

2. CANDIDATE BACKGROUND

I spent my early career working as a biomedical engineer on electronic medical devices used to treat chronic diseases. While it was exciting to contribute to breakthrough technologies, I wondered if my contribution to health could be maximized by preventing and treating infectious diseases such as HIV/AIDS, which affects 33 million people worldwide¹. Motivated by this desire, I enrolled in an MPH program at the Colorado School of Public Health and collaborated with Dr. Jason Haukoos on a CDC-funded clinical trial to expand HIV testing services in the emergency department (ED). As part of the Denver ED HIV Opt-Out Study Group, we published three manuscripts on the implementation², effectiveness and efficiency³, and cost-effectiveness⁴ (my MPH thesis) of routine HIV screening. The low HIV prevalence in this population and limited effectiveness of the intervention served as an impetus for me to work in high HIV prevalence settings of sub-Saharan Africa (SSA), which accounts for 67% of all cases of HIV and 75% of all AIDS deaths worldwide⁵.

In 2008, I began my PhD studies at the University of Colorado Denver in Health and Behavioral Sciences, an interdisciplinary program comprised of social and behavioral scientists. I began working with sociologist Dr. Sara Yeatman on *Tsogolo La Thanzi* (TLT), a study on reproduction and HIV/AIDS in Malawi. We collaborated on two publications (one as the first-author) on social responses to HIV treatment using TLT data and a set of qualitative data^{6,7}. For the last two years of graduate school, I received an NIMH-funded F31 pre-doctoral fellowship to support my dissertation research. My graduate coursework and F31 training in biostatistics, regression analysis, qualitative methods, mixed-methods, factor analysis, and structural equation modeling has given me a strong foundation to analyze both quantitative and qualitative data. For my dissertation, I developed a measure of relationship power that was added to TLT surveys and collected qualitative data to understand how gender and power dynamics influence decisions to test for HIV in Malawi. Using both sets of data, I published five first-author manuscripts⁸⁻¹² and have an additional paper under review¹³. My dissertation revealed that HIV testing behavior was strongly influenced by couple-level factors such as communication, love, and trust. These findings suggested the need for more training in couples-based research with the leading experts at CAPS.

During my NIMH-funded T32 post-doctoral fellowship at CAPS, I have been working with Drs. Lynae Darbes and Mallory Johnson on a couples-based HIV intervention to increase couples' testing in South Africa. Using baseline data from the trial, we presented two papers at international conferences^{14,15} and I have submitted one of these papers for peer-review as first-author¹⁶. As I attended CAPS seminars on the HIV care continuum (CC), I pondered what role I could play as a behavioral scientist in the shift from primary prevention towards secondary prevention with treatment. This reflection, coupled with my own research indicating high levels of HIV testing⁹ and expanding access to antiretroviral therapy (ART) in Malawi⁷, spurred my professional interests towards later stages of the HIV CC. Thus, I applied for and received a pilot study grant from UCSF to conduct a qualitative study on relationship factors and engagement in HIV care in South Africa, which is currently underway. More recently, I have started to work with Drs. Johnson, Darbes, and Neilands on a longitudinal study of male couples on ART and will be presenting a paper at the HIV Treatment and Prevention Adherence conference this June¹⁷.

My training on the HIV CC has centered on HIV testing. To commence a research career focusing on HIV+ individuals, I am in need of specialized training to enhance my knowledge and skills to conduct **dyadic research** on the **HIV CC**. I will focus on the ART period (Figure 2.1). First, my research indicated that the complexity of dyadic processes on behavior warrants formal training on interpersonal theory from psychology, which would complement my sociology-focused background. Second, while my analytic skills are strong and diverse, my training related to dyadic data has been informal and self-taught. Although I have training in qualitative methods, I have no training on the analysis of dyadic qualitative data. Mastery of these approaches calls for formal didactic training and mentorship from experts. Third, because I am not a clinician but desire to work in a clinical domain of HIV research, I am in need of training on healthcare and clinical aspects of HIV/AIDS. This training will enable me to apply dyadic theories and methods to study the HIV CC. Fourth, to have a large impact on health through behavioral interventions, it is critical for me to gain skills in intervention design and evaluation during the K01. I have no previous training on behavioral interventions. Therefore, with my mentors, I developed a comprehensive training plan providing didactic and practical experiences in theory, methods, healthcare and clinical aspects of HIV/AIDS, and interventions to be able to conduct cutting-edge, dyadic research on the HIV CC in SSA.

