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A protocol for a randomized controlled trial of a couples-focused intervention to improve engagement in HIV care

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Abstract:

Introduction. Advances in HIV treatment have proven to be effective in increasing virologic suppression, thereby decreasing morbidity, and increasing survival. However, not all people living with HIV (PLWH) in the US are engaged in care, and only a minority have achieved virologic control. Sexual and gender minorities (SGM; those who do not identify as heterosexual or those who do not identify as the sex they were assigned at birth) represent a high-risk population for poor clinical outcomes and increased risk of HIV transmission, as they face barriers that can prevent optimal engagement in HIV care. Research in dyadic support, specifically within primary romantic partnerships, offers a promising avenue to improving engagement in care and treatment outcomes among SGM couples. Dyadic interventions, especially focused on primary romantic partnerships, have the potential to have a sustained impact after the structured intervention ends.

Methods and analysis. This paper describes the protocol for a randomized control trial (RCT) of a theory-grounded, piloted intervention (DuoPACT) that cultivates and leverages the inherent sources of support within primary romantic relationships to improve engagement in HIV care and thus clinical outcomes among HIV-infected SGM couples. Eligible participants must report being in a primary romantic relationship for at least three months, speak English, at least one partner must identify as a sexual or gender minority, and at least one partner must be HIV+ with suboptimal engagement in HIV care, defined as less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or unknown viral load, or not currently on antiretroviral therapy (ART). Eligible consenting couples are allocated equally to the two study arms: a structured six-session couples counseling intervention (DuoPACT) or a three-session individually-delivered HIV adherence counseling intervention (Life Steps). The primary aim is to evaluate the efficacy of DuoPACT on virologic control among

HIV+ members of SGM couples. The DuoPACT study began its target enrollment of 150 couples (300 individuals) in August 2017, and will continue to enroll until June 2021.

Ethics and dissemination. DuoPACT has been built on years of formative work and offers the opportunity for PLWH to improve their HIV care engagement through support from their primary romantic partner. It has the potential to improve clinical outcomes and to reduce the number of new infections among populations that have a high burden of HIV through treatment optimization.[1]

Strengths and limitations of this study

- The DuoPACT intervention has been piloted and tested and is currently in its final phase testing the efficacy of a couple's-based intervention approach to increasing engagement in HIV care.
- A couples-based approach has the potential to have lasting effects after the conclusion of the formal study intervention, as partners take on more active supportive roles that can have sustained and dynamic impact over time.
- The study is designed to detect changes in laboratory-confirmed HIV viral load.
- The study is located in one geographic area, which may limit generalizability
- Relationships can be volatile leading to break-ups at various points in the study, including after consent visit and prior to study enrollment.

Introduction

Engagement in HIV care, including high levels of adherence to antiretroviral treatment (ART), is essential for managing HIV infection and for ending the HIV epidemic.[2 3] Consistent medication adherence is linked to viral suppression, which allows people living with HIV (PLWH) to live

longer and healthier lives, and viral suppression can eliminate the potential for further transmission to uninfected sexual partners.[4 5] The HIV Care Cascade (also referred to as the Care Continuum) conceptualizes the level of engagement in care in PLWH throughout the United States and has been used as a framework to address the barriers many people face managing their health and HIV treatment.[6] As of 2016, 49% of PLWH in the US were estimated to be retained in care, and only 53% of those had achieved viral suppression.[7] Barriers associated with successful medication adherence, a key component of the continuum, include medication fatigue, side effects from the medications, and forgetfulness.[8 9] In addition, there are gaps within other parts of the HIV Care Continuum, such as retention in care, that prevent PLWH from achieving viral suppression.[10] Recent research has focused on social support between dyads, specifically among romantic partnerships, which shows promise in addressing some of these gaps.[11]

Being in a primary relationship can provide health-promoting benefits through tangible and emotional support, and various kinds of social support are associated with positive outcomes for people living with chronic illnesses.[11-20] Within the context of couples affected by HIV, there is evidence that social support from primary romantic partnerships is associated with better HIV care engagement, such as ART adherence, compared to social support from people other than romantic partners.[21-25]

Although the preponderance of evidence suggests an overall positive impact from partners on many outcomes in healthcare, being in a relationship can also present challenges to HIV care engagement. Partners may have different roles in the dyad, such as a caretaker, that may prevent a person from taking care of their own HIV infection or other health demands.[26] Negative influences, such as substance use, conflict, abuse, and violence can also prevent optimal engagement in care for one or both partners in the dyad.[27 28]

Overall, however, the evidence supports the premise that social support within a relationship dyad has more positive than negative impact on HIV and other health-related outcomes. By extension, interventions designed to improve communication, emotional support, and involvement in healthcare within dyads can improve health behaviors such as engagement in care.[27] This is particularly true for some subpopulations in the US, in which the HIV epidemic continues to be concentrated, including sexual and gender minority (SGM) individuals and their sexual partners.[29] As many as half to three-quarters of HIV transmissions among sexual minority persons likely occur within the context of primary romantic relationships.[30] While there are not parallel modelling data for gender minority persons, the worldwide prevalence of HIV among transgender persons is 49 times higher than among other groups.[31] Collectively, these data support a focus on continued innovation and intervention for preventing HIV and optimizing treatment among SGM persons and their partners.

Aim of the study

The primary objective of the DuoPACT study is to test a couple-level HIV intervention designed for sexual and gender minority couples in sero-discordant or sero-concordant HIV-positive relationships. The purpose of the intervention is to leverage and shape relationship dynamics to improve engagement in HIV care. Such an approach has the potential to be a powerful, cost-effective, and sustainable tool to optimize treatment outcomes among couples affected by HIV. The study will evaluate the efficacy of DuoPACT on the primary outcome of virologic control among SGM people living with HIV in primary relationships.

Study Specific aims:

Primary Aim:

1. Evaluate the efficacy of DuoPACT on virologic control among HIV-infected sexual and gender minorities in primary relationships;

Secondary Aim:

1. Explore the effect of DuoPACT on behavioral indicators of engagement in HIV care, including ART adherence and HIV care appointment attendance and pre-exposure prophylaxis (PrEP) for HIV-uninfected partners; and
2. Explore the potential mediating effect of relationship variables DuoPACT has on patient and partner outcomes.

Methods and analysis

Study Design

The study is a randomized control trial (RCT) with 150 couples (300 individuals) in the San Francisco Bay Area in Northern California (Figure 1). Recruitment began in August 2017 and will continue until June 2021. Participation in the study takes a total of nine months, with surveys conducted at baseline, three, six, and nine months. The primary trial outcome is HIV virologic suppression, as measured by laboratory assay. Secondary outcomes include behavioral indicators of engagement in HIV care, including ART adherence, HIV care appointment attendance, as well as use of Pre-Exposure Prophylaxis (PrEP) for HIV-uninfected partners, a highly effective daily HIV medication that can prevent HIV infection following sexual exposure.

Study Participants

The study sample consists of primary romantic SMG couples, age 18 or older, who describe each other as “a partner to whom they feel committed above anyone else and with whom they have had a sexual relationship”. At least one partner must be HIV+ and report suboptimal engagement in HIV care defined as one or more of the following: less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or

unknown viral load, or is not currently (for the past 30 days) on ART. See Table 1 for full inclusion criteria.

Recruitment Strategy

Participants are recruited through venue-based and online strategies as well as referral. Flyers are posted in venues (LGBTQ resource centers, bars, coffee shops, etc.), community-based organizations (CBOs), clinics, pharmacies and community bulletin boards. Staff distribute packets with study materials, including an information sheet outlining the basic eligibility criteria, flyers, and postcards, to clinics and CBOs throughout the Greater Bay Area. Providers and CBOs are asked to place these materials in waiting areas where potential participants are likely to see them. Study advertisements are posted online on Craigslist and Facebook and through dating/hook-up apps such as Growlr and Grindr.

In-person study recruitment takes place in HIV clinic waiting rooms. Recruiters present the study at staff/provider meetings in clinics throughout the Bay Area that have a high number of patients living with HIV to facilitate referral to the study. Recruiters also staff tables at symposia, conferences, and community events to continue collaboration with HIV healthcare providers as well as connect with members of the community that may be interested in participating in the study.

All recruitment materials include a toll-free number and a link to the study webpage. Interested potential participants are directed to call the number listed on the recruitment resources or fill out the Contact Us form to learn more about the study and initiate the screening process. Study staff are notified when a potential participant completes the form and contact within one business day to ensure a higher chance of contact.

Enrolled participants have the opportunity to refer couples to the study via a “snowball” recruitment method. To maintain confidentiality of the enrolled participants, potential participants

are asked “how did you hear about the study” and must mention the name of the participant that referred them. To maintain confidentiality, staff cannot confirm nor deny whether the participant identified is enrolled in the study.

Screening Procedures

To determine eligibility, callers undergo a phone screening procedure, in which staff relay background about the study and ask a series of questions to determine eligibility, as per the criteria outlined above. Both individuals in the dyad must separately complete the phone screening process to determine eligibility. We have found in previous studies that when some individuals who are screened out figure out the particular exclusion criteria, they may call again with altered information in order to qualify. To prevent the potential for such misrepresentation, individuals are screened to the end of the phone screen form so that ineligible individuals will not readily be able to discern the criteria that excluded them. If an individual is screened as ineligible, the study will not contact their partner for screening.

Couple Status Verification

With couple-level studies that offer remuneration for participation, there is a risk of potential participants attempting to fake their relationship status or other inclusion criteria to enroll in the study. Therefore, a series of questions have been adapted from McMahon and colleagues to increase confidence that the individuals are indeed in a primary romantic relationship with each other.[32] In this screening, each individual has to corroborate details from each other’s lives such as: (1) Where did your partner live before living in the Bay Area? (2) When is your partner’s birthday? (or at least what month?) (3) How old is your partner? (4) If they report not living together, “What street does your partner live on?” Similar to McMahon’s protocol, we are lenient on the answers given between the dyad, as some relationships may be as recent as three months, and it is not uncommon for couples to live separately. Because these procedures are

not fool-proof, when inconsistencies in responses between the two members of a dyad emerge, interviewers consult with senior project leadership to determine whether answers were sufficient to verify couple status. Rarely, more in depth questions about the dyad are asked.[31]

Study Enrollment

Eligible and interested couples are scheduled for an in-person enrollment visit, requiring that both members of the couple present together in person. They are directed to bring proof of HIV status, which can be an official list of medications from their pharmacy, their HIV medication bottle with their name on it, or a letter of diagnosis from their provider. To minimize the possibility that one partner is pressuring the other to participate, partners are consented in separate rooms. Trained staff read and give a detailed explanation of what to expect in the study, potential risks, compensation, as well as their rights as a research participant. To continue with the enrollment process, both partners must independently agree to the study procedures and sign their respective consent forms. Each participant is given a copy of the consent document and another copy is securely kept with the study file. After the participant provides informed consent, staff collect detailed contact information, and a medical records release authorization form to contact HIV care providers is also obtained in order to secure CD4 and viral load results if needed. A baseline visit is scheduled for two weeks later to allow time for laboratory procedures.

Participants who are living with HIV are directed to have their blood drawn for viral load and CD4 count at their choice of one of 40 community laboratory centers located throughout the area prior to their baseline survey visit. Participants are oriented to the service center locations and hours of operation and are given a requisition for lab assays, labeled with participants' study ID and date of birth to minimize error with specimen mix-ups. Additionally, if a participant loses a paper requisition, study staff can send it electronically to the laboratory via a secure

laboratory database, and date of birth will allow laboratory staff to verify participant identity with this minimal identifier. Lab results are posted to a secure online system for controlled access by study staff.

At the in-person baseline survey visit, participants are separated into separate private rooms to complete their own computer-assisted personal interviewing (CAPI) survey using *Qualtrics* (Provo, UT). The survey contains a series of validated measures focusing on adherence, medication use, partner support, relationship dynamics, behavioral health issues, as well as other important factors in their overall engagement in health care. The survey focuses on the participant's relationship with their partner, communication, intimacy, conflict, social support, and the role of HIV medications in their relationship. Relationship quality and closeness are measured through the survey using the Kurdek Commitment Scale.[33] Partner perceptions of closeness and autonomy were previously found to be significantly associated with adherence and virologic suppression.[34-36] Therefore, the survey includes questions about Inclusion of Other in Self (IOS) using a figure that has a set of circles with varying degree of overlap which best reflects their overall relationship and another set of circles which describes their engagement in each partner's healthcare.[37] The survey questions assess reports of medication adherence,[23 38] the participant's knowledge of their partner's medication adherence,[39] adherence self-efficacy,[40] and reports of recent HIV health care appointment attendance. The baseline survey takes one and a half to two hours to complete.

Randomization

Once participants complete the baseline surveys, they are brought back together and are randomized as a couple (stratified by couple-level HIV serostatus) to one of two study conditions: (1) the DuoPACT couple intervention, which comprises a series of six couple sessions delivered weekly; or (2) LifeSteps, a three-session individual intervention for HIV-positive partners who meet inclusion criterion suggesting suboptimal engagement in HIV care.

Reflecting the stratified nature of the study design, separate randomization lists were created for HIV-discordant and HIV-concordant negative couples. Randomization is done via Research Electronic Data Capture (REDCap). REDCap is a secure platform that is HIPPAA compliant and stores highly sensitive information.[41] The first counseling session is usually scheduled within the subsequent week.

Intervention Conditions

Experimental Intervention

The DuoPACT intervention comprises six weekly couples' sessions. Each session lasts 60 to 90 minutes and focuses on communication in the relationship and support for each other's health and adherence to medical regimens (both ART for treatment and PrEP). The partners learn and practice communication skills, work on aligning support tactics (e.g., reminding to take meds, go to clinic appointment with partner), and set goals related to their own health and medication adherence as well as supporting their partner's health. They also practice problem solving as a couple and amplifying positive moments in the relationship. In between sessions, the couples are asked to track times each of them felt supported by their partner around their health. See Table 2 for the focus of the DuoPACT intervention.

Comparison Intervention.

The LifeSteps arm consists of an adaptation of a previously-validated HIV treatment adherence enhancement intervention.[40] For this study, three one-on-one meetings with a trained counselor are delivered weekly and last 60 to 90 minutes each. The curriculum is an 11-step process designed to improve the participant's adherence to HIV treatment and medication regimens. The counselors help the participants identify and problem solve any existing barriers to maximizing treatment. The participants also learn guided relaxation techniques and cue control strategies. See Table 2 for an outline of the topics covered in the interventions.

Intervention Quality Assurance

The sessions in both study arms are facilitated by trained counselors and are audio-recorded and systematically reviewed for fidelity to the intervention. Counselors complete a structured training program that includes directed readings, mock sessions, and instruction in ethics of human subjects' research.

Follow-Up Data Collection

Participants living with HIV complete three follow-up blood draws, and all participants complete three, six, and nine month surveys. Once each follow-up blood draw has been completed, each participant is electronically sent a personal Qualtrics link to a follow-up survey that they can complete on their own device at any WIFI enabled convenient location. Each participant is asked to complete the assessment separately. If a participant does not have email, or a WIFI enabled device/access, they can come to our study office to complete the follow-up survey on our tablet. Follow-up surveys take approximately one hour to compete and include the core measures from the baseline. The final (nine month) assessment also includes a satisfaction and acceptability measure based on the Patient Satisfaction Questionnaire.[42]

Break-Ups

Participants who report breaking-up with their partner are encouraged to continue participation in the study as originally planned, with the exclusion of any remaining couple intervention sessions, which would be contraindicated following breakup. Survey questions following break-ups are adapted to include measures about the break-up and omit all relationship measures.

Retention

A significant number of participants are from marginalized communities throughout the San Francisco Bay Area. Some are unstably housed, financially impoverished, and may have other

life circumstances that make it difficult to engage throughout the course of the study. During the enrollment process, study staff collect a detailed list of contacts to maintain retention throughout the nine months of study participation, including three personal contacts that do not have to live locally, as well as any social workers and case managers at organizations or clinics throughout the Bay Area.

To maintain contact with participants throughout their involvement in the study, study researchers conduct monthly phone check-ins between the follow up activities (see figure 1). The check-ins are meant to maintain stable contact, to update contact information for each participant, break-ups and collect timely information about their overall engagement in HIV care (e.g., recent medication adherence and medical provider appointments). Check-ins are also useful to learn about participant's whereabouts, including incarceration or hospitalizations.

Incentives

Participants are compensated for their participation in each study procedure using Greenphire Clincards, a reloadable debit card that allows them to immediately receive payments for each study procedure. The incentives, ranging from $20 for surveys to $50 for blood draws, are designed to be enough to compensate for time and travel to study visits but not so high as to coerce enrollment.

Participant and Public Involvement

The current study builds on 10 years of formative work with participants, in which qualitative and quantitative data were used to guide the development of the intervention. This includes a pilot trial with participants, in which feedback on intervention components was solicited. Participants were involved in the pilot intervention, and their input was used to guide refinements in the protocol. They were not involved in the recruitment to and conduct of the study. At study exit, we assess qualitatively and quantitatively how patients perceived all aspects of the intervention and

other study components. We ask participants if they would like to be sent reports and publications resulting from the study.

Confidentiality and Data Security

Participant data are identified only by a coded study number. Information collected on paper is kept in locked filing cabinets accessible only to study staff. Information collected on CASI computers or encrypted tablets is stored on a secure server behind secure firewalls and is accessible only to study staff. Any records linking study numbers to identifiers (such as tracking and contact information) are kept in a password protected database on a secure server and are accessible only to study staff members. All audio recordings are moved onto a secure password protected server and erased off the recorder immediately after the interview. Recordings are labeled with a coded study number.

Quality Assurance

The Project Director and Data Manager/Statistician perform weekly data audits. Overall recruitment goals, missing data and follow-up failures are continuously tracked and audited and are reviewed. The study's biostatistician provides ongoing monitoring of study progress. Audio recordings of baseline assessments are reviewed on a weekly basis, and approximately 20% of the experimental and comparison intervention sessions are reviewed by the supervising clinician for intervention fidelity. In the event an emergency or adverse event arises, staff have been trained and have access to a Manual of Operations, which details the appropriate measures, and the supervising clinician will be consulted and the Principal Investigator, a licensed clinical psychologist, will be immediately notified.

Ethics and dissemination

All procedures are approved by the Institutional Review Board (IRB) at the University of California, San Francisco. Written informed consent is obtained from all participants at enrollment, and study progress is reviewed twice yearly by an external Safety Monitoring Committee (SMC). The trial is registered at ClinicalTrials.gov under registration number NCT02925949.

