fidelity to MI will be labeled by a session number, facilitator, and date. These will be kept on a secure server with limited password protected access. If transcribed, the transcriptionist will follow a strict confidentiality procedure for transcribing recordings; no names/identifiers will be used when transcribing, analyzing, or reporting the data. In addition to the above procedures regarding the slight possibility of emotional response or anxiety, all our staff are trained to provide emotional support to anxious or stressed out participants. We have an established protocol for mental health referrals and there is an existing mental health referral system at the site, which we will use if needed. Participants will be informed they may stop participation in the project if it is stressful to them.

g. Potential Benefits of the Proposed Research to Human Subjects and Others

The primary risk for participation in this study relates to breaks in confidentiality. As noted above, several steps will be taken so that data are never associated with the name of a particular participant and that information discussed in with participants during study activities will not be shared. Each week the project coordinator will meet with the PIs to discuss issues which have arisen. While we cannot control ahead of time possible adverse events related to emotional issues, we do know based on our experience with both palliative care and MI, the potential for adverse events is low. The benefits of our intervention include learning about ways to problem solve and develop personal strategies for coping with AIDS, ways to self-manage symptoms, and receipt of the incentives to promote retention in the project. We believe that the benefits of the intervention outweigh the possible negative consequences.

h. Data analysis

Sample size calculations and rationale

The target sample size is 128 participants with 64 allocated to each group. Given our approach using multi-level longitudinal models (MLM) for the repeated measures modeling for these 128 subjects, in 2 groups at 4 time points, moderate-to-large effect sizes (ES) (Cohen's f) will be detectable at 80% power and 5% significance level: ES 0.25 at 80.09% for between groups effect, ES 0.30 at 80.38% power

for within subjects time effect, and ES 0.30 at 80.38% power for the group-by-time interaction effect. Covariate adjustments will further reduce variability and detectable effect sizes while increasing power. Additionally, to address the differences in proportion initiating ART, achieving virologic suppression and mortality, a chi-square test for a sample size of 128 yields a moderate effect size (W) of 0.25 for 1 degree of freedom (2 x 2 table) at 80% power and 5% level of significance.

Data management Procedures for data management and monitoring will be initiated during the start-up phase. The project coordinator will coordinate the organization and processing of forms, and schedule and implement checks of data quality and completeness. Data from the ACASI files will be saved in the QDS data warehouse. Data will be backed up on a regular basis to prevent loss of data. Data will be transferred electronically from the sites to a secure password protected study web drive where it will be checked and downloaded. A data-checking plan based on each questionnaire will be used to look for suspicious entries. Data monitoring will include scheduled checks for completeness every 2-4 weeks. Data sets from all assessment points will be merged as necessary to answer the research questions. Dr. Higgins will oversee the final quality assurance/quality control data reviews. She will design and conduct the statistical analyses; assist as needed with designing research forms and data entry; and collaborate with the investigators on analysis and interpretation. We have successfully used these procedures in our research projects.

Analysis Initial analysis will include descriptive statistics of sample characteristics (demographics, substance use, depression scores, etc. and CD4 and Viral Load) and psychometric evaluation of all scored instruments. A combination of statistical software will be used for statistical analysis and data visualization, including SPSS (v.19), SAS (v. 9.2), and R (v. 2.14). Distributions, potential outliers, and patterns of missing data will be assessed to assure that the data meet assumptions for subsequent inferential tests such as evaluating whether the criteria for missing completely at random (MCAR) or missing at random (MAR) are met. Any key variables associated with missing data will be included in subsequent models. Missing data imputation methods may be used for small amounts (<5%) of missing data such that final estimates are unbiased. All statistical tests will be performed at the 5% level of significance, with exact p-values reported. Intent-to-treat procedures will be employed. For non-normal data, transformations may be performed to improve deviations from normality. However, it is well known that CD4, viral loads and other measures such as depression and costs are often skewed and experience floor and/or ceiling effects. Therefore, generalized linear models (GLM)/generalized estimating equations (GEE) frameworks will be employed to more accurately reflect the true underlying distributions generating these data. It is expected that logistic (logit)[82] and log-gamma[83] may be appropriate as well as Poisson, zero-inflated/hurdle variations for the Poisson and negative binomial distributions.[82,83] Additionally, it is expected that some attrition over time will occur. Mixed/multi-level models (MLM) will be used instead of repeated measures analysis of variance (RM-ANOVA) methods since MLM uses all available data (does not delete cases with missing values over time), handles data that are missing at random (MAR) which RM-ANOVA cannot, does not assume independence across time, provides a breakdown of variance both within and between subjects, and allows for both time-invariant and time-varying covariates[82,83] It is expected that the majority of the analyses will occur in SPSS. However additional MLM and GLM/GEE models will be run using SAS (PROC MIXED, PROC NLMIXED) and R (packages: LME4, GAMLSS as well as BRugs, which employs Bayesian estimation methods).[84-86]