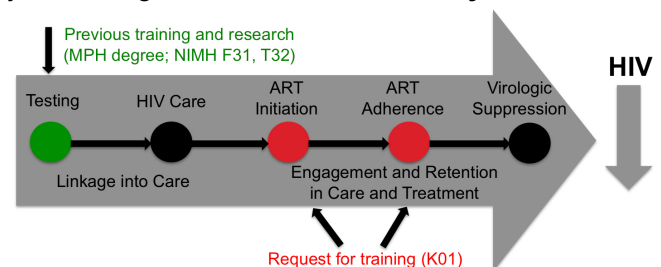


Figure 2.1. Previous training and current training needs on the HIV care continuum

3. CAREER GOALS AND OBJECTIVES

My immediate career goal is to become an independent behavioral scientist with expertise on couples-based approaches to understand and improve engagement in the HIV CC. This K01 will allow me to fill an important gap in knowledge, build upon my current set of research skills, and commence a long-term research program with the ultimate goal of reducing the burden of HIV infection among heterosexual couples in SSA. To meet these immediate and long-term goals, my mentors and I have devised a training and research plan that will facilitate four career objectives:

- (1) To gain knowledge of interpersonal theories used to understand health behavior in couples
- (2) To develop advanced methods skills to collect and analyze dyadic qualitative and quantitative data
- (3) To obtain training on healthcare and clinical aspects of HIV/AIDS
- (4) To acquire knowledge and skills related to behavioral intervention development and evaluation

In the following section, I present a detailed career development plan to acquire the training and mentored research experiences needed to address my current deficiencies and successfully compete for R-level funding, thereby achieving independence as a behavioral scientist.

4. CAREER DEVELOPMENT ACTIVITIES DURING AWARD PERIOD

A. Mentorship Team

I have assembled a team of experienced mentors and advisors committed to guiding me at each stage of my training to achieve my career objectives and research aims (Table 4.1). Dr. Lynae Darbes will be the primary mentor and will oversee all training, research, and career development activities. Dr. Darbes is a clinical psychologist and has over 15+ years of experience conducting couples-based HIV research in the US and SSA using theory-based approaches and focusing on how relationship dynamics influence sexual risk behavior and uptake of HIV testing. My secondary mentors are Drs. Mallory Johnson and Torsten Neilands. Like Dr. Darbes, Dr. Johnson is also a clinical psychologist who studies couples, however, his work focuses on people living with HIV/AIDS and the HIV CC, including research on drug side-effects and coping with HIV/AIDS, ART adherence, adherence interventions, and patient-centered measures of engagement in care. Dr. Johnson is recognized for his mentoring of early career investigators and will provide additional career development support. Dr. Neilands is a quantitative methodological expert with knowledge of dyadic data analysis and will provide mentorship on the research design, survey development, and analysis during the quantitative phase.

Table 4.1. Mentorship Team Expertise

Primary Mentor	Title and Affiliation	Expertise	Meeting Frequency/Mode
Lynae Darbes, PhD	Associate Professor, UCSF, CAPS	Couples-based research and interventions in Africa; relationship dynamics; interpersonal theory	Weekly; as needed (in-person meetings)
Secondary Mentors			
Mallory Johnson, PhD	Professor, UCSF, CAPS	Coping with HIV/AIDS; ART side effects; ART adherence; adherence interventions; measures of engagement	Monthly; as needed (in-person meetings)
Torsten Neilands, PhD	Professor, UCSF, CAPS	Methodological expertise; quantitative dyadic data analysis	Monthly; as needed (in-person meetings)
Scientific Advisors			
Megan Comfort, PhD	Senior Research Sociologist, RTI International; Assistant Professor, UCSF, CAPS	Qualitative research; novel methods for analyzing dyadic qualitative data	Monthly; as needed (in-person meetings)
Monica Gandhi, MD, MPH	Professor of Medicine, UCSF; Director of Positive Health Program, SF General Hospital	Medical management of HIV/AIDS; Pharmacokinetic measures of ART drug levels (hair biomarkers)	Monthly; as needed (in-person meetings)
Joep Van Oosterhout, MD, PhD	Medical and Research Director, Dignitas International (Malawi)	Healthcare delivery system for HIV/AIDS in Malawi	Quarterly; as needed (Skype calls, in-person meetings)
Adamson Muula, MD, MPH	Professor, University of Malawi, College of Medicine	Public health interventions for HIV/AIDS in Malawi; cultural expertise	Quarterly; as needed (Skype calls, in-person meetings)