If effective, this program could be easily implemented in clinics and community settings. A high priority of this work is to make findings available and to export effective components of the intervention into real world settings. In addition to traditional publications and presentations, we plan to create user-friendly "Science to Community" publications. At the study's conclusion, we will host forums in which we invite former participants, other researchers, and clinic and agency staff to hear and discuss findings. Finally, we will make study materials available online and in print format. The CAPS Community Engagement Core is widely recognized for its dissemination activities.

Analysis Plan

Preliminary analyses

Frequency tables for all variables and measures of central tendency and variability for continuous variables will characterize the sample and will be stratified by randomization group (i.e., intervention versus control) to check for imbalances. If the two groups differ significantly at baseline on one or more covariates (e.g., on ART vs. not), we will use methods based on the Rubin causal model (e.g., propensity scores, double-robust estimation) to obtain the desired marginal effect estimates under the counterfactual assumption of balanced groups.[43-47] We will address incomplete data with multiple imputation (MI)[48 49] which makes the relatively mild assumption that incomplete data arise from a conditionally random (MAR) mechanism.[50] Auxiliary variables will be included to help meet the MAR assumption[51 52] and sensitivity

analyses will be conducted with pattern-mixture models and weighted MI [53] to assess the robustness of the MAR assumption.[54] SAS[55] will be used to perform the proposed analyses.

Primary Analyses to address Specific Aim 1

We hypothesize that, following the intervention, the odds of undetectable viral load will be higher for intervention participants than for control participants (Hypothesis 1). Our primary interest is to estimate the marginal or population-average effect of intervention participation on each outcome rather than the effect for a hypothetical average subject or couple.[56] Moreover, within-subject and within-couple correlations among outcomes are considered nuisance parameters, not quantities of interest to be modeled explicitly. Finally, recent recommendations in the literature point to the superior performance of generalized estimating equations (GEE) relative to generalized linear mixed models (GLMMs) for the analysis of dyadic data with categorical outcomes (e.g., virologic control).[57] Accordingly, GEE will be used to perform the proposed primary analysis, which is a planned time-averaged comparison of post-baseline measurements across the intervention and control groups to test primary Hypothesis 1. Alpha will be set at .05 for this planned comparison. Any additional post-hoc comparisons (e.g., paired comparisons of the two study arms at each time point) will maintain nominal α=.05 through the use of simulation-based stepdown multiple comparison methods.[58] The alternating logistic regression (ALR) approach implemented in SAS PROC GENMOD can be used to address the 3-level clustering of observations within participants and participants within dyads. Though GEE estimates are consistent even if the correlation structure is misspecified, GEE's statistical efficiency improves as the working correlation structure more closely approximates the actual correlation structure,[59] so various correlation structures suitable for the study's design will be considered (e.g., exchangeable; nested-1).[60] The QIC statistic will be used to select the final correlation structure.[61] Couple HIV serostatus will be included in all models as required by the

stratified randomized design.[62] Additional covariates such as couple cohabitation status and relationship length will be included if they improve QIC. Robust standard errors will be used to obtain correct inferences even if the chosen correlation structure remains slightly misspecified.

Secondary Analysis to address Specific Aim 2

To explore the effect of the intervention on hypothesized mechanisms of action, secondary analyses will evaluate whether participants assigned to the intervention report higher mean scores on theory-based constructs such as health care empowerment, adherence self-efficacy, adherence, social support, HIV treatment information, and treatment beliefs and expectancies. These analyses will also investigate whether these constructs mediate the relationship between intervention group assignment and virologic control and whether couple HIV-serostatus and cohabitation moderate these associations. Main and interaction effects of couple drug and alcohol use and racial concordance will also be evaluated in these models. Mediation and moderation will be assessed using the causal inference-based approach of Valeri and VanderWeele, which yields optimal estimates of indirect effects in the presence of binary outcomes and moderator-mediator interactions.[63] M*plus* will be used to fit causal mediation models because it can adjust standard errors for nesting of participants within couples.[64] Additional secondary analyses will consider the effects of intervention dose exposure on virologic suppression as a main effect and as moderated and mediated by theory-based constructs described above to determine for whom and via which mechanisms of action intervention dosing is most efficacious.

Secondary Analysis to address Specific Aim 3

Analyses with intact dyads enable investigation of couple-based research questions that explore how relationship dynamics affect behavior change in partnerships. We will extend the analyses

described above to include actor and partner effects for continuous covariates and mediators. *Actor effects* describe the influence that one's standing on independent or mediating variables of interest (e.g., communication, intimacy) has on one's own dependent variables (e.g., self's virologic control) whereas *partner effects* describe the influence that one's standing on independent variables has on the dependent variables of one's partner (e.g., partner's virologic control). This technique illuminates the effects that partners in intimate relationships can have on both their own and their partner's behavior. Actor and partner effects can be evaluated in models with either continuous[65] (e.g., health care empowerment, adherence self-efficacy) or categorical dependent variables (e.g., virologic control).[66] A closely related approach uses sums and differences of continuous covariates and mediators to quantify within-couple and between-couple effects. For continuous dependent variables, within-couple hypotheses will be tested with a GEE model, in which couple-level difference scores on the outcome variable (e.g., adherence self-efficacy) will be regressed onto both the couple-level difference and sum scores for the predictor variable (e.g., communication).[67] Computing sums and differences for categorical outcomes is not feasible, but it is still possible to investigate the effects of sums and differences of individuals' continuous covariates and mediators on individual-level categorical responses (e.g., virologic control) to quantify the separate influences of between-couple and within-couple effects of continuous mediators on individuals' categorical outcomes.[68]

Statistical power analysis

Power analyses were generated using the two-group repeated proportions module in NCSS PASS 13[69] to compute minimum detectable effect sizes for the primary analysis to address Hypothesis 1. The study will begin with 300 participants from 150 couples evenly assigned to the intervention and control groups. Assuming 20% attrition, data from 240 participants from 120 couples will be available for analysis at all time points. Due to the clustered nature of the dyadic data, observations from participants who belong to the same couple will be correlated. In our

previous Duo observational study of couples, for instance, the average within-couple correlation of virologic control measurements was *r*=.23. Accordingly, we lowered the effective sample size (ESS) input for the power analyses to be ESS = N/DEFF, where DEFF is the design effect or variance inflation attributable to using correlated data. DEFF is computed as 1+(*M*-1)**r*, where *M* is the number of participants per dyad (i.e., two). Therefore DEFF=1+(2-1)*.23 = 1.23, so ESS=240/1.23=195. Assuming, α=.05, power=.80, and ESS=195, we computed the minimum detectable odds ratio (*OR*), proportion difference (*pdiff*), and standardized proportion difference (*h*) for the proposed time-averaged comparisons, assuming three post-baseline measurements and assuming a wide range of virologic control base rates P_0 and the within-subject correlation ρ was varied between .20 and .80. Effect size estimates for our primary analyses fall between cutoffs of .20 and .50 for small and medium standardized effect sizes,[70] respectively, suggesting that primary analyses have sufficient power to detect small to small-medium effects across a variety of conditions.

Discussion

HIV care is a lifelong process that can create challenges for PLWH. Dyadic support within couple relationships provides an opportunity for partners in primary romantic relationships to help address the barriers associated with their HIV care engagement. By developing an intervention that focuses on partner support, communication, problem solving as a couple, relationship strengths, and social support, couples can develop important skills to maintain active and successful engagement in their HIV care. Couple-level interventions have the potential to continue to have a sustained impact after the formal intervention ends, as the partner takes on an active and sustained role in supporting target behaviors. Optimal engagement in care will subsequently lead to virologic control, leading to increased survival and

quality of life, decreased morbidity, and reduced likelihood of transmission of HIV to previously uninfected partners.

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Contributors: AT took the lead on drafting the manuscript and is involved in study data recruitment, enrollment, and data collection. LC contributed to drafting and revising the manuscript and serves as Project Director for the project. DO drafted sections of the manuscript and oversees intervention delivery and supervision. TN drafted sections of the manuscript and is the senior statistician for the study. MJ contributed conception of the study, contributed to drafting the protocol, and provides scientific oversight of the project.

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Competing interests: None

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Provence and peer review: This protocol was reviewed by a standing review study section through the Center for Scientific Review at the National Institutes of Health.

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Tabrisky, DuoPACT Protocol Paper

Figure 1:

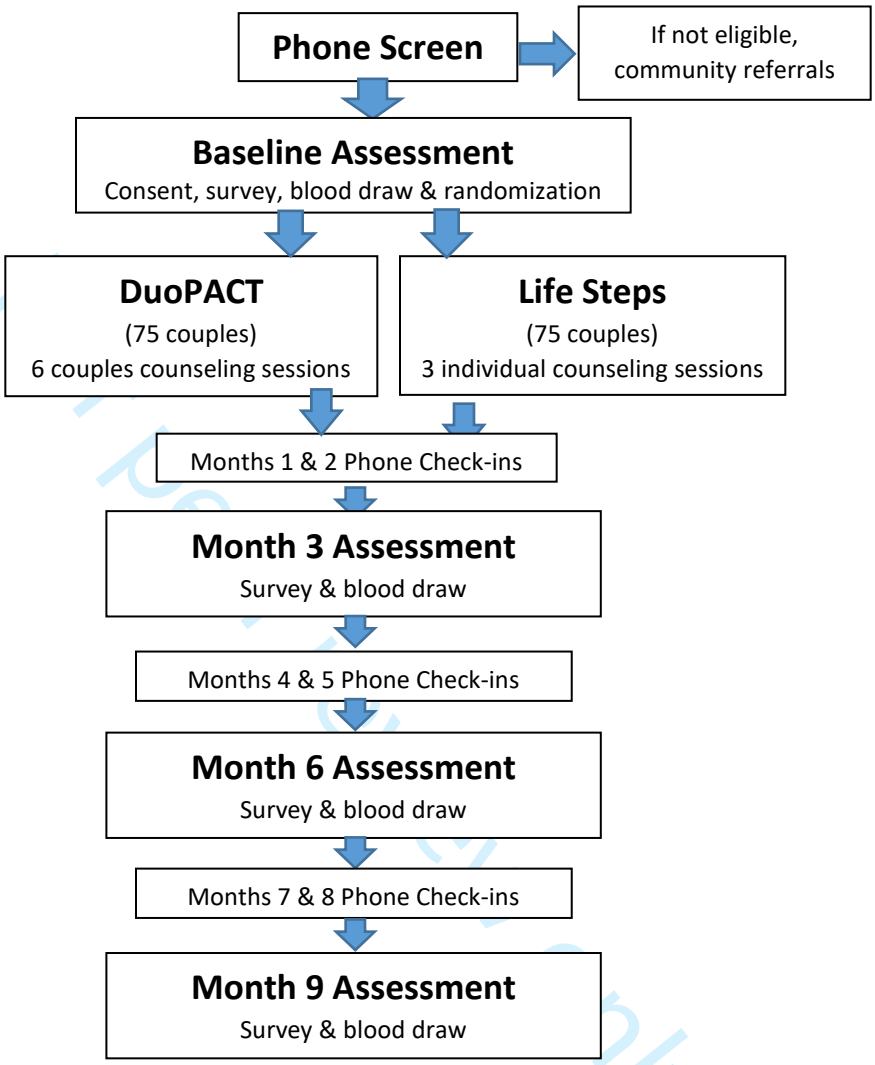

Table 1: Inclusion and exclusion criteria

Inclusion criteria:

- Both participants are 18+ years old;
- Identifies as a sexual or gender minority;
- In a primary romantic relationship for at least 3 months;
- At least one partner is HIV+;
- English-speaking;
- Able to provide informed consent; and
- For HIV+ participants: Evidence of suboptimal engagement in HIV care, as indicated by one or more of the following: (a) Not on ART; (b) Reporting most recent viral load as detectable/unknown; or (c) If on ART, reporting less than excellent adherence on a validated adherence rating scale (report by self or partner); or (d) Reporting no HIV primary care appointments in the prior 8 months.

Exclusion criteria

- Evidence of severe cognitive impairment or active psychosis, as determined by the PI.
- Unable to provide informed consent.
- Relocating out of the Bay Area within 6 months of screening.
- Participation as the same couple in the DuoPACT Pilot.

Table 2: Skills Covered in Counseling Sessions

Couples Sessions	LifeSteps
• Communication • Partner support • Problem solving as a couple • Relationship strengths • Supporting each other's' goals • Social support	• Problem solving • Provider communication • Coping with side affects • Organizational skills (in connection with adherence) • Cueing strategies

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A protocol for a randomized controlled trial of a couples-focused intervention to improve engagement in HIV care

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Abstract:

Introduction. Advances in HIV treatment have proven to be effective in increasing virologic suppression, thereby decreasing morbidity, and increasing survival. High medication adherence, is an important factor in reducing viral load among people living with HIV (PLWH) and in the elimination of transmission of HIV to uninfected partners. However, not all PLWH in the US are engaged in care, and only a minority have achieved virologic control. Sexual and gender minorities (SGM; those who do not identify as heterosexual or those who do not identify as the sex they were assigned at birth) represent a high-risk population for poor clinical outcomes and increased risk of HIV transmission, as they face barriers that can prevent optimal engagement in HIV care. Research in dyadic support, specifically within primary romantic partnerships, offers a promising avenue to improving engagement in care and treatment outcomes among SGM couples. Dyadic interventions, especially focused on primary romantic partnerships, have the potential to have a sustained impact after the structured intervention ends.

Methods and analysis. This paper describes the protocol for a randomized control trial (RCT) of a theory-grounded, piloted intervention (DuoPACT) that cultivates and leverages the inherent sources of support within primary romantic relationships to improve engagement in HIV care and thus clinical outcomes among HIV-infected SGM couples. Eligible participants must report being in a primary romantic relationship for at least three months, speak English, at least one partner must identify as a sexual or gender minority, and at least one partner must be HIV+ with suboptimal engagement in HIV care, defined as less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or unknown viral load, or not currently on antiretroviral therapy (ART). Eligible consenting couples are allocated equally to the two study arms: a structured six-session couples counseling intervention (DuoPACT) or a three-session individually-delivered HIV adherence counseling intervention (Life Steps). The primary aim is to evaluate the efficacy of DuoPACT on virologic control among

HIV+ members of SGM couples with suboptimal engagement in care. The DuoPACT study began its target enrollment of 150 couples (300 individuals) in August 2017, and will continue to enroll until June 2021.

Ethics and dissemination. DuoPACT has been built on years of formative work and offers the opportunity for PLWH to improve their HIV care engagement through support from their primary romantic partner. It has the potential to improve clinical outcomes and to reduce the number of new infections among populations that have a high burden of HIV through treatment optimization.

Strengths and limitations of this study

- The DuoPACT intervention has been piloted and tested and is currently in its final phase testing the efficacy of a couple's-based intervention approach to increasing engagement in HIV care.
- A couples-based approach has the potential to have lasting effects after the conclusion of the formal study intervention, as partners take on more active supportive roles that can have sustained and dynamic impact over time.
- The study is designed to detect changes in laboratory-confirmed HIV viral load, whereas other studies use self-reported viral load data (prone to reporting bias) or health record extraction (prone to missing or suboptimally-timed data).
- The study is located in one geographic area, which may limit generalizability
- Relationships can be volatile leading to break-ups at various points in the study, including after consent visit and prior to study enrollment.

Introduction

Engagement in HIV care, including high levels of adherence to antiretroviral treatment (ART), is essential for managing HIV infection and for ending the HIV epidemic.[1 2] Consistent medication adherence is linked to viral suppression, which allows people living with HIV (PLWH) to live longer and healthier lives, and viral suppression can eliminate the potential for further transmission to uninfected sexual partners.[3] Less than excellent medication adherence, meaning taking less than the daily prescribed amount, reduces the chances of suppressing HIV viral load in PLWH. The HIV Care Cascade (also referred to as the Care Continuum) conceptualizes the level of engagement in care in PLWH throughout the United States and has been used as a framework to address the barriers many people face managing their health and HIV treatment.[4] As of 2016, 49% of PLWH in the US were estimated to be retained in care, and only 53% of those had achieved viral suppression.[5] Barriers associated with successful medication adherence, a key component of the continuum, include medication fatigue, side effects from the medications, and forgetfulness.[6 7] In addition, there are gaps within other parts of the HIV Care Continuum, such as retention in care, that prevent PLWH from achieving viral suppression.[8 9] Recent research has focused on social support between dyads, specifically among romantic partnerships, which shows promise in addressing some of these gaps.[10]

Being in a primary relationship can provide health-promoting benefits through tangible and emotional support, and various kinds of social support are associated with positive outcomes for people living with chronic illnesses.[10-19] Within the context of couples affected by HIV, there is evidence that social support from primary romantic partnerships is associated with better HIV care engagement, such as ART adherence, compared to social support from people other than romantic partners.[20-24]

Although the preponderance of evidence suggests an overall positive impact from partners on many outcomes in healthcare, being in a relationship can also present challenges to HIV care engagement. Partners may have different roles in the dyad, such as a caretaker, that may

prevent a person from taking care of themselves while taking care of their partner, which includes preventing them from taking care of their own HIV infection or other health demands.[25] Negative influences, such as substance use, conflict, abuse, and violence can also prevent optimal engagement in care for one or both partners in the dyad.[26]

Overall, however, the evidence supports the premise that social support within a relationship dyad has more positive than negative impact on HIV and other health-related outcomes. By extension, interventions designed to improve communication, emotional support, and involvement in healthcare within dyads can improve health behaviors such as engagement in care. This is particularly true for some subpopulations in the US, in which the HIV epidemic continues to be concentrated, including sexual and gender minority (SGM) individuals and their sexual partners.[27] As many as half to three-quarters of HIV transmissions among sexual minority persons likely occur within the context of primary romantic relationships.[28] While there are not parallel modelling data for gender minority persons, the worldwide prevalence of HIV among transgender persons is 49 times higher than among other groups.[29] Collectively, these data support a focus on continued innovation and intervention for preventing HIV and optimizing treatment among SGM persons and their partners.

Aim of the study

The primary objective of the DuoPACT study is to test a couple-level HIV intervention designed for sexual and gender minority couples in sero-discordant or sero-concordant HIV-positive relationships that have evidence of poor engagement in care. The purpose of the intervention is to leverage and shape relationship dynamics to improve engagement in HIV care. Such an approach has the potential to be a powerful, cost-effective, and sustainable tool to optimize treatment outcomes among couples affected by HIV. The study will evaluate the efficacy of

DuoPACT on the primary outcome of virologic control among SGM people living with HIV in primary relationships.