AIM 1: All covariates will be evaluated to determine if any differences exist at baseline between the 2 groups (AIDS EPC Package, SOC), as well as testing for interactions (moderation) between groups and time. Inter-correlation among the covariates will also be evaluated. Multicollinearity diagnostics (variance inflation factors, tolerance, condition index) will be used to determine which covariates should remain in the subsequent models. MLM longitudinal models as detailed above will be used for each outcome (QOL, mortality, ART initiation, CD4, viral load, OI, hospitalizations, depression, symptoms, coping, perceived social support, spirituality, self-advocacy, substance use, advance care planning) to test differences between the 2 groups (group main effect), test for changes/differences from baseline to 3, 6 and 12 month (time main effect) and test for group by time effects (i.e. changes from baseline that are differences between the 2 groups) adjusting for significant covariates/moderators as needed. Appropriate distributions and associated link functions (e.g. logit, poisson, negative binomial, zero-inflated/hurdle and other joint distributions) will be assessed for each outcome within the MLM.

AIM 2: For the economic evaluation we will focus on the differences in health care resource use, survival, and quality-adjusted life years between the intervention and the SOC groups. The perspective will be that of the health care system. We will calculate two measures: 1) the incremental cost per life-year gained and 2) the incremental cost per QALY gained at three, six and twelve month intervals for the AIDS EPC Package compared to the SOC group. We will calculate costs from health care utilization for both groups, along with staff time associated with the intervention. We will price utilization and staff time according to GHS billing charges, which will then be adjusted using the Medicare cost-charge ratio, so the final figures reflect true resource costs. Costs will be combined with effect measures to calculate the incremental ratios.

We will combine the cost data at the appropriate intervals with the effect measures, namely survival and QALYs. QALYs will be calculated by multiplying the quality-adjustor produced via the SF-12 survey to the survival period. For QALYs for example, we will then calculate the incremental value:
$\text{Cost}_{\text{AIDS EPC Package}} - \text{Cost}_{\text{SOC}} / \ \text{QALY}_{\text{AIDS EPC Package}} - \text{QALY}_{\text{SOC}}$
which will show the additional cost to the system for the gain in quality-adjusted survival. The analyses will be repeated for life years unadjusted.

AIM 3: We will describe the proportion of AIDS EPC Package appointments kept by the AIDS EPC group and will conduct sub-analyses based on "dose" to determine differences by categories such as depression, substance use, demographics. We will use a generalized linear models approach to examine differences in the proportion of usual care HIV care clinic appointments kept and satisfaction with care between the groups. In addition to the proportion of the number of appointments kept, length of participation time during study may also be compared between the groups by survival analysis methods (Kaplan-Meier) and Cox proportional hazards regression. This approach would focus on subjects who leave the study early at various times compared to those who complete the study to see what, if any, covariates predict "risk" of leaving their care regimen relative to this study.

3. Training Research Personnel

Interviewer training. Experienced interviewers will be trained to conduct baseline and follow-up interviews. To control for measurement error, we will be using ACASI to administer most of the items. We will develop a procedures manual which includes all the important elements of interviewing along with specific information related to each item on the questionnaires/surveys. This manual will serve as the basis for training. Interviewers will use standardized scripts to introduce the participant to the study and explain the questionnaires/surveys, and procedures. The interviewers will practice the survey,

screening, baseline, and follow-up scripts with each other. Weekly meetings and contact with the PI will be held to discuss problems and issues that may arise.

Training staff in MI. Our consultant from the United Kingdom (UK), Dr. Caroline Watkins, has successfully and innovatively used MI to help stroke patients adjust to their diagnosis[2,3] and will assist us with developing and structuring the four MI sessions using her study manual. The MI nurse counselors will receive four days of training in MI conducted by Dr. Holstad, who is an MI trainer and member of Motivational Interviewing Network of Trainers (MINT). Dr. Amit Shahane, a psychologist, who is experienced in MI will assist. This will be followed by practice sessions and approximately 12 role plays per nurse with standardized patients (actors trained to portray patients with AIDS). We will hire persons diagnosed with HIV as standardized patients. They will primarily be from our recruitment site (e.g., members of the Community Boards at the site). They will be trained as standardized patients by Dr. Holstad. Dr. Holstad is experienced in both MI training and use of standardized patients to evaluate MI in trainees in previous studies.