My scientific advisors will bring unique expertise in other areas of this K01. Dr. Megan Comfort is a qualitative researcher and the only member of my team with novel expertise on the analysis of dyadic qualitative data. Dr. Monica Gandhi is the medical director of the Positive Health Program, a premier HIV clinic at San Francisco General Hospital (SFGH), and has pioneered methods on pharmacokinetic measures of ART adherence using in hair samples. Dr. Joep Van Oosterhout is the medical and research director at Dignitas International, which operates an HIV clinic in Zomba that I will recruit from, and has conducted extensive clinical research on the ART delivery system in Malawi. Dr. Adamson Muula is a Professor of Public Health in Malawi and conducts research on public health aspects of HIV/AIDS. As the only native Malawian on the team, he will provide cultural and logistical expertise related to the intervention design and development.

B. Career Development Plan

To achieve my career objectives, I have proposed a combination of didactic training (e.g., coursework, conferences, directed readings), mentorship, and practical training in the form of original research (see Table 4.2). These training activities will allow me to meet my long-term career goal of becoming an independent researcher and leading expert on couples-based approaches to optimize engagement in the HIV CC in SSA.

Table 4.2. Plan to Achieve Career Development Objectives

Career Objective	Didactic Training	Mentorship	Practical Training
Training aim 1: To gain knowledge of interpersonal theories used to understand health behavior in couples	- CSU, PSY 792: Close Relationships - Directed readings on interpersonal theory and theory-based interventions for couples, tailored towards HIV/AIDS (Darbes) - IARR conference	Darbes	Specific aim 1 and 2: Develop a conceptual model using interpersonal theory Specific aim 3: Develop a theory-guided intervention for couples
Training aim 2: To develop advanced methods skills to collect and analyze dyadic data	- UConn, Dyadic Data Analysis workshop - Directed readings on the recruitment, sampling, study instruments for couples (Darbes), qualitative dyadic data analysis (Comfort), and quantitative dyadic data analysis (Neilands)	- Darbes - Comfort - Neilands	Specific aim 1: Collect and analyze qualitative dyadic data Specific aim 2: Collect and analyze quantitative dyadic data
Training aim 3: To obtain training on healthcare and clinical aspects of HIV/AIDS	- Directed readings on the healthcare delivery system for HIV/AIDS in Malawi (Van Oosterhout), medical management of HIV/AIDS (Gandhi), and patient/psychological perspectives related to engagement in care (Johnson) - HIV Grand Rounds at SF General Hospital - Observations in clinics and treatment literacy classes, meetings with clinic staff in Malawi - HIV Treatment and Prevention Adherence conference	- Van Oosterhout - Gandhi - Johnson	Specific aim 2: In the process of carrying out this specific aim, I will develop a toolkit for measuring the broader HIV CC (from linkage to care, to viral suppression) in Malawi. A subset of these measures will be used for hypothesis testing in specific aim 2.
Training aim 4: To acquire knowledge and skills related to behavioral intervention development and evaluation	- UCSF, EPI 209: Biostatistical Methods for Clinical Research - UCSF, EPI 240: Designing Clinical Research - UCSF, EPI 245: Translating Evidence to Practice - Directed readings on behavioral interventions for couples (Darbes); behavioral interventions to increase engagement in care (Johnson); cultural considerations of interventions in Malawi (Muula) - UMich, Adaptive Interventions workshop - NIH summer institute on behavioral RCTs - IAS conference	- Darbes - Johnson - Neilands - Van Oosterhout - Muula	Specific aim 3: Qualitative interviews with couples, community members, and stakeholders to develop the relationship-focused intervention; meetings with key mentors to map out intervention components; incorporation of an adaptive design

B.1. Knowledge and application of interpersonal theories for couples

Didactic Training. I will enroll in PSY 792: Close Relationships at Colorado State University (CSU), which is a graduate course focusing on the theory of close relationships. The course is taught by my dissertation advisor, Dr. Jennifer Harman, who will allow me to participate remotely. I will attend the International Association of Relationship Research (IARR) conference to learn about evolving theory and its application to health studies.