Study Specific aims:

Primary Aim:

1. Evaluate the efficacy of DuoPACT on virologic control among PLWH who identify as a sexual or gender minority in primary relationships;

Secondary Aim:

1. Explore the effect of DuoPACT on behavioral indicators of engagement in HIV care, including ART adherence and HIV care appointment attendance and pre-exposure prophylaxis (PrEP) for HIV-uninfected partners; and
2. Explore the potential mediating effect of relationship variables DuoPACT has on patient and partner outcomes.

Methods and analysis

Study Design

The study is a randomized control trial (RCT) with 150 couples (300 individuals) in the San Francisco Bay Area in Northern California (Figure 1). Recruitment began in August 2017 and will continue until June 2021. Participation in the study takes a total of nine months, with surveys conducted at baseline, three, six, and nine months. The primary trial outcome is HIV virologic suppression, as measured by laboratory assay. Secondary outcomes include behavioral indicators of engagement in HIV care, including ART adherence, HIV care appointment

attendance, as well as use of Pre-Exposure Prophylaxis (PrEP) for HIV-uninfected partners, a highly effective daily HIV medication that can prevent HIV infection following sexual exposure.

Study Participants

The study sample consists of primary romantic SMG couples, age 18 or older, who describe each other as "a partner to whom they feel committed above anyone else and with whom they have had a sexual relationship". At least one partner must be HIV+ and report suboptimal engagement in HIV care defined as one or more of the following: less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or unknown viral load, or is not currently (for the past 30 days) on ART. Less than medication adherence is operationalized as reporting anything less than "excellent" on a validated 30-day adherence rating scale.[30] See Table 1 for full inclusion criteria.

Table 1: Inclusion and exclusion criteria

Inclusion criteria:

- Both participants are 18+ years old;
- Identifies as a sexual or gender minority;
- In a primary romantic relationship for at least 3 months;
- At least one partner is HIV+;
- English-speaking;
- Able to provide informed consent; and
- For HIV+ participants: Evidence of suboptimal engagement in HIV care, as indicated by one or more of the following: (a) Not on ART; (b) Reporting most recent viral load as detectable/unknown; or (c) If on ART, reporting less than excellent adherence on a validated adherence rating scale (report by self or partner); or (d) Reporting no HIV primary care appointments in the prior 8 months.

Exclusion criteria:

- Evidence of severe cognitive impairment or active psychosis, as determined by the PI.
- Unable to provide informed consent.
- Relocating out of the Bay Area within 6 months of screening.
- Participation as the same couple in the DuoPACT Pilot.

Recruitment Strategy

Participants are recruited through venue-based and online strategies as well as referral. Flyers are posted in venues (LGBTQ resource centers, bars, coffee shops, etc.), community-based organizations (CBOs), clinics, pharmacies and community bulletin boards. Staff distribute packets with study materials, including an information sheet outlining the basic eligibility criteria, flyers, and postcards, to clinics and CBOs throughout the Greater Bay Area. Providers and CBOs are asked to place these materials in waiting areas where potential participants are likely to see them. Study advertisements are posted online on Craigslist and Facebook and through dating/hook-up apps such as Growlr and Grindr.

In-person study recruitment takes place in HIV clinic waiting rooms. Recruiters present the study at staff/provider meetings in clinics throughout the Bay Area that have a high number of patients living with HIV to facilitate referral to the study. Recruiters also staff tables at symposia, conferences, and community events to continue collaboration with HIV healthcare providers as well as connect with members of the community that may be interested in participating in the study.

All recruitment materials include a toll-free number and a link to the study webpage. Interested potential participants are directed to call the number listed on the recruitment resources or fill out the Contact Us form to learn more about the study and initiate the screening process. Study staff are notified when a potential participant completes the form and contact within one business day to ensure a higher chance of contact.

Enrolled participants have the opportunity to refer couples to the study via a “snowball” recruitment method. To maintain confidentiality of the enrolled participants, potential participants are asked “how did you hear about the study” and must mention the name of the participant that

referred them. To maintain confidentiality, staff cannot confirm nor deny whether the participant identified is enrolled in the study.

Screening Procedures

To determine eligibility, callers undergo a phone screening procedure, in which staff relay background about the study and ask a series of questions to determine eligibility, as per the criteria outlined above. Both individuals in the dyad must separately complete the phone screening process to determine eligibility. We have found in previous studies that when some individuals who are screened out figure out the particular exclusion criteria, they may call again with altered information in order to qualify. To prevent the potential for such misrepresentation, individuals are screened to the end of the phone screen form so that ineligible individuals will not readily be able to discern the criteria that excluded them. If an individual is screened as ineligible, the study will not contact their partner for screening.

Couple Status Verification

With couple-level studies that offer remuneration for participation, there is a risk of potential participants attempting to fake their relationship status or other inclusion criteria to enroll in the study. Therefore, a series of questions have been adapted from McMahon and colleagues to increase confidence that the individuals are indeed in a primary romantic relationship with each other.[31] In this screening, each individual has to corroborate details from each other's lives such as: (1) Where did your partner live before living in the Bay Area? (2) When is your partner's birthday? (or at least what month?) (3) How old is your partner? (4) If they report not living together, "What street does your partner live on?" Similar to McMahon's protocol, we are lenient on the answers given between the dyad, as some relationships may be as recent as three months, and it is not uncommon for couples to live separately. Because these procedures are not fool-proof, when inconsistencies in responses between the two members of a dyad emerge,

interviewers consult with senior project leadership to determine whether answers were sufficient to verify couple status. Rarely, more in depth questions about the dyad are asked.

Study Enrollment

Eligible and interested couples are scheduled for an in-person enrollment visit, requiring that both members of the couple present together in person. They are directed to bring proof of HIV status, which can be an official list of medications from their pharmacy, their HIV medication bottle with their name on it, or a letter of diagnosis from their provider. To minimize the possibility that one partner is pressuring the other to participate, partners are consented in separate rooms. Trained staff read and give a detailed explanation of what to expect in the study, potential risks, compensation, as well as their rights as a research participant. To continue with the enrollment process, both partners must independently agree to the study procedures and sign their respective consent forms. Each participant is given a copy of the consent document and another copy is securely kept with the study file. After the participant provides informed consent, staff collect detailed contact information, and a medical records release authorization form to contact HIV care providers is also obtained in order to secure CD4 and viral load results if needed. A baseline visit is scheduled for two weeks later to allow time for laboratory procedures.

Participants who are living with HIV are directed to have their blood drawn for viral load and CD4 count at their choice of one of 40 community laboratory centers located throughout the area prior to their baseline survey visit. Participants are oriented to the service center locations and hours of operation and are given a requisition for lab assays, labeled with participants' study ID and date of birth to minimize error with specimen mix-ups. Additionally, if a participant loses a paper requisition, study staff can send it electronically to the laboratory via a secure laboratory database, and date of birth will allow laboratory staff to verify participant identity with

this minimal identifier. Lab results are posted to a secure online system for controlled access by study staff.

At the in-person baseline survey visit, participants are separated into separate private rooms to complete their own computer-assisted personal interviewing (CAPI) survey using *Qualtrics* (Provo, UT). The survey contains a series of validated measures focusing on adherence, medication use, partner support, relationship dynamics, behavioral health issues, as well as other important factors in their overall engagement in health care. The survey focuses on the participant's relationship with their partner, communication, intimacy, conflict, social support, and the role of HIV medications in their relationship. Relationship quality and closeness are measured through the survey using the Kurdek Commitment Scale.[32] Partner perceptions of closeness and autonomy were previously found to be significantly associated with adherence and virologic suppression.[33 34] Therefore, the survey includes questions about Inclusion of Other in Self (IOS) using a figure that has a set of circles with varying degree of overlap which best reflects their overall relationship and another set of circles which describes their engagement in each partner's healthcare.[35] The survey questions assess reports of medication adherence,[30 36] the participant's knowledge of their partner's medication adherence,[37] adherence self-efficacy,[38] and reports of recent HIV health care appointment attendance. The baseline survey takes one and a half to two hours to complete.

Randomization

Once participants complete the baseline surveys, they are brought back together and are randomized as a couple (stratified by couple-level HIV serostatus) to one of two study conditions: (1) the DuoPACT couple intervention, which comprises a series of six couple sessions delivered weekly; or (2) LifeSteps, a three-session individual intervention for HIV-positive partners who meet inclusion criterion suggesting suboptimal engagement in HIV care. Couples are randomized to study conditions via a 1:1 allocation ratio. Reflecting the stratified

nature of the study design, separate randomization lists were created for HIV-discordant and HIV-concordant negative couples. Within each stratum, couples are randomized using randomly-permuted block sizes of 2, 4, and 6. Randomization is done via Research Electronic Data Capture (REDCap). REDCap is a secure platform that is HIPPAA compliant and stores highly sensitive information.[39] The first counseling session is usually scheduled within the subsequent week.

Intervention Conditions

Experimental Intervention

The DuoPACT intervention comprises six weekly couples' sessions. Each session lasts 60 to 90 minutes and focuses on communication in the relationship and support for each other's health and adherence to medical regimens (both ART for treatment and PrEP). The partners learn and practice communication skills, work on aligning support tactics (e.g., reminding to take meds, go to clinic appointment with partner), and set goals related to their own health and medication adherence as well as supporting their partner's health. They also practice problem solving as a couple and amplifying positive moments in the relationship. In between sessions, the couples are asked to track times each of them felt supported by their partner around their health. See Table 2 for the focus of the DuoPACT intervention.

Table 2: Skills Covered in Counseling Sessions

Couples Sessions	**LifeSteps**
• Communication • Partner support • Problem solving as a couple • Relationship strengths • Supporting each other's goals • Social support	• Problem solving • Provider communication • Coping with side affects • Organizational skills (in connection with adherence) • Cueing strategies

Comparison Intervention.

The LifeSteps arm consists of an adaptation of a previously-validated HIV treatment adherence enhancement intervention.[40] For this study, three one-on-one meetings with a trained counselor are delivered weekly and last 60 to 90 minutes each. The curriculum is an 11-step process designed to improve the participant's adherence to HIV treatment and medication regimens. The counselors help the participants identify and problem solve any existing barriers to maximizing treatment. The participants also learn guided relaxation techniques and cue control strategies. See Table 2 for an outline of the topics covered in the interventions.

Intervention Quality Assurance

The sessions in both study arms are facilitated by trained counselors and are audio-recorded and systematically reviewed for fidelity to the intervention. Counselors complete a structured training program that includes directed readings, mock sessions, and instruction in ethics of human subjects' research.

Follow-Up Data Collection

Participants living with HIV complete three follow-up blood draws, and all participants complete three, six, and nine month surveys. Once each follow-up blood draw has been completed, each participant is electronically sent a personal Qualtrics link to a follow-up survey that they complete on their own device at any WIFI enabled convenient location. Each participant is asked to complete the assessment separately. If a participant does not have email, or a WIFI enabled device/access, they can come to our study office to complete the follow-up survey on our tablet. Follow-up surveys take approximately one hour to compete and include the core

measures from the baseline. The final (nine month) assessment also includes a satisfaction and acceptability measure based on the Patient Satisfaction Questionnaire.[41]

Break-Ups

Participants who report breaking-up with their partner are encouraged to continue participation in the study as originally planned, with the exclusion of any remaining couple intervention sessions, which would be contraindicated following breakup. Survey questions following break-ups are adapted to include measures about the break-up and omit all relationship measures.

Retention

A significant number of participants are from marginalized communities throughout the San Francisco Bay Area. Some are unstably housed, financially impoverished, and may have other life circumstances that make it difficult to engage throughout the course of the study. During the enrollment process, study staff collect a detailed list of contacts to maintain retention throughout the nine months of study participation, including three personal contacts that do not have to live locally, as well as any social workers and case managers at organizations or clinics throughout the Bay Area.

To maintain contact with participants throughout their involvement in the study, study researchers conduct monthly phone check-ins between the follow up activities (see figure 1). The check-ins are meant to maintain stable contact, to update contact information for each participant, break-ups and collect timely information about their overall engagement in HIV care (e.g., recent medication adherence and medical provider appointments). Check-ins are also useful to learn about participant's whereabouts, including incarceration or hospitalizations.

Incentives

Participants are compensated for their participation in each study procedure using Greenphire Clincards, a reloadable debit card that allows them to immediately receive payments for each study procedure. The incentives, ranging from $20 for surveys to $50 for blood draws, are designed to be enough to compensate for time and travel to study visits but not so high as to coerce enrollment.

Participant and Public Involvement

The current study builds on 10 years of formative work with participants, in which qualitative and quantitative data were used to guide the development of the intervention. This includes a pilot trial with participants, in which feedback on intervention components was solicited. Participants were involved in the pilot intervention, and their input was used to guide refinements in the protocol. They were not involved in the recruitment to and conduct of the study. At study exit, we assess qualitatively and quantitatively how patients perceived all aspects of the intervention and other study components. We ask participants if they would like to be sent reports and publications resulting from the study.

Confidentiality and Data Security

Participant data are identified only by a coded study number. Information collected on paper is kept in locked filing cabinets accessible only to study staff. Information collected on CASI computers or encrypted tablets is stored on a secure server behind secure firewalls and is accessible only to study staff. Any records linking study numbers to identifiers (such as tracking and contact information) are kept in a password protected database on a secure server and are accessible only to study staff members. All audio recordings are moved onto a secure password protected server and erased off the recorder immediately after the interview. Recordings are labeled with a coded study number.

Quality Assurance

The Project Director and Data Manager/Statistician perform weekly data audits. Overall recruitment goals, missing data and follow-up failures are continuously tracked and audited and are reviewed. The study's biostatistician provides ongoing monitoring of study progress. Audio recordings of baseline assessments are reviewed on a weekly basis, and approximately 20% of the experimental and comparison intervention sessions are reviewed by the supervising clinician for intervention fidelity. In the event an emergency or adverse event arises, staff have been trained and have access to a Manual of Operations, which details the appropriate measures, and the supervising clinician will be consulted and the Principal Investigator, a licensed clinical psychologist, will be immediately notified.

Ethics and dissemination

All procedures are approved by the Institutional Review Board (IRB) at the University of California, San Francisco. Written informed consent is obtained from all participants at enrollment, and study progress is reviewed twice yearly by an external Safety Monitoring Committee (SMC). The trial is registered at ClinicalTrials.gov under registration number NCT02925949.

If effective, this program could be easily implemented in clinics and community settings. A high priority of this work is to make findings available and to export effective components of the intervention into real world settings. In addition to traditional publications and presentations, we plan to create user-friendly "Science to Community" publications. At the study's conclusion, we will host forums in which we invite former participants, other researchers, and clinic and agency staff to hear and discuss findings. Finally, we will make study materials available online and in print format. The CAPS Community Engagement Core is widely recognized for its dissemination activities.

Analysis Plan

Preliminary analyses

Frequency tables for all variables and measures of central tendency and variability for continuous variables will characterize the sample and will be stratified by randomization group (i.e., intervention versus control) to check for imbalances. If the two groups differ significantly at baseline on one or more covariates (e.g., on ART vs. not), we will use methods based on the Rubin causal model (e.g., propensity scores, double-robust estimation) to obtain the desired marginal effect estimates under the counterfactual assumption of balanced groups.[42-46] We will address incomplete data with multiple imputation (MI)[47 48] which makes the relatively mild assumption that incomplete data arise from a conditionally random (MAR) mechanism.[49] Auxiliary variables will be included to help meet the MAR assumption[50 51] and sensitivity analyses will be conducted with pattern-mixture models and weighted MI [52] to assess the robustness of the MAR assumption.[53] As part of the sensitivity analyses, we will also perform analyses using complete-caes analysis (CCA); if results from sensitivity analyses (including CCA) yield different substantive conclusions from the original MI-based analyses, both sets of results will be reported. SAS[54] will be used to perform the proposed analyses.

Primary Analyses to address Specific Aim 1

We hypothesize that, following the intervention, the odds of undetectable viral load will be higher for intervention participants than for control participants (Hypothesis 1). Our primary interest is to estimate the marginal or population-average effect of intervention participation on each outcome rather than the effect for a hypothetical average subject or couple.[55] Moreover, within-subject and within-couple correlations among outcomes are considered nuisance parameters, not quantities of interest to be modeled explicitly. Finally, recent recommendations

in the literature point to the superior performance of generalized estimating equations (GEE) relative to generalized linear mixed models (GLMMs) for the analysis of dyadic data with categorical outcomes (e.g., virologic control).[56] Accordingly, GEE will be used to perform the proposed primary analysis, which is a planned time-averaged comparison of post-baseline measurements across the intervention and control groups to test primary Hypothesis 1. Alpha will be set at .05 for this planned comparison. Any additional post-hoc comparisons (e.g., paired comparisons of the two study arms at each time point) will maintain nominal α=.05 through the use of simulation-based stepdown multiple comparison methods.[57] The alternating logistic regression (ALR) approach implemented in SAS PROC GENMOD can be used to address the 3-level clustering of observations within participants and participants within dyads. Though GEE estimates are consistent even if the correlation structure is misspecified, GEE's statistical efficiency improves as the working correlation structure more closely approximates the actual correlation structure,[58] so various correlation structures suitable for the study's design will be considered (e.g., exchangeable; nested-1).[59] The QIC statistic will be used to select the final correlation structure.[60] Couple HIV serostatus will be included in all models as required by the stratified randomized design.[61] Additional covariates such as couple cohabitation status and relationship length will be included if they improve QIC. Robust standard errors will be used to obtain correct inferences even if the chosen correlation structure remains slightly misspecified. The primary analysis will be performed under the intention-to-treat (ITT) principle.

Secondary Analysis to address Specific Aim 2

To explore the effect of the intervention on hypothesized mechanisms of action, secondary analyses will evaluate whether participants assigned to the intervention report higher mean scores on theory-based constructs such as health care empowerment, adherence self-efficacy, adherence, social support, HIV treatment information, and treatment beliefs and expectancies.

These analyses will also investigate whether these constructs mediate the relationship between intervention group assignment and virologic control and whether couple HIV-serostatus and cohabitation moderate these associations. Main and interaction effects of couple drug and alcohol use and racial concordance will also be evaluated in these models. Mediation and moderation will be assessed using the causal inference-based approach of Valeri and VanderWeele, which yields optimal estimates of indirect effects in the presence of binary outcomes and moderator-mediator interactions.[62] M*plus* will be used to fit causal mediation models because it can adjust standard errors for nesting of participants within couples.[63] Additional secondary analyses will consider the effects of intervention dose exposure on virologic suppression as a main effect and as moderated and mediated by theory-based constructs described above to determine for whom and via which mechanisms of action intervention dosing is most efficacious. These secondary exploratory data analyses will be defined in a data analysis plan prior to conducting final analyses.