4. Data management and monitoring
A safety monitoring committee (SMC) will be established. This committee will be composed of:

Chair: **Dr. Elizabeth Corwin**, PhD, Professor, Associate Dean for Research, School of Nursing; Emory University

Members: **Kimberly A. Workowski**, MD Professor of Medicine, Emory University School of Medicine
Weihua Zhang, PhD, RN, Assistant Professor, School of Nursing, Emory University
Bryan Williams, PhD, Biostatistician, Associate Research Professor, School of Nursing, Emory University

The SMC will meet with the PIs annually or as needed to review conduct of the trial, including informed consent procedures, accrual, recruitment and retention, violations in protocols, adverse events, breaches in confidentiality, or other data related to the protection of human subjects. They will also review and make recommendations on the data transfer and warehousing procedures. The primary role of the SMC will be to ensure data integrity and the safety of participants. They will have the power to recommend conclusion of the trial and provision of the intervention to the control group if significant improvements in outcomes occur. They will also have the power to recommend conclusion of the trial if significant risks develop, or if the project is unlikely to conclude successfully.

The first meeting will occur at the beginning of the trial and at this meeting the committee will review and make recommendations about the consent procedures, and situations within which confidentiality may be broken, such as if a participant becomes a threat of physical harm to self or others. In addition, study protocols, recruitment, and retention procedures will be examined for timeliness, practicality, safety, and protection of human subjects.

At the subsequent regular annual meetings, the SMC will review:

a. adherence to the goals for recruitment and retention;
b. adherence to the study protocols;
c. cumulative data for evidence of study related adverse events;

d. quality, completeness, and timeliness of the data collected;
e. factors that could affect the outcome or compromise participant/data confidentiality;
f. other factors outside the study (e.g., therapeutic developments, agency related policies) that could impact the safety of participants or the ethical conduct of the study.

In general, recommendations the SMC may make include:

a. continue the study without change;
b. modifications to the study protocol;
c. suspension or early termination;
d. alternative approaches to consider (e.g., if there is a failure to accrue participants as anticipated).

All Adverse Events that occur during the study will be sent to the SMC chairman, who will distribute them to the other members of the committee. The relatedness of the event to the study will be provided at the time of presentation of the information. In addition the Emory University IRB and NINR Program Officer will be notified within a week of the event. The SMC chairperson will transmit an annual report of its findings to the funding agency, the local IRB, and the study PIs.

In compliance with the NINR Policy on Data Safety and Monitoring, the PIs will report the following to NINR:

a. Unanticipated problems or unexpected serious adverse events that may be related to the study protocol.
b. IRB-approved revisions to the study protocol that indicate a change in risk for participants.
c. A summary of recommendations made by the SMC and (if applicable) the action plan for response.
d. Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions.

5. Confidentiality

See “f: Risks” above.

6. Informed consent

The Oral Consent for Screening, Screening Consent, and study informed consent forms have been downloaded to the e-IRB application. Individuals who express interest in the study will first talk to study staff on the phone or in person. The study will be explained in detail including the purpose of the study, the participant’s role in the study, study requirements, and time commitments (including for the intervention and assessments), and eligibility criteria. Questions will be answered. Candidates will be assured that their care at the agency will not be affected in any way by their decision whether or not to participate in the study. During this initial telephone or in-person discussion:

- If a candidate states that s/he meets the eligibility criteria, s/he can immediately be scheduled for an in-person Screening visit.
- If further information is needed to determine eligibility, staff will read an Oral Consent for Study Screening (if discussion is via phone) or Screening Consent (if in-person); if the candidate agrees to be screened, study staff will ask screening questions and review the medical record, then schedule eligible candidates for the in-person Screening Visit.

At the Screening Visit, the study informed consent will be reviewed, which includes an explanation of the study, the risks and benefits of participation, the duration and type of participation, description of the procedures, contact person for the research including the chair of the IRB, the voluntary nature of participation, and the right to withdraw without penalty. The candidate will be given an opportunity to ask questions and receive additional information. If the candidate passes the informed consent quiz and is still interested, s/he will be asked to sign the informed consent form and will be given a copy of the form to keep.

7. Plans to inform participants of new findings or research results that might affect health

The following language is included in the study consent form:
"It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study."

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