Secondary Analysis to address Specific Aim 3

Analyses with intact dyads enable investigation of couple-based research questions that explore how relationship dynamics affect behavior change in partnerships. We will extend the analyses described above to include actor and partner effects for continuous covariates and mediators. *Actor effects* describe the influence that one's standing on independent or mediating variables of interest (e.g., communication, intimacy) has on one's own dependent variables (e.g., self's virologic control) whereas *partner effects* describe the influence that one's standing on independent variables has on the dependent variables of one's partner (e.g., partner's virologic control). This technique illuminates the effects that partners in intimate relationships can have on both their own and their partner's behavior. Actor and partner effects can be evaluated in models with either continuous[64] (e.g., health care empowerment, adherence self-efficacy) or

categorical dependent variables (e.g., virologic control).[65] A closely related approach uses sums and differences of continuous covariates and mediators to quantify within-couple and between-couple effects. For continuous dependent variables, within-couple hypotheses will be tested with a GEE model, in which couple-level difference scores on the outcome variable (e.g., adherence self-efficacy) will be regressed onto both the couple-level difference and sum scores for the predictor variable (e.g., communication).[66] Computing sums and differences for categorical outcomes is not feasible, but it is still possible to investigate the effects of sums and differences of individuals' continuous covariates and mediators on individual-level categorical responses (e.g., virologic control) to quantify the separate influences of between-couple and within-couple effects of continuous mediators on individuals' categorical outcomes.[67] These secondary exploratory data analyses will be defined in a data analysis plan prior to conducting final analyses.

Interim analyses

No interim analyses are planned.

Statistical power analysis

Power analyses were generated using the two-group repeated proportions module in NCSS PASS [68] to compute minimum detectable effect sizes for the primary analysis to address Hypothesis 1. The study will begin with 300 participants from 150 couples evenly assigned to the intervention and control groups. We further assume half of the couples will be HIV sero-discordant (N=150) and half will be sero-concordant (N=150). Under these assumptions, three quarters (N=180) of the 240 participants will be living with HIV and therefore have virologic suppression outcome data. Due to the clustered nature of the dyadic data, observations from participants who belong to the same couple who are living with HIV will be correlated. In our previous Duo observational study of couples, for instance, the average within-couple correlation

of virologic control measurements was *r*=.23. Accordingly, we lowered the effective sample size (ESS) input for the power analyses to be ESS=N/DEFF for these couples, where DEFF is the design effect or variance inflation attributable to using correlated data. DEFF is computed as 1+(*M*-1)*r*, where *M* is the number of participants per dyad (i.e., two). Therefore DEFF=1+(2-1)*.23 = 1.23, so ESS for HIV-concordant couples is 150 HIV participants in HIV-concordant couples/1.23=122. For HIV-discordant couples, 75 participants will be living with HIV and since their outcome values should be statistically independent, no design effect adjustment is required for this subset of couples. Thus, the total ESS for the proposed primary analysis incorporating members from both sero-concordant and sero-discordant couples is 122 + 75=197. Further assuming 20% attrition, the post-attrition ESS will be 197*(1-.20)=158 for analysis at all time points. Assuming, α=.05, power=.80, and ESS=158, we computed the minimum detectable odds ratio (*OR*), proportion difference (*pdiff*), and standardized proportion difference (*h*) for the proposed time-averaged comparisons, assuming three post-baseline measurements and assuming a wide range within-subject correlation values, ρ, which were varied between .20 and .80. Since the virologic control base rates P_0 are also unknown, we considered several scenarios: low (P_0 = 30%), medium (P_0 = 50%), and high (P_0 = 80%). Under these assumptions, the minimum detectable effect size estimates for our primary analyses range from 10.4% to 20.1% for raw proportion differences (*Pdiff*); standardized effect size estimates (*h*) range from .30 to .41, which are between published benchmarks of .20 and .50 for small and medium standardized effect sizes,[69] respectively. These results suggest that our primary analysis will have sufficient power to detect effects that are between small and medium across a wide range of potential analytic scenarios (see Table 3).

Table 3: Minimum Detectable Effect Sizes

Within-Subject Correlation	Control Group Proportion								
	P_0 = .30 (Low)			P_0 = .50 (Medium)			P_0 = .80 (High)		
ρ	*OR*	*Pdiff*	*h*	*OR*	*Pdiff*	*h*	*OR*	*Pdiff*	*h*
.20	1.88	14.6%	.303	1.86	15.0%	.305	2.37	10.4%	.297
.30	1.96	15.7%	.325	1.94	16.0%	.326	2.53	11.0%	.318
.40	2.04	16.7%	.345	2.02	16.9%	.345	2.70	11.5%	.336
.50	2.12	17.6%	.363	2.10	17.8%	.364	2.87	12.0%	.354
.60	2.20	18.5%	.382	2.18	18.6%	.381	3.04	12.4%	.369
.70	2.27	19.3%	.398	2.27	19.4%	.398	3.22	12.8%	.384
.80	2.35	20.1%	.414	2.35	20.1%	.414	3.40	13.2%	.400

Discussion

HIV care is a lifelong process that can create challenges for PLWH. Dyadic support within couple relationships provides an opportunity for partners in primary romantic relationships to help address the barriers associated with their HIV care engagement. By developing an intervention that focuses on partner support, communication, problem solving as a couple, relationship strengths, and social support, couples can develop important skills to maintain active and successful engagement in their HIV care. Couple-level interventions have the potential to continue to have a sustained impact after the formal intervention ends, as the partner takes on an active and sustained role in supporting target behaviors. Optimal engagement in care will subsequently lead to virologic control, leading to increased survival and quality of life, decreased morbidity, and reduced likelihood of transmission of HIV to previously uninfected partners.

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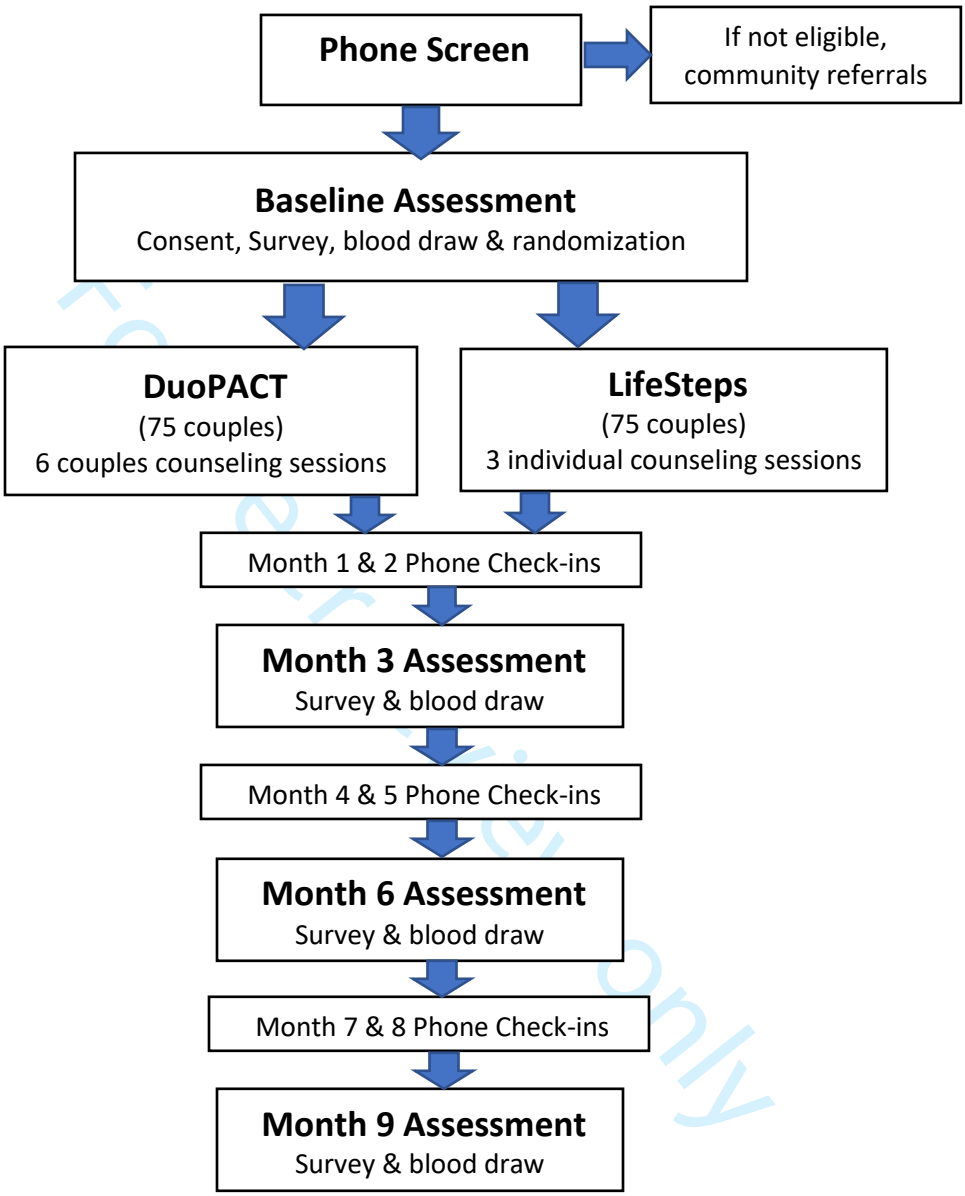
Tabrisky, DuoPACT Protocol Paper

Figure 1:


Phone Screen
If not eligible, community referrals
Baseline Assessment
Consent, Survey, blood draw & randomization
DuoPACT
(75 couples)
6 couples counseling sessions
LifeSteps
(75 couples)
3 individual counseling sessions
Month 1 & 2 Phone Check-ins
Month 3 Assessment
Survey & blood draw
Month 4 & 5 Phone Check-ins
Month 6 Assessment
Survey & blood draw
Month 7 & 8 Phone Check-ins
Month 9 Assessment
Survey & blood draw

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A protocol for a randomized controlled trial of a couples-focused intervention to improve engagement in HIV care

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Abstract:

Introduction. Advances in HIV treatment have proven to be effective in increasing virologic suppression, thereby decreasing morbidity, and increasing survival. Medication adherence is an important factor in reducing viral load among people living with HIV (PLWH) and in the elimination of transmission of HIV to uninfected partners. Achieving optimal medication adherence involves individuals taking their medications every day or as prescribed by their provider. However, not all PLWH in the US are engaged in care, and only a minority have achieved suppressed viral load (viral load that is lower than the detectable limit of the assay). Sexual and gender minorities (SGM; those who do not identify as heterosexual or those who do not identify as the sex they were assigned at birth) represent a high-risk population for poor clinical outcomes and increased risk of HIV transmission, as they face barriers that can prevent optimal engagement in HIV care. Research in dyadic support, specifically within primary romantic partnerships, offers a promising avenue to improving engagement in care and treatment outcomes among SGM couples. Dyadic interventions, especially focused on primary romantic partnerships, have the potential to have a sustained impact after the structured intervention ends.

Methods and analysis. This paper describes the protocol for a randomized control trial (RCT) of a theory-grounded, piloted intervention (DuoPACT) that cultivates and leverages the inherent sources of support within primary romantic relationships to improve engagement in HIV care and thus clinical outcomes among persons who are living with HIV and who identify as SGM (or their partners). Eligible participants must report being in a primary romantic relationship for at least three months, speak English, at least one partner must identify as a sexual or gender minority, and at least one partner must be HIV+ with suboptimal engagement in HIV care, defined as less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or unknown viral load, or not currently on antiretroviral

therapy (ART). Eligible consenting couples are allocated equally to the two study arms: a structured six-session couples counseling intervention (DuoPACT) or a three-session individually-delivered HIV adherence counseling intervention (Life Steps). The primary aim is to evaluate the efficacy of DuoPACT on virologic suppression among HIV+ members of SGM couples with suboptimal engagement in care. The DuoPACT study began its target enrollment of 150 couples (300 individuals) in August 2017, and will continue to enroll until June 2021.

Ethics and dissemination. DuoPACT has been built on years of formative work and offers the opportunity for PLWH to improve their HIV care engagement through support from their primary romantic partner. It has the potential to improve clinical outcomes and to reduce the number of new infections among populations that have a high burden of HIV through treatment optimization.

Strengths and limitations of this study

- The DuoPACT intervention has been piloted and tested and is currently in its final phase testing the efficacy of a couple's-based intervention approach to increasing engagement in HIV care.
- A couples-based approach has the potential to have lasting effects after the conclusion of the formal study intervention, as partners take on more active supportive roles that can have sustained and dynamic impact over time.
- The study is designed to detect changes in laboratory-confirmed HIV viral load, whereas other studies use self-reported viral load data (prone to reporting bias) or health record extraction (prone to missing or suboptimally-timed data).
- The study is located in one geographic area, which may limit generalizability

- Relationships can be volatile leading to break-ups at various points in the study, including after consent visit and prior to study enrollment.

Introduction

Engagement in HIV care, including high levels of adherence to antiretroviral treatment (ART), is essential for managing HIV infection and for ending the HIV epidemic.[1 2] Consistent medication adherence is linked to viral suppression, which allows people living with HIV (PLWH) to live longer and healthier lives, and viral suppression can eliminate the potential for further transmission to uninfected sexual partners.[3] Suboptimal medication adherence reduces the chances of suppressing HIV viral load in PLWH. The HIV Care Cascade (also referred to as the Care Continuum) conceptualizes the level of engagement in care in PLWH throughout the United States and has been used as a framework to address the barriers many people face managing their health and HIV treatment.[4] As of 2016, 49% of PLWH in the US were estimated to be retained in care, and only 53% of those had achieved viral suppression.[5] Barriers associated with successful medication adherence, a key component of the continuum, include medication fatigue, side effects from the medications, and forgetfulness.[6 7] In addition, there are gaps within other parts of the HIV Care Continuum, such as retention in care, that prevent PLWH from achieving viral suppression.[8 9] Recent research has focused on social support between dyads, specifically among romantic partnerships, which shows promise in addressing some of these gaps.[10]

Being in a primary relationship can provide health-promoting benefits through tangible and emotional support, and various kinds of social support are associated with positive outcomes for people living with chronic illnesses.[10-19] Within the context of couples affected by HIV, there is evidence that social support from primary romantic partnerships is associated with better HIV

care engagement, such as ART adherence, compared to social support from people other than romantic partners.[20-24]

Although the preponderance of evidence suggests an overall positive impact from partners on many outcomes in healthcare, being in a relationship can also present challenges to HIV care engagement. Partners may have different roles in the dyad, such as a caretaker, that may prevent a person from taking care of themselves while taking care of their partner, which includes preventing them from taking care of their own HIV infection or other health demands.[25] Negative influences, such as substance use, conflict, abuse, and violence can also prevent optimal engagement in care for one or both partners in the dyad.[26]

Overall, however, the evidence supports the premise that social support within a relationship dyad has more positive than negative impact on HIV and other health-related outcomes. By extension, interventions designed to improve communication, emotional support, and involvement in healthcare within dyads can improve health behaviors such as engagement in care. This is particularly true for some subpopulations in the US, in which the HIV epidemic continues to be concentrated, including sexual and gender minority (SGM) individuals and their sexual partners.[27] As many as half to three-quarters of HIV transmissions among sexual minority persons likely occur within the context of primary romantic relationships.[28] While there are not parallel modelling data for gender minority persons, the worldwide prevalence of HIV among transgender persons is 49 times higher than among other groups.[29] Collectively, these data support a focus on continued innovation and intervention for preventing HIV and optimizing treatment among SGM persons and their partners.

Aim of the study

The primary objective of the DuoPACT study is to test a couple-level HIV intervention designed for sexual and gender minority couples in sero-discordant or sero-concordant HIV-positive

relationships that have evidence of poor engagement in care. The purpose of the intervention is to leverage and shape relationship dynamics to improve engagement in HIV care. Such an approach has the potential to be a powerful, cost-effective, and sustainable tool to optimize treatment outcomes among couples affected by HIV. Due to lower viral loads being a quantitative element associated with better engagement in care, the study team uses HIV-1 RNA quantitative real-time PCR to analyze the trend of viral loads among participants living with HIV. The study will evaluate the efficacy of DuoPACT on the primary outcome of virologic suppression among SGM people living with HIV in primary relationships.

Study Specific aims:

Primary Aim:

1. Evaluate the efficacy of DuoPACT on virologic suppression among people living with HIV in primary relationships in which at least one partner identifies as sexual or gender minority.

Secondary Aim:

1. Explore the effect of DuoPACT on behavioral indicators of engagement in HIV care, including ART adherence and HIV care appointment attendance and pre-exposure prophylaxis (PrEP) for HIV-uninfected partners; and
2. Explore the potential mediating effect of relationship variables DuoPACT has on patient and partner outcomes.

Methods and analysis

Study Design

The study is a randomized control trial (RCT) with 150 couples (300 individuals) in the San Francisco Bay Area in Northern California (Figure 1). Recruitment began in August 2017 and will continue until June 2021, with final data collection complete in March 2022. Participation in the study takes a total of nine months, with surveys conducted at baseline, three, six, and nine months. The primary trial outcome is HIV virologic suppression, as measured by laboratory assay. Secondary outcomes include behavioral indicators of engagement in HIV care, including ART adherence, HIV care appointment attendance, as well as use of Pre-Exposure Prophylaxis (PrEP) for HIV-uninfected partners, a highly effective daily HIV medication that can prevent HIV infection following sexual exposure.

Study Participants

The study sample consists of primary romantic couples, in which at least one partner identifies as SGM, both are age 18 or older, and who describe each other as “a partner to whom they feel committed above anyone else and with whom they have had a sexual relationship”. At least one partner must be HIV+ and report suboptimal engagement in HIV care defined as one or more of the following: less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or unknown viral load, or is not currently (for the past 30 days) on ART. Less than excellent medication adherence is operationalized as reporting anything other than excellent on a validated single item adherence rating scale that asks “Thinking back over the past 30 days, how would you rate your ability to take your HIV medications as prescribed?” Response choices include excellent, very good, good, poor, and very poor, with responses validated with viral load and electronic adherence measurements.[30 31] See Table 1 for full inclusion criteria.

Table 1: Inclusion and exclusion criteria

Inclusion criteria:

- Both participants are 18+ years old;
- Identifies as a sexual or gender minority;
- In a primary romantic relationship for at least 3 months;
- At least one partner is HIV+;
- English-speaking;
- Able to provide informed consent; and
- For HIV+ participants: Evidence of suboptimal engagement in HIV care, as indicated by one or more of the following: (a) Not on ART; (b) Reporting most recent viral load as detectable/unknown; or (c) If on ART, reporting less than excellent adherence on a validated adherence rating scale (report by self or partner); or (d) Reporting no HIV primary care appointments in the prior 8 months.

Exclusion criteria:

- Evidence of severe cognitive impairment or active psychosis, as determined by the PI.
- Unable to provide informed consent.
- Relocating out of the Bay Area within 6 months of screening.
- Participation as the same couple in the DuoPACT Pilot.

Recruitment Strategy

Participants are recruited through venue-based and online strategies as well as referral. Flyers are posted in venues (LGBTQ resource centers, bars, coffee shops, etc.), community-based organizations (CBOs), clinics, pharmacies and community bulletin boards. Staff distribute packets with study materials, including an information sheet outlining the basic eligibility criteria, flyers, and postcards, to clinics and CBOs throughout the Greater Bay Area. Providers and CBOs are asked to place these materials in waiting areas where potential participants are likely to see them. Study advertisements are posted online on Craigslist and Facebook and through dating/hook-up apps such as Growlr and Grindr.

In-person study recruitment takes place in HIV clinic waiting rooms. Recruiters present the study at staff/provider meetings in clinics throughout the Bay Area that have a high number of patients

living with HIV to facilitate referral to the study. Recruiters also staff tables at symposia, conferences, and community events to continue collaboration with HIV healthcare providers as well as connect with members of the community that may be interested in participating in the study.

All recruitment materials include a toll-free number and a link to the study webpage. Interested potential participants are directed to call the number listed on the recruitment resources or fill out the Contact Us form to learn more about the study and initiate the screening process. Study staff are notified when a potential participant completes the form and contact within one business day to ensure a higher chance of contact.

Enrolled participants have the opportunity to refer couples to the study via a "snowball" recruitment method. To maintain confidentiality of the enrolled participants, potential participants are asked "how did you hear about the study" and must mention the name of the participant that referred them. To maintain confidentiality, staff cannot confirm nor deny whether the participant identified is enrolled in the study.

Screening Procedures

To determine eligibility, callers undergo a phone screening procedure, in which staff relay background about the study and ask a series of questions to determine eligibility, as per the criteria outlined above. Both individuals in the dyad must separately complete the phone screening process to determine eligibility. We have found in previous studies that when some individuals who are screened out figure out the particular exclusion criteria, they may call again with altered information in order to qualify. To prevent the potential for such misrepresentation, individuals are screened to the end of the phone screen form so that ineligible individuals will not readily be able to discern the criteria that excluded them. If an individual is screened as ineligible, the study will not contact their partner for screening.

Couple Status Verification

With couple-level studies that offer remuneration for participation, there is a risk of potential participants attempting to fake their relationship status or other inclusion criteria to enroll in the study. Therefore, a series of questions have been adapted from McMahon and colleagues to increase confidence that the individuals are indeed in a primary romantic relationship with each other.[32] In this screening, each individual has to corroborate details from each other's lives such as: (1) Where did your partner live before living in the Bay Area? (2) When is your partner's birthday? (or at least what month?) (3) How old is your partner? (4) If they report not living together, "What street does your partner live on?" Similar to McMahon's protocol, we are lenient on the answers given between the dyad, as some relationships may be as recent as three months, and it is not uncommon for couples to live separately. Because these procedures are not fool-proof, when inconsistencies in responses between the two members of a dyad emerge, interviewers consult with senior project leadership to determine whether answers were sufficient to verify couple status. Rarely, more in depth questions about the dyad are asked.

Study Enrollment

Eligible and interested couples are scheduled for an in-person enrollment visit, requiring that both members of the couple present together in person. They are directed to bring proof of HIV status, which can be an official list of medications from their pharmacy, their HIV medication bottle with their name on it, or a letter of diagnosis from their provider. To minimize the possibility that one partner is pressuring the other to participate, partners are consented in separate rooms. Trained staff read and give a detailed explanation of what to expect in the study, potential risks, compensation, as well as their rights as a research participant. To continue with the enrollment process, both partners must independently agree to the study procedures and sign their respective consent forms. Each participant is given a copy of the

consent document and another copy is securely kept with the study file. After the participant provides informed consent, staff collect detailed contact information, and a medical records release authorization form to contact HIV care providers is also obtained in order to secure CD4 and viral load results if needed. A baseline visit is scheduled for two weeks later to allow time for laboratory procedures.

Participants who are living with HIV are directed to have their blood drawn for viral load and CD4 count at their choice of one of 40 community laboratory centers located throughout the area prior to their baseline survey visit. Participants are oriented to the service center locations and hours of operation and are given a requisition for lab assays, labeled with participants' study ID and date of birth to minimize error with specimen mix-ups. Additionally, if a participant loses a paper requisition, study staff can send it electronically to the laboratory via a secure laboratory database, and date of birth will allow laboratory staff to verify participant identity with this minimal identifier. Lab results are posted to a secure online system for controlled access by study staff.

At the in-person baseline survey visit, participants are separated into separate private rooms to complete their own computer-assisted personal interviewing (CAPI) survey using *Qualtrics* (Provo, UT). The survey contains a series of validated measures focusing on adherence, medication use, partner support, relationship dynamics, behavioral health issues, as well as other important factors in their overall engagement in health care. The survey focuses on the participant's relationship with their partner, communication, intimacy, conflict, social support, and the role of HIV medications in their relationship. Relationship quality and closeness are measured through the survey using the Kurdek Commitment Scale.[33] Partner perceptions of closeness and autonomy were previously found to be significantly associated with adherence and virologic suppression.[34 35] Therefore, the survey includes questions about Inclusion of Other in Self (IOS) using a figure that has a set of circles with varying degree of overlap which

best reflects their overall relationship and another set of circles which describes their engagement in each partner's healthcare.[36] The survey questions assess reports of medication adherence,[30 37] the participant's knowledge of their partner's medication adherence,[38] adherence self-efficacy,[39] and reports of recent HIV health care appointment attendance. The baseline survey takes one and a half to two hours to complete.

Randomization

Once participants complete the baseline surveys, they are brought back together and are randomized as a couple (stratified by couple-level HIV serostatus) to one of two study conditions: (1) the DuoPACT couple intervention, which comprises a series of six couple sessions delivered weekly; or (2) LifeSteps, a three-session individual intervention for HIV-positive partners who meet inclusion criterion suggesting suboptimal engagement in HIV care. Couples are randomized to study conditions via a 1:1 allocation ratio. Reflecting the stratified nature of the study design, separate randomization lists were created for HIV-discordant and HIV-concordant negative couples. Within each stratum, couples are randomized using randomly-permuted block sizes of 2, 4, and 6. Randomization is done via Research Electronic Data Capture (REDCap). REDCap is a secure platform that is HIPPAA compliant and stores highly sensitive information.[40] The first counseling session is usually scheduled within the subsequent week.

Intervention Conditions

Experimental Intervention

The DuoPACT intervention comprises six weekly couples' sessions. Each session lasts 60 to 90 minutes and focuses on communication in the relationship and support for each other's health and adherence to medical regimens (both ART for treatment and PrEP). The partners learn and practice communication skills, work on aligning support tactics (e.g., reminding to take meds, go

to clinic appointment with partner), and set goals related to their own health and medication adherence as well as supporting their partner's health. They also practice problem solving as a couple and amplifying positive moments in the relationship. In between sessions, the couples are asked to track times each of them felt supported by their partner around their health. See Table 2 for the focus of the DuoPACT intervention.

Table 2: Skills Covered in Counseling Sessions

Couples Sessions	LifeSteps
• Communication • Partner support • Problem solving as a couple • Relationship strengths • Supporting each other's goals • Social support	• Problem solving • Provider communication • Coping with side affects • Organizational skills (in connection with adherence) • Cueing strategies

Comparison Intervention.

The LifeSteps arm consists of an adaptation of a previously-validated HIV treatment adherence enhancement intervention.[41] For this study, three one-on-one meetings with a trained counselor are delivered weekly and last 60 to 90 minutes each. The curriculum is an 11-step process designed to improve the participant's adherence to HIV treatment and medication regimens. The counselors help the participants identify and problem solve any existing barriers to maximizing treatment. The participants also learn guided relaxation techniques and cue control strategies. See Table 2 for an outline of the topics covered in the interventions.

Intervention Quality Assurance

The sessions in both study arms are facilitated by trained counselors and are audio-recorded and systematically reviewed for fidelity to the intervention. Counselors complete a structured

training program that includes directed readings, mock sessions, and instruction in ethics of human subjects' research.

The intervention staff make careful considerations during either arm of the intervention to determine if they feel the intervention is harming the participant. The participant is also given their participant rights during the consent process detailing if they feel the intervention is harming them in any way, they can discontinue the intervention.

Follow-Up Data Collection

Participants living with HIV complete three follow-up blood draws, and all participants complete three, six, and nine month surveys regardless of study arm. Once each follow-up blood draw has been completed, each participant is electronically sent a personal Qualtrics link to a follow-up survey that they complete on their own device at any WIFI enabled convenient location. Each participant is asked to complete the assessment separately. If a participant does not have email, or a WIFI enabled device/access, they can come to our study office to complete the follow-up survey on our tablet. Follow-up surveys take approximately one hour to compete and include the core measures from the baseline. The final (nine month) assessment also includes a satisfaction and acceptability measure based on the Patient Satisfaction Questionnaire.[42]

Break-Ups

Participants who report breaking-up with their partner are encouraged to continue participation in the study as originally planned, with the exclusion of any remaining couple intervention sessions, which would be contraindicated following breakup. Survey questions following break-ups are adapted to include measures about the break-up and omit all relationship measures.

Retention

A significant number of participants are from marginalized communities throughout the San Francisco Bay Area. Some are unstably housed, financially impoverished, and may have other life circumstances that make it difficult to engage throughout the course of the study. During the enrollment process, study staff collect a detailed list of contacts to maintain retention throughout the nine months of study participation, including three personal contacts that do not have to live locally, as well as any social workers and case managers at organizations or clinics throughout the Bay Area.

To maintain contact with participants throughout their involvement in the study, study researchers conduct monthly phone check-ins between the follow up activities (see figure 1). The check-ins are meant to maintain stable contact, to update contact information for each participant, break-ups and collect timely information about their overall engagement in HIV care (e.g., recent medication adherence and medical provider appointments). Check-ins are also useful to learn about participant's whereabouts, including incarceration or hospitalizations.

Incentives

Participants are compensated for their participation in each study procedure using Greenphire Clincards, a reloadable debit card that allows them to immediately receive payments for each study procedure. The incentives, ranging from $20 for surveys to $50 for blood draws, are designed to be enough to compensate for time and travel to study visits but not so high as to coerce enrollment.

Participant and Public Involvement

The current study builds on 10 years of formative work with participants, in which qualitative and quantitative data were used to guide the development of the intervention. This includes a pilot trial with participants, in which feedback on intervention components was solicited. Participants were involved in the pilot intervention, and their input was used to guide refinements in the

protocol. They were not involved in the recruitment to and conduct of the study. At study exit, we assess qualitatively and quantitatively how patients perceived all aspects of the intervention and other study components. We ask participants if they would like to be sent reports and publications resulting from the study.

Confidentiality and Data Security

Participant data are identified only by a coded study number. Information collected on paper is kept in locked filing cabinets accessible only to study staff. Information collected on CASI computers or encrypted tablets is stored on a secure server behind secure firewalls and is accessible only to study staff. Any records linking study numbers to identifiers (such as tracking and contact information) are kept in a password protected database on a secure server and are accessible only to study staff members. All audio recordings are moved onto a secure password protected server and erased off the recorder immediately after the interview. Recordings are labeled with a coded study number.

Quality Assurance

The Project Director and Data Manager/Statistician perform weekly data audits. Overall recruitment goals, missing data and follow-up failures are continuously tracked and audited and are reviewed. All surveys are administered via online methods using Qualtrics, which includes range checks and skip logic programming. The study's biostatistician provides ongoing monitoring of study progress. Audio recordings of baseline assessments are reviewed on a weekly basis, and approximately 20% of the experimental and comparison intervention sessions are reviewed by the supervising clinician for intervention fidelity. In the event an emergency or adverse event arises, staff have been trained and have access to a Manual of Operations,

which details the appropriate measures, and the supervising clinician will be consulted and the Principal Investigator, a licensed clinical psychologist, will be immediately notified.

Ethics and dissemination

All procedures are approved by the Institutional Review Board (IRB) at the University of California, San Francisco. Written informed consent is obtained from all participants at enrollment, and study progress is reviewed twice yearly by an external Safety Monitoring Committee (SMC). The trial is registered at ClinicalTrials.gov under registration number NCT02925949.

If effective, this program could be easily implemented in clinics and community settings. A high priority of this work is to make findings available and to export effective components of the intervention into real world settings. In addition to traditional publications and presentations, we plan to create user-friendly “Science to Community” publications. At the study’s conclusion, we will host forums in which we invite former participants, other researchers, and clinic and agency staff to hear and discuss findings. Finally, we will make study materials available online and in print format. The CAPS Community Engagement Core is widely recognized for its dissemination activities.

Analysis Plan

Preliminary analyses

Frequency tables for all variables and measures of central tendency and variability for continuous variables will characterize the sample and will be stratified by randomization group (i.e., intervention versus control) to check for imbalances. If the two groups differ significantly at baseline on one or more covariates (e.g., on ART vs. not), we will use methods based on the Rubin causal model (e.g., propensity scores, double-robust estimation) to obtain the desired

marginal effect estimates under the counterfactual assumption of balanced groups.[43-47] We will address incomplete data with multiple imputation (MI)[48 49] which makes the relatively mild assumption that incomplete data arise from a conditionally random (MAR) mechanism.[50]Auxiliary variables will be included to help meet the MAR assumption[51 52] and sensitivity analyses will be conducted with pattern-mixture models and weighted MI [53] to assess the robustness of the MAR assumption.[54] As part of the sensitivity analyses, we will also perform analyses using complete-caes analysis (CCA); if results from sensitivity analyses (including CCA) yield different substantive conclusions from the original MI-based analyses, both sets of results will be reported.SAS[55] will be used to perform the proposed analyses.

Primary Analyses to address Specific Aim 1

We hypothesize that, following the intervention, the odds of suppressed viral load will be higher for intervention participants than for control participants (Hypothesis 1). Our primary interest is to estimate the marginal or population-average effect of intervention participation on each outcome rather than the effect for a hypothetical average subject or couple.[56] Moreover, within-subject and within-couple correlations among outcomes are considered nuisance parameters, not quantities of interest to be modeled explicitly. Finally, recent recommendations in the literature point to the superior performance of generalized estimating equations (GEE) relative to generalized linear mixed models (GLMMs) for the analysis of dyadic data with categorical outcomes (e.g., virologic suppression).[57] Accordingly, GEE will be used to perform the proposed primary analysis, which is a planned time-averaged comparison of post-baseline measurements across the intervention and control groups to test primary Hypothesis 1. Alpha will be set at .05 for this planned comparison. Any additional post-hoc comparisons (e.g., paired comparisons of the two study arms at each time point) will maintain nominal α=.05 through the use of simulation-based stepdown multiple comparison methods.[58] The alternating logistic regression

(ALR) approach implemented in SAS PROC GENMOD can be used to address the 3-level clustering of observations within participants and participants within dyads. Though GEE estimates are consistent even if the correlation structure is misspecified, GEE's statistical efficiency improves as the working correlation structure more closely approximates the actual correlation structure,[59] so various correlation structures suitable for the study's design will be considered (e.g., exchangeable; nested-1).[60] The QIC statistic will be used to select the final correlation structure.[61] Couple HIV serostatus will be included in all models as required by the stratified randomized design.[62] Additional covariates such as couple cohabitation status and relationship length will be included if they improve QIC. Robust standard errors will be used to obtain correct inferences even if the chosen correlation structure remains slightly misspecified. The primary analysis will be performed under the intention-to-treat (ITT) principle.

Secondary Analysis to address Specific Aim 2

To explore the effect of the intervention on hypothesized mechanisms of action, secondary analyses will evaluate whether participants assigned to the intervention report higher mean scores on theory-based constructs such as health care empowerment, adherence self-efficacy, adherence, social support, HIV treatment information, and treatment beliefs and expectancies. These analyses will also investigate whether these constructs mediate the relationship between intervention group assignment and virologic suppression and whether couple HIV-serostatus and cohabitation moderate these associations. Main and interaction effects of couple drug and alcohol use and racial concordance will also be evaluated in these models. Mediation and moderation will be assessed using the causal inference-based approach of Valeri and VanderWeele, which yields optimal estimates of indirect effects in the presence of binary outcomes and moderator-mediator interactions.[63] M*plus* will be used to fit causal mediation models because it can adjust standard errors for nesting of participants within couples.[64]

Additional secondary analyses will consider the effects of intervention dose exposure on virologic suppression as a main effect and as moderated and mediated by theory-based constructs described above to determine for whom and via which mechanisms of action intervention dosing is most efficacious. These secondary exploratory data analyses will be defined in a data analysis plan prior to conducting final analyses.

Secondary Analysis to address Specific Aim 3

Analyses with intact dyads enable investigation of couple-based research questions that explore how relationship dynamics affect behavior change in partnerships. We will extend the analyses described above to include actor and partner effects for continuous covariates and mediators. *Actor effects* describe the influence that one's standing on independent or mediating variables of interest (e.g., communication, intimacy) has on one's own dependent variables (e.g., self's virologic suppression) whereas *partner effects* describe the influence that one's standing on independent variables has on the dependent variables of one's partner (e.g., partner's virologic suppression). This technique illuminates the effects that partners in intimate relationships can have on both their own and their partner's behavior. Actor and partner effects can be evaluated in models with either continuous[65] (e.g., health care empowerment, adherence self-efficacy) or categorical dependent variables (e.g., virologic suppression).[66] A closely related approach uses sums and differences of continuous covariates and mediators to quantify within-couple and between-couple effects. For continuous dependent variables, within-couple hypotheses will be tested with a GEE model, in which couple-level difference scores on the outcome variable (e.g., adherence self-efficacy) will be regressed onto both the couple-level difference and sum scores for the predictor variable (e.g., communication).[67] Computing sums and differences for categorical outcomes is not feasible, but it is still possible to investigate the effects of sums and differences of individuals' continuous covariates and mediators on individual-level categorical

responses (e.g., virologic suppression) to quantify the separate influences of between-couple and within-couple effects of continuous mediators on individuals' categorical outcomes.[68] These secondary exploratory data analyses will be defined in a data analysis plan prior to conducting final analyses.

Interim analyses

No interim analyses are planned.

Statistical power analysis

Power analyses were generated using the two-group repeated proportions module in NCSS PASS [69] to compute minimum detectable effect sizes for the primary analysis to address Hypothesis 1. The study will begin with 300 participants from 150 couples evenly assigned to the intervention and control groups. We further assume half of the couples will be HIV sero-discordant (N=150) and half will be sero-concordant (N=150). Under these assumptions, three quarters (N=180) of the 240 participants will be living with HIV and therefore have virologic suppression outcome data. Due to the clustered nature of the dyadic data, observations from participants who belong to the same couple who are living with HIV will be correlated. In our previous Duo observational study of couples, for instance, the average within-couple correlation of viral load measurements was r=.23. Accordingly, we lowered the effective sample size (ESS) input for the power analyses to be ESS=N/DEFF for these couples, where DEFF is the design effect or variance inflation attributable to using correlated data. DEFF is computed as 1+(M-1)*r, where M is the number of participants per dyad (i.e., two). Therefore DEFF=1+(2-1)*.23 = 1.23, so ESS for HIV-concordant couples is 150 HIV participants in HIV-concordant couples /1.23=122. For HIV-discordant couples, 75 participants will be living with HIV and since their outcome values should be statistically independent, no design effect adjustment is required for this subset of couples. Thus, the total ESS for the proposed primary analysis incorporating

members from both sero-concordant and sero-discordant couples is 122 + 75=197. Further assuming 20% attrition, the post-attrition ESS will be 197*(1-.20)=158 for analysis at all time points. Assuming, α=.05, power=.80, and ESS=158, we computed the minimum detectable odds ratio (*OR*), proportion difference (*pdiff*), and standardized proportion difference (*h*) for the proposed time-averaged comparisons, assuming three post-baseline measurements and assuming a wide range within-subject correlation values, ρ, which were varied between .20 and .80. Because the virologic suppression base rates P_0 are also unknown, we considered several scenarios: low (P_0 = 30%), medium (P_0 = 50%), and high (P_0 = 80%). Under these assumptions, the minimum detectable effect size estimates for our primary analyses range from 10.4% to 20.1% for raw proportion differences (*Pdiff*); standardized effect size estimates (*h*) range from .30 to .41, which are between published benchmarks of .20 and .50 for small and medium standardized effect sizes,[70] respectively. These results suggest that our primary analysis will have sufficient power to detect effects that are between small and medium across a wide range of potential analytic scenarios (see Table 3).

Table 3. Minimum Detectable Effect Sizes

Within-Subject Correlation	Control Group Proportion								
	P_0 = .30 (Low)			P_0 = .50 (Medium)			P_0 = .80 (High)		
ρ	*OR*	*Pdiff*	*h*	*OR*	*Pdiff*	*h*	*OR*	*Pdiff*	*h*
.20	1.88	14.6%	.303	1.86	15.0%	.305	2.37	10.4%	.297
.30	1.96	15.7%	.325	1.94	16.0%	.326	2.53	11.0%	.318
.40	2.04	16.7%	.345	2.02	16.9%	.345	2.70	11.5%	.336
.50	2.12	17.6%	.363	2.10	17.8%	.364	2.87	12.0%	.354
.60	2.20	18.5%	.382	2.18	18.6%	.381	3.04	12.4%	.369
.70	2.27	19.3%	.398	2.27	19.4%	.398	3.22	12.8%	.384
.80	2.35	20.1%	.414	2.35	20.1%	.414	3.40	13.2%	.400

Discussion

HIV care is a lifelong process that can create challenges for PLWH. Dyadic support within couple relationships provides an opportunity for partners in primary romantic relationships to

help address the barriers associated with their HIV care engagement. By developing an intervention that focuses on partner support, communication, problem solving as a couple, relationship strengths, and social support, couples can develop important skills to maintain active and successful engagement in their HIV care. Couple-level interventions have the potential to continue to have a sustained impact after the formal intervention ends, as the partner takes on an active and sustained role in supporting target behaviors. Optimal engagement in care will subsequently lead to virologic suppression, leading to increased survival and quality of life, decreased morbidity, and reduced likelihood of transmission of HIV to previously uninfected partners.

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Contributors: AT took the lead on drafting the manuscript and is involved in study data recruitment, enrollment, and data collection. LC contributed to drafting and revising the manuscript and serves as Project Director for the project. DO drafted sections of the manuscript and oversees intervention delivery and supervision. TN drafted sections of the manuscript and is the senior statistician for the study. MJ contributed conception of the study, contributed to drafting the protocol, and provides scientific oversight of the project.

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Competing interests: None

Ethics approval: Ethics approval for this trial was granted by the Committee on Human Research at the University of California, San Francisco.

Provence and peer review: This protocol was reviewed by a standing review study section through the Center for Scientific Review at the National Institutes of Health.

Tabrisky, DuoPACT Protocol Paper

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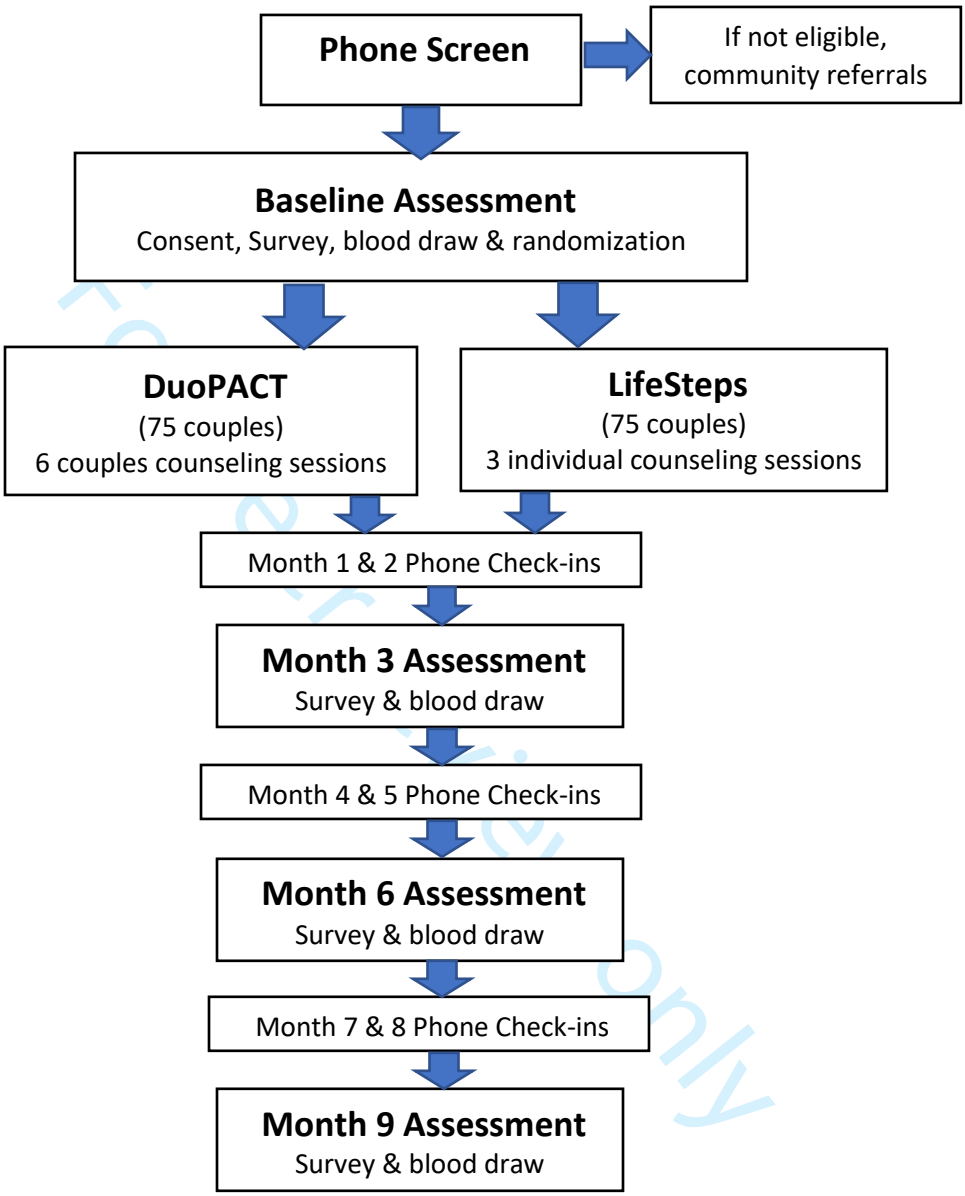
Figure 1:


Phone Screen
If not eligible, community referrals
Baseline Assessment
Consent, Survey, blood draw & randomization
DuoPACT
(75 couples)
6 couples counseling sessions
LifeSteps
(75 couples)
3 individual counseling sessions
Month 1 & 2 Phone Check-ins
Month 3 Assessment
Survey & blood draw
Month 4 & 5 Phone Check-ins
Month 6 Assessment
Survey & blood draw
Month 7 & 8 Phone Check-ins
Month 9 Assessment
Survey & blood draw

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page # in Manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	23
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	3 & 21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Included as attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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A protocol for a randomized controlled trial of a couples-focused intervention to improve engagement in HIV care

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Abstract:

Introduction. Advances in HIV treatment have proven to be effective in increasing virologic suppression, thereby decreasing morbidity, and increasing survival. Medication adherence is an important factor in reducing viral load among people living with HIV (PLWH) and in the elimination of transmission of HIV to uninfected partners. Achieving optimal medication adherence involves individuals taking their medications every day or as prescribed by their provider. However, not all PLWH in the US are engaged in care, and only a minority have achieved suppressed viral load (viral load that is lower than the detectable limit of the assay). Sexual and gender minorities (SGM; those who do not identify as heterosexual or those who do not identify as the sex they were assigned at birth) represent a high-risk population for poor clinical outcomes and increased risk of HIV transmission, as they face barriers that can prevent optimal engagement in HIV care. Research in dyadic support, specifically within primary romantic partnerships, offers a promising avenue to improving engagement in care and treatment outcomes among SGM couples. Dyadic interventions, especially focused on primary romantic partnerships, have the potential to have a sustained impact after the structured intervention ends.

Methods and analysis. This paper describes the protocol for a randomized control trial (RCT) of a theory-grounded, piloted intervention (DuoPACT) that cultivates and leverages the inherent sources of support within primary romantic relationships to improve engagement in HIV care and thus clinical outcomes among persons who are living with HIV and who identify as SGM (or their partners). Eligible participants must report being in a primary romantic relationship for at least three months, speak English, at least one partner must identify as a sexual or gender minority, and at least one partner must be HIV+ with suboptimal engagement in HIV care, defined as less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or unknown viral load, or not currently on antiretroviral

therapy (ART). Eligible consenting couples are allocated equally to the two study arms: a structured six-session couples counseling intervention (DuoPACT) or a three-session individually-delivered HIV adherence counseling intervention (Life Steps). The primary aim is to evaluate the efficacy of DuoPACT on virologic suppression among HIV+ members of SGM couples with suboptimal engagement in care. The DuoPACT study began its target enrollment of 150 couples (300 individuals) in August 2017, and will continue to enroll until June 2021.

Ethics and dissemination. DuoPACT has been built on years of formative work and offers the opportunity for PLWH to improve their HIV care engagement through support from their primary romantic partner. It has the potential to improve clinical outcomes and to reduce the number of new infections among populations that have a high burden of HIV through treatment optimization.

Strengths and limitations of this study

- The DuoPACT intervention has been piloted and tested and is currently in its final phase testing the efficacy of a couple's-based intervention approach to increasing engagement in HIV care.
- A couples-based approach has the potential to have lasting effects after the conclusion of the formal study intervention, as partners take on more active supportive roles that can have sustained and dynamic impact over time.
- The study is designed to detect changes in laboratory-confirmed HIV viral load, whereas other studies use self-reported viral load data (prone to reporting bias) or health record extraction (prone to missing or suboptimally-timed data).
- The study is located in one geographic area, which may limit generalizability

- Relationships can be volatile leading to break-ups at various points in the study, including after consent visit and prior to study enrollment.

Introduction

Engagement in HIV care, including high levels of adherence to antiretroviral treatment (ART), is essential for managing HIV infection and for ending the HIV epidemic.[1 2] Consistent medication adherence is linked to viral suppression, which allows people living with HIV (PLWH) to live longer and healthier lives, and viral suppression can eliminate the potential for further transmission to uninfected sexual partners.[3] Suboptimal medication adherence reduces the chances of suppressing HIV viral load in PLWH. The HIV Care Cascade (also referred to as the Care Continuum) conceptualizes the level of engagement in care in PLWH throughout the United States and has been used as a framework to address the barriers many people face managing their health and HIV treatment.[4] As of 2016, 49% of PLWH in the US were estimated to be retained in care, and only 53% of those had achieved viral suppression.[5] Barriers associated with successful medication adherence, a key component of the continuum, include medication fatigue, side effects from the medications, and forgetfulness.[6 7] In addition, there are gaps within other parts of the HIV Care Continuum, such as retention in care, that prevent PLWH from achieving viral suppression.[8 9] Recent research has focused on social support between dyads, specifically among romantic partnerships, which shows promise in addressing some of these gaps.

Being in a primary relationship can provide health-promoting benefits through tangible and emotional support, and various kinds of social support are associated with positive outcomes for people living with chronic illnesses.[10-19] Within the context of couples affected by HIV, there is evidence that social support from primary romantic partnerships is associated with better HIV

care engagement, such as ART adherence, compared to social support from people other than romantic partners.[20-24]

Although the preponderance of evidence suggests an overall positive impact from partners on many outcomes in healthcare, being in a relationship can also present challenges to HIV care engagement. Partners may have different roles in the dyad, such as a caretaker, that may prevent a person from taking care of themselves while taking care of their partner, which includes preventing them from taking care of their own HIV infection or other health demands.[25] Negative influences, such as substance use, conflict, abuse, and violence can also prevent optimal engagement in care for one or both partners in the dyad.[26]

Overall, however, the evidence supports the premise that social support within a relationship dyad has more positive than negative impact on HIV and other health-related outcomes. By extension, interventions designed to improve communication, emotional support, and involvement in healthcare within dyads can improve health behaviors such as engagement in care. This is particularly true for some subpopulations in the US, in which the HIV epidemic continues to be concentrated, including sexual and gender minority (SGM) individuals and their sexual partners.[27] As many as half to three-quarters of HIV transmissions among sexual minority persons likely occur within the context of primary romantic relationships.[28] While there are not parallel modelling data for gender minority persons, the worldwide prevalence of HIV among transgender persons is 49 times higher than among other groups.[29] Collectively, these data support a focus on continued innovation and intervention for preventing HIV and optimizing treatment among SGM persons and their partners.

Aim of the study

The primary objective of the DuoPACT study is to test a couple-level HIV intervention designed for sexual and gender minority couples in sero-discordant or sero-concordant HIV-positive

relationships that have evidence of poor engagement in care. The purpose of the intervention is to leverage and shape relationship dynamics to improve engagement in HIV care. Such an approach has the potential to be a powerful, cost-effective, and sustainable tool to optimize treatment outcomes among couples affected by HIV. Due to lower viral loads being a quantitative element associated with better engagement in care, the study team uses HIV-1 RNA quantitative real-time PCR to analyze the trend of viral loads among participants living with HIV. The study will evaluate the efficacy of DuoPACT on the primary outcome of virologic suppression among SGM people living with HIV in primary relationships.

Study Specific aims:

Primary Aim:

1. Evaluate the efficacy of DuoPACT on virologic suppression among people living with HIV in primary relationships in which at least one partner identifies as sexual or gender minority.

Secondary Aim:

1. Explore the effect of DuoPACT on behavioral indicators of engagement in HIV care, including ART adherence and HIV care appointment attendance and pre-exposure prophylaxis (PrEP) for HIV-uninfected partners; and
2. Explore the potential mediating effect of relationship variables DuoPACT has on patient and partner outcomes.

Methods and analysis

Study Design

The study is a randomized control trial (RCT) with 150 couples (300 individuals) in the San Francisco Bay Area in Northern California (Figure 1). Recruitment began in August 2017 and will continue until June 2021, with final data collection complete in March 2022. Participation in the study takes a total of nine months, with surveys conducted at baseline, three, six, and nine months. The primary trial outcome is HIV virologic suppression, as measured by laboratory assay. Secondary outcomes include behavioral indicators of engagement in HIV care, including ART adherence, HIV care appointment attendance, as well as use of Pre-Exposure Prophylaxis (PrEP) for HIV-uninfected partners, a highly effective daily HIV medication that can prevent HIV infection following sexual exposure.

The Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT[30]; online supplemental form 1) provided guidance in implementing this protocol.

Study Participants

The study sample consists of primary romantic couples, in which at least one partner identifies as SGM, both are age 18 or older, and who describe each other as “a partner to whom they feel committed above anyone else and with whom they have had a sexual relationship”. At least one partner must be HIV+ and report suboptimal engagement in HIV care defined as one or more of the following: less than excellent medication adherence, having not seen a provider in at least the past eight months, having a detectable or unknown viral load, or is not currently (for the past 30 days) on ART. Less than excellent medication adherence is operationalized as reporting anything other than excellent on a validated single item adherence rating scale that asks “Thinking back over the past 30 days, how would you rate your ability to take your HIV medications as prescribed?” Response choices include excellent, very good, good, poor, and very poor, with responses validated with viral load and electronic adherence measurements.[31 32] See Table 1 for full inclusion criteria.

Table 1: Inclusion and exclusion criteria

Inclusion criteria:

- Both participants are 18+ years old;
- Identifies as a sexual or gender minority;
- In a primary romantic relationship for at least 3 months;
- At least one partner is HIV+;
- English-speaking;
- Able to provide informed consent; and
- For HIV+ participants: Evidence of suboptimal engagement in HIV care, as indicated by one or more of the following: (a) Not on ART; (b) Reporting most recent viral load as detectable/unknown; or (c) If on ART, reporting less than excellent adherence on a validated adherence rating scale (report by self or partner); or (d) Reporting no HIV primary care appointments in the prior 8 months.

Exclusion criteria:

- Evidence of severe cognitive impairment or active psychosis, as determined by the PI.
- Unable to provide informed consent.
- Relocating out of the Bay Area within 6 months of screening.
- Participation as the same couple in the DuoPACT Pilot.

Recruitment Strategy

Participants are recruited through venue-based and online strategies as well as referral. Flyers are posted in venues (LGBTQ resource centers, bars, coffee shops, etc.), community-based organizations (CBOs), clinics, pharmacies and community bulletin boards. Staff distribute packets with study materials, including an information sheet outlining the basic eligibility criteria, flyers, and postcards, to clinics and CBOs throughout the Greater Bay Area. Providers and CBOs are asked to place these materials in waiting areas where potential participants are likely to see them. Study advertisements are posted online on Craigslist and Facebook and through dating/hook-up apps such as Growlr and Grindr.

In-person study recruitment takes place in HIV clinic waiting rooms. Recruiters present the study at staff/provider meetings in clinics throughout the Bay Area that have a high number of patients

living with HIV to facilitate referral to the study. Recruiters also staff tables at symposia, conferences, and community events to continue collaboration with HIV healthcare providers as well as connect with members of the community that may be interested in participating in the study.

All recruitment materials include a toll-free number and a link to the study webpage. Interested potential participants are directed to call the number listed on the recruitment resources or fill out the Contact Us form to learn more about the study and initiate the screening process. Study staff are notified when a potential participant completes the form and contact within one business day to ensure a higher chance of contact.

Enrolled participants have the opportunity to refer couples to the study via a "snowball" recruitment method. To maintain confidentiality of the enrolled participants, potential participants are asked "how did you hear about the study" and must mention the name of the participant that referred them. To maintain confidentiality, staff cannot confirm nor deny whether the participant identified is enrolled in the study.

Screening Procedures

To determine eligibility, callers undergo a phone screening procedure, in which staff relay background about the study and ask a series of questions to determine eligibility, as per the criteria outlined above. Both individuals in the dyad must separately complete the phone screening process to determine eligibility. We have found in previous studies that when some individuals who are screened out figure out the particular exclusion criteria, they may call again with altered information in order to qualify. To prevent the potential for such misrepresentation, individuals are screened to the end of the phone screen form so that ineligible individuals will not readily be able to discern the criteria that excluded them. If an individual is screened as ineligible, the study will not contact their partner for screening.

Couple Status Verification

With couple-level studies that offer remuneration for participation, there is a risk of potential participants attempting to fake their relationship status or other inclusion criteria to enroll in the study. Therefore, a series of questions have been adapted from McMahon and colleagues to increase confidence that the individuals are indeed in a primary romantic relationship with each other.[33] In this screening, each individual has to corroborate details from each other's lives such as: (1) Where did your partner live before living in the Bay Area? (2) When is your partner's birthday? (or at least what month?) (3) How old is your partner? (4) If they report not living together, "What street does your partner live on?" Similar to McMahon's protocol, we are lenient on the answers given between the dyad, as some relationships may be as recent as three months, and it is not uncommon for couples to live separately. Because these procedures are not fool-proof, when inconsistencies in responses between the two members of a dyad emerge, interviewers consult with senior project leadership to determine whether answers were sufficient to verify couple status. Rarely, more in depth questions about the dyad are asked.

Study Enrollment

Eligible and interested couples are scheduled for an in-person enrollment visit, requiring that both members of the couple present together in person. They are directed to bring proof of HIV status, which can be an official list of medications from their pharmacy, their HIV medication bottle with their name on it, or a letter of diagnosis from their provider. To minimize the possibility that one partner is pressuring the other to participate, partners are consented in separate rooms. Trained staff read and give a detailed explanation of what to expect in the study, potential risks, compensation, as well as their rights as a research participant. To continue with the enrollment process, both partners must independently agree to the study procedures and sign their respective consent forms (online supplemental form 2). Each

participant is given a copy of the consent document and another copy is securely kept with the study file. After the participant provides informed consent, staff collect detailed contact information, and a medical records release authorization form to contact HIV care providers is also obtained in order to secure CD4 and viral load results if needed. A baseline visit is scheduled for two weeks later to allow time for laboratory procedures.

Participants who are living with HIV are directed to have their blood drawn for viral load and CD4 count at their choice of one of 40 community laboratory centers located throughout the area prior to their baseline survey visit. Participants are oriented to the service center locations and hours of operation and are given a requisition for lab assays, labeled with participants' study ID and date of birth to minimize error with specimen mix-ups. Additionally, if a participant loses a paper requisition, study staff can send it electronically to the laboratory via a secure laboratory database, and date of birth will allow laboratory staff to verify participant identity with this minimal identifier. Lab results are posted to a secure online system for controlled access by study staff.

At the in-person baseline survey visit, participants are separated into separate private rooms to complete their own computer-assisted personal interviewing (CAPI) survey using *Qualtrics* (Provo, UT). The survey contains a series of validated measures focusing on adherence, medication use, partner support, relationship dynamics, behavioral health issues, as well as other important factors in their overall engagement in health care. The survey focuses on the participant's relationship with their partner, communication, intimacy, conflict, social support, and the role of HIV medications in their relationship. Relationship quality and closeness are measured through the survey using the Kurdek Commitment Scale.[34] Partner perceptions of closeness and autonomy were previously found to be significantly associated with adherence and virologic suppression.[35 36] Therefore, the survey includes questions about Inclusion of Other in Self (IOS) using a figure that has a set of circles with varying degree of overlap which best

reflects their overall relationship and another set of circles which describes their engagement in each partner's healthcare.[37] The survey questions assess reports of medication adherence,[31 38] the participant's knowledge of their partner's medication adherence,[39] adherence self-efficacy,[40] and reports of recent HIV health care appointment attendance. The baseline survey takes one and a half to two hours to complete.

Randomization

Once participants complete the baseline surveys, they are brought back together and are randomized as a couple (stratified by couple-level HIV serostatus) to one of two study conditions: (1) the DuoPACT couple intervention, which comprises a series of six couple sessions delivered weekly; or (2) LifeSteps, a three-session individual intervention for HIV-positive partners who meet inclusion criterion suggesting suboptimal engagement in HIV care. Couples are randomized to study conditions via a 1:1 allocation ratio. Reflecting the stratified nature of the study design, separate randomization lists were created for HIV-discordant and HIV-concordant negative couples. Within each stratum, couples are randomized using randomly-permuted block sizes of 2, 4, and 6. Randomization is done via Research Electronic Data Capture (REDCap). REDCap is a secure platform that is HIPPAA compliant and stores highly sensitive information.[41] The first counseling session is usually scheduled within the subsequent week.

Intervention Conditions

Experimental Intervention

The DuoPACT intervention comprises six weekly couples' sessions. Each session lasts 60 to 90 minutes and focuses on communication in the relationship and support for each other's health and adherence to medical regimens (both ART for treatment and PrEP). The partners learn and practice communication skills, work on aligning support tactics (e.g., reminding to take meds, go

to clinic appointment with partner), and set goals related to their own health and medication adherence as well as supporting their partner's health. They also practice problem solving as a couple and amplifying positive moments in the relationship. In between sessions, the couples are asked to track times each of them felt supported by their partner around their health. See Table 2 for the focus of the DuoPACT intervention.

Table 2: Skills Covered in Counseling Sessions

Couples Sessions	LifeSteps
• Communication • Partner support • Problem solving as a couple • Relationship strengths • Supporting each other's goals • Social support	• Problem solving • Provider communication • Coping with side affects • Organizational skills (in connection with adherence) • Cueing strategies

Comparison Intervention.

The LifeSteps arm consists of an adaptation of a previously-validated HIV treatment adherence enhancement intervention.[42] For this study, three one-on-one meetings with a trained counselor are delivered weekly and last 60 to 90 minutes each. The curriculum is an 11-step process designed to improve the participant's adherence to HIV treatment and medication regimens. The counselors help the participants identify and problem solve any existing barriers to maximizing treatment. The participants also learn guided relaxation techniques and cue control strategies. See Table 2 for an outline of the topics covered in the interventions.

Intervention Quality Assurance

The sessions in both study arms are facilitated by trained counselors and are audio-recorded and systematically reviewed for fidelity to the intervention. Counselors complete a structured

training program that includes directed readings, mock sessions, and instruction in ethics of human subjects' research.

The intervention staff make careful considerations during either arm of the intervention to determine if they feel the intervention is harming the participant. The participant is also given their participant rights during the consent process detailing if they feel the intervention is harming them in any way, they can discontinue the intervention.

Follow-Up Data Collection

Participants living with HIV complete three follow-up blood draws, and all participants complete three, six, and nine month surveys regardless of study arm. Once each follow-up blood draw has been completed, each participant is electronically sent a personal Qualtrics link to a follow-up survey that they complete on their own device at any WIFI enabled convenient location. Each participant is asked to complete the assessment separately. If a participant does not have email, or a WIFI enabled device/access, they can come to our study office to complete the follow-up survey on our tablet. Follow-up surveys take approximately one hour to compete and include the core measures from the baseline. The final (nine month) assessment also includes a satisfaction and acceptability measure based on the Patient Satisfaction Questionnaire.[43]

Break-Ups

Participants who report breaking-up with their partner are encouraged to continue participation in the study as originally planned, with the exclusion of any remaining couple intervention sessions, which would be contraindicated following breakup. Survey questions following break-ups are adapted to include measures about the break-up and omit all relationship measures.

Retention

A significant number of participants are from marginalized communities throughout the San Francisco Bay Area. Some are unstably housed, financially impoverished, and may have other life circumstances that make it difficult to engage throughout the course of the study. During the enrollment process, study staff collect a detailed list of contacts to maintain retention throughout the nine months of study participation, including three personal contacts that do not have to live locally, as well as any social workers and case managers at organizations or clinics throughout the Bay Area.

To maintain contact with participants throughout their involvement in the study, study researchers conduct monthly phone check-ins between the follow up activities (see figure 1). The check-ins are meant to maintain stable contact, to update contact information for each participant, break-ups and collect timely information about their overall engagement in HIV care (e.g., recent medication adherence and medical provider appointments). Check-ins are also useful to learn about participant's whereabouts, including incarceration or hospitalizations.

Incentives

Participants are compensated for their participation in each study procedure using Greenphire Clincards, a reloadable debit card that allows them to immediately receive payments for each study procedure. The incentives, ranging from $20 for surveys to $50 for blood draws, are designed to be enough to compensate for time and travel to study visits but not so high as to coerce enrollment.

Participant and Public Involvement

The current study builds on 10 years of formative work with participants, in which qualitative and quantitative data were used to guide the development of the intervention. This includes a pilot trial with participants, in which feedback on intervention components was solicited. Participants were involved in the pilot intervention, and their input was used to guide refinements in the

protocol. They were not involved in the recruitment to and conduct of the study. At study exit, we assess qualitatively and quantitatively how patients perceived all aspects of the intervention and other study components. We ask participants if they would like to be sent reports and publications resulting from the study.

Confidentiality and Data Security

Participant data are identified only by a coded study number. Information collected on paper is kept in locked filing cabinets accessible only to study staff. Information collected on CASI computers or encrypted tablets is stored on a secure server behind secure firewalls and is accessible only to study staff. Any records linking study numbers to identifiers (such as tracking and contact information) are kept in a password protected database on a secure server and are accessible only to study staff members. All audio recordings are moved onto a secure password protected server and erased off the recorder immediately after the interview. Recordings are labeled with a coded study number.

Quality Assurance

The Project Director and Data Manager/Statistician perform weekly data audits. Overall recruitment goals, missing data and follow-up failures are continuously tracked and audited and are reviewed. All surveys are administered via online methods using Qualtrics, which includes range checks and skip logic programming. The study's biostatistician provides ongoing monitoring of study progress. Audio recordings of baseline assessments are reviewed on a weekly basis, and approximately 20% of the experimental and comparison intervention sessions are reviewed by the supervising clinician for intervention fidelity. In the event an emergency or adverse event arises, staff have been trained and have access to a Manual of Operations,

which details the appropriate measures, and the supervising clinician will be consulted and the Principal Investigator, a licensed clinical psychologist, will be immediately notified.

Ethics and dissemination

All procedures are approved by the Institutional Review Board (IRB) at the University of California, San Francisco. Written informed consent is obtained from all participants at enrollment, and study progress is reviewed twice yearly by an external Safety Monitoring Committee (SMC). The trial is registered at ClinicalTrials.gov under registration number NCT02925949.

If effective, this program could be easily implemented in clinics and community settings. A high priority of this work is to make findings available and to export effective components of the intervention into real world settings. In addition to traditional publications and presentations, we plan to create user-friendly “Science to Community” publications. At the study’s conclusion, we will host forums in which we invite former participants, other researchers, and clinic and agency staff to hear and discuss findings. Finally, we will make study materials available online and in print format. The CAPS Community Engagement Core is widely recognized for its dissemination activities.

Analysis Plan

Preliminary analyses

Frequency tables for all variables and measures of central tendency and variability for continuous variables will characterize the sample and will be stratified by randomization group (i.e., intervention versus control) to check for imbalances. If the two groups differ significantly at baseline on one or more covariates (e.g., on ART vs. not), we will use methods based on the Rubin causal model (e.g., propensity scores, double-robust estimation) to obtain the desired

marginal effect estimates under the counterfactual assumption of balanced groups.[44-48] We will address incomplete data with multiple imputation (MI)[49 50] which makes the relatively mild assumption that incomplete data arise from a conditionally random (MAR) mechanism.[51] Auxiliary variables will be included to help meet the MAR assumption[52 53] and sensitivity analyses will be conducted with pattern-mixture models and weighted MI[54] to assess the robustness of the MAR assumption.[55] As part of the sensitivity analyses, we will also perform analyses using complete-caes analysis (CCA); if results from sensitivity analyses (including CCA) yield different substantive conclusions from the original MI-based analyses, both sets of results will be reported. SAS[56] will be used to perform the proposed analyses.

Primary Analyses to address Specific Aim 1

We hypothesize that, following the intervention, the odds of suppressed viral load will be higher for intervention participants than for control participants (Hypothesis 1). Our primary interest is to estimate the marginal or population-average effect of intervention participation on each outcome rather than the effect for a hypothetical average subject or couple.[57] Moreover, within-subject and within-couple correlations among outcomes are considered nuisance parameters, not quantities of interest to be modeled explicitly. Finally, recent recommendations in the literature point to the superior performance of generalized estimating equations (GEE) relative to generalized linear mixed models (GLMMs) for the analysis of dyadic data with categorical outcomes (e.g., virologic suppression).[58] Accordingly, GEE will be used to perform the proposed primary analysis, which is a planned time-averaged comparison of post-baseline measurements across the intervention and control groups to test primary Hypothesis 1. Alpha will be set at .05 for this planned comparison. Any additional post-hoc comparisons (e.g., paired comparisons of the two study arms at each time point) will maintain nominal α=.05 through the use of simulation-based stepdown multiple comparison methods.[59] The alternating logistic regression

(ALR) approach implemented in SAS PROC GENMOD can be used to address the 3-level clustering of observations within participants and participants within dyads. Though GEE estimates are consistent even if the correlation structure is misspecified, GEE's statistical efficiency improves as the working correlation structure more closely approximates the actual correlation structure,[60] so various correlation structures suitable for the study's design will be considered (e.g., exchangeable; nested-1).[61] The QIC statistic will be used to select the final correlation structure.[62] Couple HIV serostatus will be included in all models as required by the stratified randomized design.[63] Additional covariates such as couple cohabitation status and relationship length will be included if they improve QIC. Robust standard errors will be used to obtain correct inferences even if the chosen correlation structure remains slightly misspecified. The primary analysis will be performed under the intention-to-treat (ITT) principle.

Secondary Analysis to address Specific Aim 2

To explore the effect of the intervention on hypothesized mechanisms of action, secondary analyses will evaluate whether participants assigned to the intervention report higher mean scores on theory-based constructs such as health care empowerment, adherence self-efficacy, adherence, social support, HIV treatment information, and treatment beliefs and expectancies. These analyses will also investigate whether these constructs mediate the relationship between intervention group assignment and virologic suppression and whether couple HIV-serostatus and cohabitation moderate these associations. Main and interaction effects of couple drug and alcohol use and racial concordance will also be evaluated in these models. Mediation and moderation will be assessed using the causal inference-based approach of Valeri and VanderWeele, which yields optimal estimates of indirect effects in the presence of binary outcomes and moderator-mediator interactions.[64] M*plus* will be used to fit causal mediation models because it can adjust standard errors for nesting of participants within couples.[65]

Additional secondary analyses will consider the effects of intervention dose exposure on virologic suppression as a main effect and as moderated and mediated by theory-based constructs described above to determine for whom and via which mechanisms of action intervention dosing is most efficacious. These secondary exploratory data analyses will be defined in a data analysis plan prior to conducting final analyses.

Secondary Analysis to address Specific Aim 3

Analyses with intact dyads enable investigation of couple-based research questions that explore how relationship dynamics affect behavior change in partnerships. We will extend the analyses described above to include actor and partner effects for continuous covariates and mediators. *Actor effects* describe the influence that one's standing on independent or mediating variables of interest (e.g., communication, intimacy) has on one's own dependent variables (e.g., self's virologic suppression) whereas *partner effects* describe the influence that one's standing on independent variables has on the dependent variables of one's partner (e.g., partner's virologic suppression). This technique illuminates the effects that partners in intimate relationships can have on both their own and their partner's behavior. Actor and partner effects can be evaluated in models with either continuous[66] (e.g., health care empowerment, adherence self-efficacy) or categorical dependent variables (e.g., virologic suppression).[67] A closely related approach uses sums and differences of continuous covariates and mediators to quantify within-couple and between-couple effects. For continuous dependent variables, within-couple hypotheses will be tested with a GEE model, in which couple-level difference scores on the outcome variable (e.g., adherence self-efficacy) will be regressed onto both the couple-level difference and sum scores for the predictor variable (e.g., communication).[68] Computing sums and differences for categorical outcomes is not feasible, but it is still possible to investigate the effects of sums and differences of individuals' continuous covariates and mediators on individual-level categorical

responses (e.g., virologic suppression) to quantify the separate influences of between-couple and within-couple effects of continuous mediators on individuals' categorical outcomes.[69] These secondary exploratory data analyses will be defined in a data analysis plan prior to conducting final analyses.

Interim analyses

No interim analyses are planned.

Statistical power analysis

Power analyses were generated using the two-group repeated proportions module in NCSS PASS[70] to compute minimum detectable effect sizes for the primary analysis to address Hypothesis 1. The study will begin with 300 participants from 150 couples evenly assigned to the intervention and control groups. We further assume half of the couples will be HIV sero-discordant (N=150) and half will be sero-concordant (N=150). Under these assumptions, three quarters (N=180) of the 240 participants will be living with HIV and therefore have virologic suppression outcome data. Due to the clustered nature of the dyadic data, observations from participants who belong to the same couple who are living with HIV will be correlated. In our previous Duo observational study of couples, for instance, the average within-couple correlation of viral load measurements was r=.23. Accordingly, we lowered the effective sample size (ESS) input for the power analyses to be ESS=N/DEFF for these couples, where DEFF is the design effect or variance inflation attributable to using correlated data. DEFF is computed as 1+(M-1)*r, where M is the number of participants per dyad (i.e., two). Therefore DEFF=1+(2-1)*.23 = 1.23, so ESS for HIV-concordant couples is 150 HIV participants in HIV-concordant couples /1.23=122. For HIV-discordant couples, 75 participants will be living with HIV and since their outcome values should be statistically independent, no design effect adjustment is required for this subset of couples. Thus, the total ESS for the proposed primary analysis incorporating

members from both sero-concordant and sero-discordant couples is 122 + 75=197. Further assuming 20% attrition, the post-attrition ESS will be 197*(1-.20)=158 for analysis at all time points. Assuming, α=.05, power=.80, and ESS=158, we computed the minimum detectable odds ratio (*OR*), proportion difference (*pdiff*), and standardized proportion difference (*h*) for the proposed time-averaged comparisons, assuming three post-baseline measurements and assuming a wide range within-subject correlation values, ρ, which were varied between .20 and .80. Because the virologic suppression base rates P_0 are also unknown, we considered several scenarios: low (P_0 = 30%), medium (P_0 = 50%), and high (P_0 = 80%). Under these assumptions, the minimum detectable effect size estimates for our primary analyses range from 10.4% to 20.1% for raw proportion differences (*Pdiff*); standardized effect size estimates (*h*) range from .30 to .41, which are between published benchmarks of .20 and .50 for small and medium standardized effect sizes,[71] respectively. These results suggest that our primary analysis will have sufficient power to detect effects that are between small and medium across a wide range of potential analytic scenarios (see Table 3).

Table 3. Minimum Detectable Effect Sizes

Within-Subject Correlation	Control Group Proportion								
	P_0 = .30 (Low)			P_0 = .50 (Medium)			P_0 = .80 (High)		
ρ	*OR*	*Pdiff*	*h*	*OR*	*Pdiff*	*h*	*OR*	*Pdiff*	*h*
.20	1.88	14.6%	.303	1.86	15.0%	.305	2.37	10.4%	.297
.30	1.96	15.7%	.325	1.94	16.0%	.326	2.53	11.0%	.318
.40	2.04	16.7%	.345	2.02	16.9%	.345	2.70	11.5%	.336
.50	2.12	17.6%	.363	2.10	17.8%	.364	2.87	12.0%	.354
.60	2.20	18.5%	.382	2.18	18.6%	.381	3.04	12.4%	.369
.70	2.27	19.3%	.398	2.27	19.4%	.398	3.22	12.8%	.384
.80	2.35	20.1%	.414	2.35	20.1%	.414	3.40	13.2%	.400

Discussion

HIV care is a lifelong process that can create challenges for PLWH. Dyadic support within couple relationships provides an opportunity for partners in primary romantic relationships to

help address the barriers associated with their HIV care engagement. By developing an intervention that focuses on partner support, communication, problem solving as a couple, relationship strengths, and social support, couples can develop important skills to maintain active and successful engagement in their HIV care. Couple-level interventions have the potential to continue to have a sustained impact after the formal intervention ends, as the partner takes on an active and sustained role in supporting target behaviors. Optimal engagement in care will subsequently lead to virologic suppression, leading to increased survival and quality of life, decreased morbidity, and reduced likelihood of transmission of HIV to previously uninfected partners.

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Contributors: AT took the lead on drafting the manuscript and is involved in study data recruitment, enrollment, and data collection. LC contributed to drafting and revising the manuscript and serves as Project Director for the project. DO drafted sections of the manuscript and oversees intervention delivery and supervision. TN drafted sections of the manuscript and is the senior statistician for the study. MJ contributed conception of the study, contributed to drafting the protocol, and provides scientific oversight of the project.

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Competing interests: None

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Provence and peer review: This protocol was reviewed by a standing review study section through the Center for Scientific Review at the National Institutes of Health.

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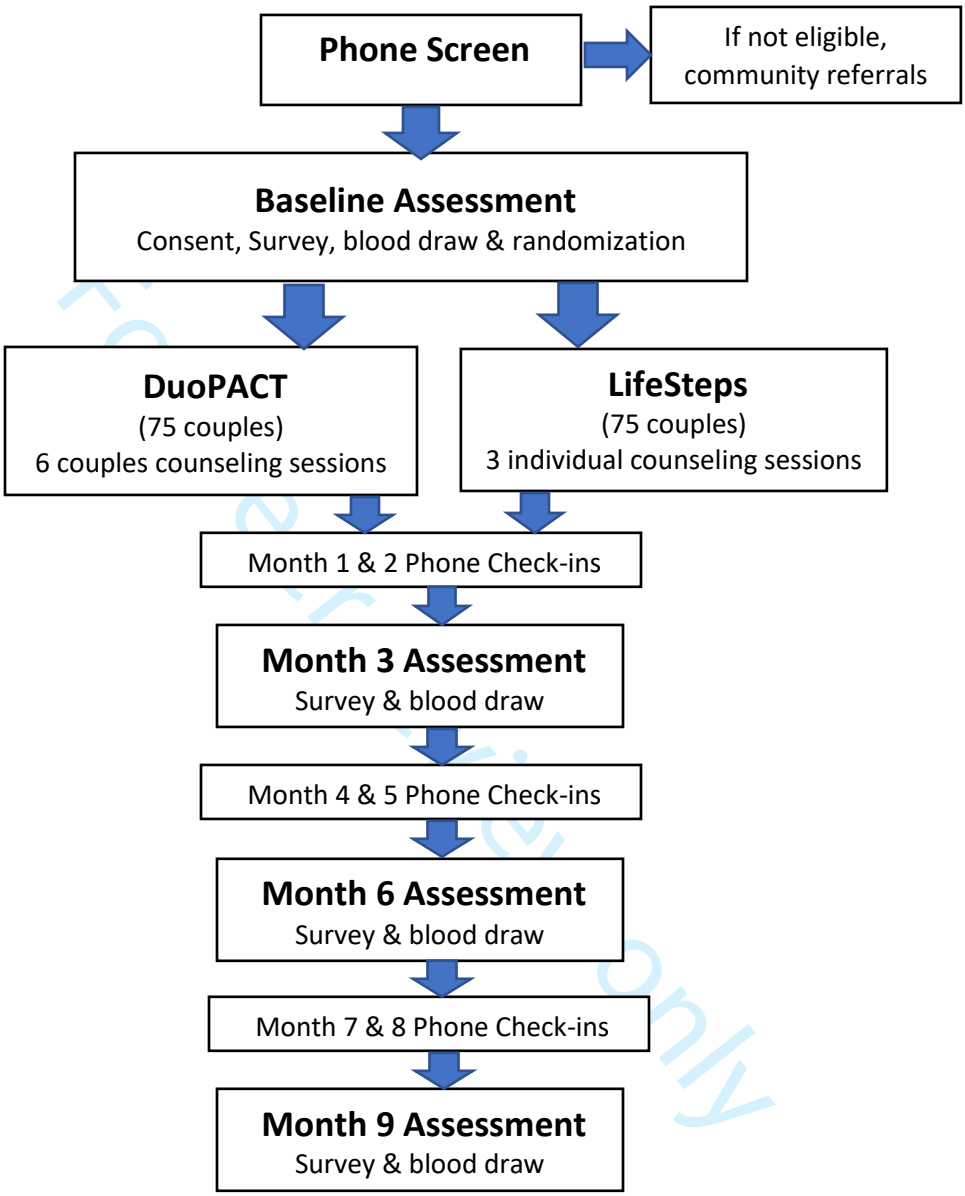
Tabrisky, DuoPACT Protocol Paper

Figure 1:



IRB NUMBER: 16-19267
IRB APPROVAL DATE: 12/17/2019
IRB EXPIRATION DATE: 12/16/2020

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A couples-based approach to improving engagement in HIV care

This is a research study about primary relationships and HIV. Dr. Mallory Johnson, Ph.D., or his research staff from the UCSF Department of Medicine, Center for AIDS Prevention Studies, will explain this study to you.

Research studies include only people who choose to take part. Please take your time to make your decision about participating, and discuss your decision with your family or friends if you wish. If you have any questions, you may ask the researchers.

You are being asked to take part in this study because you are 18 years or older, involved in a primary romantic relationship with another person who is also 18 years or older, and one or both of you is HIV-positive. The research project is focused on couples that have not been traditionally well represented in research. Your responses to our screening indicate there are potential areas of improvement in your or your partner's HIV treatment adherence. Your primary romantic partner is also being asked to participate in the study and, to enroll as a couple, you must both participate.

Why is this study being done?

The purpose of this study is to test a program designed to help HIV-positive partners improve their HIV treatment adherence and overall engagement in their HIV treatment. The ultimate goal of this research is to develop programs that will assist HIV-positive people to live longer and healthier lives. The study is funded by the National Institutes of Health (NIH).

How many people will take part in this study?

About 300 people (150 couples) will take part in this study.

What will happen if I take part in this research study?

Study Location: All in-person study procedures will take place at our study offices. Bloodwork takes place at any convenient Bay Area Quest Diagnostic Service Center.

If you are eligible for the study and you choose to continue, you and your partner will meet with a research staff member who will explain the study to you and answer your questions. If you agree to participate, you will sign this consent form and the following procedures will occur:

Interviews

- You will be asked to complete four private, individual computer-assisted surveys (one baseline and three follow-ups) during your 12 months of study participation. Baseline visits usually take about 2 hours on average to complete, while follow-ups take around 1 hour each. If you are HIV-positive and taking antiretroviral medications, a research staff member will verify your medications and then show you how to complete the survey on the computer. You will be asked questions about yourself and your relationship with your partner, your communication, intimacy, conflict, social support, and the role of HIV medications in your relationship. You will also be asked about your medical history, and your history of drug and alcohol use. The data collected on the computer screen will have no identifying data and will be coded by a participant identification number. If you finish your survey before your partner, you will be asked to wait while your partner completes the survey separately. This part of the interview may be audio recorded. The recordings will be destroyed after their content is reviewed and studied by the researchers. Follow-up surveys take place online through an online link we sent to your email. You can access the follow-up survey on your own device at any Wi-Fi enabled convenient location. You may also come to our study office to complete follow-ups on a study tablet in a private room if you prefer. At your final interview survey, you may be asked for your thoughts, feelings, and opinions about the study's surveys or program sessions and your study participation in general.

- Blood draws and laboratory tests: If you are HIV-positive, an experienced phlebotomist at Quest Diagnostics will draw a blood sample prior to your four surveys. The amount of blood drawn each time will be approximately 30 ml (2 tablespoons). Your blood will be used to test your CD4 count and viral load. The CD4 test will be done at the first survey visit only, and the viral load test will be done prior to all four surveys. You will have the opportunity to receive your CD4 and viral load test results as they become available.

Randomization

- You will be randomized to one of two study conditions: Group A or Group B. The group you are randomized to depends on chance, something like the toss of a coin.

- Group A: This is a program for couples. You and your partner will meet together with a counselor for 6 weekly sessions. These sessions usually last about 60 minutes. During the sessions, you will discuss your health, your relationship with your partner, and steps for improving HIV treatment adherence. Sessions are scheduled with as much flexibility as possible and tailored to meet your needs. Sessions will be audio recorded to make sure they are done correctly, and the recordings will be destroyed at the end of the study.

- Group B: This is a program for HIV-positive individuals. You will meet individually with a counselor for 3 weekly sessions. These sessions usually last about 60 minutes. During the sessions, you will discuss your health and steps for improving HIV treatment adherence. Sessions are scheduled with as much flexibility as possible and tailored to meet your needs. Sessions will be audio recorded to make sure they are done correctly, and the recordings will be destroyed at the end of the study.

If both you and your partner are HIV-positive, one or both of you will attend these individual sessions, based on the responses you each provided in the study screening and interviews.

If you are HIV-negative, you will not attend the program sessions, but you will participate in the interviews as described above.

Other Procedures

- Contact Information: A research staff member will ask you for detailed information about how best to contact you (for example, you will receive confirmation phone calls and/or written reminders about your study visits) and how we could find you if you miss an appointment for a study visit. You will be asked to provide the names of people and agencies who know how to reach you. Any location information that you provide will be kept in secure password protected files, and you can ask to have these contact procedures stopped at any time.

- Monthly Check-ins: During the months between your study visits, a staff member will call you for a brief check-in and to ask you a few questions. You can also come to the study offices in person for these check-ins if you'd prefer.

How long will I be in the study?

Participation in the study will take a total of about 12 months.

If you are randomized to Group A, your total time in the study will be approximately 15 hours over the course of the year.

If you are randomized to Group B, your total time in the study will be approximately 12 hours over the course of the year.

Can I stop being in the study?

Yes. You can decide to stop at any time. Just tell the study researcher or staff right away if you wish to stop being in the study.

Also, the study researchers may stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

- Privacy and confidentiality: Participation in research may involve a risk to your privacy. Your identity and research records will be handled as confidentially as possible. The information that you give will be coded with a number to help protect your privacy, and the records linking names with numbers will be kept in secure password protected files. Only the study staff will have access to the study files. At no time will any public reports about the study mention your name or the names of other participants.

No one other than the research staff and transcriptionists will be permitted to listen to study audio recordings. The audio recordings will be labeled with your study identification number, not your name, and will be kept in secure password protected files and destroyed after their use in this research project is completed.

- Randomization: You will be assigned to a group by chance, to receive either a couples intervention or an individual intervention. One condition may prove to be less effective than the other condition or other available treatments in helping you make informed decisions about your healthcare. However, we won't know if either Group A or Group B is better than the other until after the study is completed and the data have been analyzed.
- Study topics: Some of the questions in the interviews or discussions with study staff might make you uncomfortable; talking about your own or your partner's HIV infection, your relationship, your sexual behaviors and your drug-using behaviors may make you feel embarrassed, angry, uneasy, or sad in some way.

  Among the areas of interest in this study are communication and conflict among couples. Discussing these topics may be uncomfortable or may result in tense or difficult interactions with your partner following your participation in the study. You are free to decline to answer any questions or to take part in any discussions at any time. You will be given a list of resources including agencies that provide couples counseling and domestic violence services, as well as up-to-date phone numbers for crisis centers, hotlines, and referral agencies.
- Blood draws: The risks of drawing blood include temporary discomfort from the needle stick and bruising. Very rarely an infection can occur at the injection site.
- Inconvenience: Being in the study may sometimes be inconvenient. The study staff will make every effort to schedule interviews and sessions at convenient times.

Are there benefits to taking part in the study?

There may be no direct benefit to you from participating in this study. However, you may learn new ways to take better care of your health, and the information that you provide may help researchers understand the role of HIV medications among individuals in primary relationships.

What other choices do I have if I do not take part in this study?

You are free to choose not to participate in the study. If you decide not to take part, the research staff will offer you a resource list of agencies giving support and services for people with HIV.

Will information about me be kept private?

We will do our best to make sure that the personal information gathered for this study is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institute of Nursing Research (at NIH). With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

Organizations that may look at and/or copy your research records for research, quality assurance, and data analysis include:

- UCSF Committee on Human Research, who protect your rights as a research participant;
- Representatives from the National Institutes of Health, who sponsor this study.

Exceptions: A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about you, without your consent. For example, we will voluntarily disclose information about incidents such as child abuse, elder abuse, and intent to hurt yourself or others. In addition, a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. Finally, the Certificate may not be used to withhold information from the Federal government needed for auditing or evaluating Federally-funded projects.

What are the costs of taking part in this study?

You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?

Yes. In return for your time, effort and travel expenses, you will be paid as follows:

- Consent: You will be paid $30 in cash for today's consent visit.
- Interviews: You will be paid $40 on a reloadable debit card when you complete the baseline visit, and $20 on a reloadable debit card when you complete each follow-up survey.
- Program sessions: You will be paid $45 on a reloadable debit card when you complete each program session.
- Blood draws: If you are HIV-positive, you will be paid $50 on a reloadable debit card for each blood sample obtained from Quest Diagnostics. Payment will not be given for labs acquired from your medical provider through a Release of Information.
- Referral: You will be paid $20 per referral if you refer eligible participants to the study.

The reloadable debit cards, called ClinCard, can be used anywhere a Mastercard can be used, including an ATM. ClinCard requires that your legal name and date of birth be linked to the card.

UCSF University of California San Francisco
IRB NUMBER: 16-19267
IRB APPROVAL DATE: 12/17/2019
IRB EXPIRATION DATE: 12/16/2020

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way.

Who can answer my questions about the study?

You can talk to the researchers about any questions, concerns, or complaints you have about this study. The Principal Investigator is Dr. Johnson, who may be reached at Mallory.Johnson@ucsf.edu or the Project Director, Lara Coffin, who may be reached at (415) 502-5216 or Lara.Coffin@ucsf.edu.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at (415) 476-1814.

We are often asked about other studies. Would you like to be contacted if we have other studies for which you might be eligible?

☐ Yes ☐ No

CONSENT

You have been given a copy of this consent form to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to be in this study, or to withdraw from it at any point without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

_____ _____

Date Participant's Signature for Consent

_____ _____

Date Person Obtaining Consent

IRB NUMBER: 16-19267
IRB APPROVAL DATE: 12/17/2019
IRB EXPIRATION DATE: 12/16/2020

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

EXPERIMENTAL SUBJECT'S

BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject I have the following rights:

1) To be told what the study is trying to find out,

2) To be told what will happen to me and whether any of the procedures, drugs, or devices is different from what would be used in standard practice,

3) To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to me for research purposes,

4) To be told if I can expect any benefit from participating, and, if so, what the benefit might be,

5) To be told of the other choices I have and how they may be better or worse than being in the study,

6) To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study,

7) To be told what sort of medical treatment is available if any complications arise,

8) To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study,

9) To receive a copy of the signed and dated consent form,

10) To be free of pressure when considering whether I wish to agree to be in the study.

If I have other questions I should ask the researcher or the research assistant. In addition, I may contact the Committee on Human Research, which is concerned with protection of volunteers in research projects. I may reach the committee office by calling: (415) 476-1814 from 8:00 AM to 5:00 PM, Monday to Friday, or by writing to the Committee on Human Research, Box 0962, University of California, San Francisco, CA 94143.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page # in Manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	23
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	3 & 21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Included as attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.