Mentorship. Dr. Darbes will serve as the primary mentor for this training aim given her knowledge and application of interpersonal theory to couples research in Africa. With Dr. Darbes, I will develop a syllabus on theory and concepts in couples' health research, and the application of interpersonal theory to study HIV health behaviors within couples. Mentorship meetings will provide a forum to discuss and critique the readings.

Practical Training. I will work closely with Dr. Darbes to develop the qualitative interview guides based on theory (specific aim 1), a conceptual model to explain engagement in the HIV CC (specific aims 1 and 2), and a theory-guided intervention to improve engagement in the HIV CC (specific aim 3).

Competencies. I will gain both broad and HIV-specific knowledge of key interpersonal theories used to understand couple interactions and behavior, which will equip me with the conceptual tools needed to understand health within couples over a long-term research career.

B.2. Methods for collecting and analyzing dyadic data

Didactic Training. With my mentors, I will develop a syllabus on research design issues for couples studies including recruitment, sampling, and instrument development (Dr. Darbes), qualitative dyadic data analysis (Dr. Comfort), and quantitative dyadic data analysis (Dr. Neilands). I will attend a workshop at the University of Connecticut summer training institute (DATIC). This workshop provides hands-on, analysis-driven training to build skills to conduct dyadic data analysis for couples through multi-level modeling, the actor-partner interdependence model (APIM), mediation and moderation of dyadic effects, and over-time analyses.

Mentorship. For specific aims 1 and 2, Dr. Darbes will mentor me on data collection of couples' data. For specific aim 1, Dr. Comfort will mentor me on qualitative research methods related to couples including the research design, analysis, and interpretation of findings. For specific aim 2, Dr. Neilands will mentor me on the quantitative data analysis by helping me apply learned techniques to the couples' dataset.

Practical Training. For specific aim 1, I will analyze dyadic qualitative data to describe how the relationship context influences engagement in the HIV CC using both partners' perspectives. As part of this effort, I will also publish a paper describing the analytic approach—contributing to the methodological literature base. For specific aim 2, I will test for statistical associations between relationship factors (e.g., using multilevel models) and partner influences (e.g., using APIM) on engagement in the HIV CC.

Competencies. I will gain advanced methodological skills needed to conduct HIV research on couples across all stages of the research life cycle including sampling, recruitment, analysis, and interpretation of findings.

B.3. Training on healthcare and clinical aspects of HIV/AIDS

Didactic Training. To gain broad training in the clinical domain of HIV/AIDS from the top-down (system level) and bottom-up (patient level), I will develop a syllabus with my mentors on the healthcare delivery system for HIV/AIDS in Malawi (Dr. Van Oosterhout), the medical management of HIV/AIDS (Dr. Gandhi), and psychological/patient aspects related to HIV care such as coping and side-effects (Dr. Johnson). I will attend monthly HIV Grand Rounds at SF General Hospital to learn about healthcare and medical management of HIV/AIDS, where Dr. Gandhi is the medical director. In Malawi, I will spend time observing clinical operations and treatment literacy classes, and meeting with clinic staff at the Zomba District Hospital, where Dr. Van Oosterhout is the medical director. Finally, I will attend the International HIV Treatment and Prevention Adherence conference each year, which includes sessions on linkage, retention in care, and ART adherence.

Mentorship. Dr. Van Oosterhout will provide mentorship to support the collection of healthcare-related measures of engagement in care. Dr. Gandhi will provide mentorship on the collection procedures for hair biomarkers, anticipated feasibility or logistical challenges, methods to analyze drug levels in hair, and interpretation of the hair results. Dr. Johnson is currently developing a patient-centered index of engagement in HIV care and will mentor me on the development and potential use of such measures.

Practical Training. I will apply my training on healthcare and clinical aspects of HIV/AIDS to develop a toolkit consisting of a comprehensive list of measures on engagement in care specific to the Malawi healthcare system (i.e., from linkage into care to viral suppression). For specific aim 2, I will use a subset of these measures to test for associations with relationship factors. As my research expands to study other aspects of the CC in the future, the toolkit will provide a useful repository of measures to draw upon.

Competencies. I will gain broad, interdisciplinary knowledge of healthcare and clinical aspects of HIV/AIDS within resource-rich (San Francisco) and resource-poor settings (Malawi), providing the necessary background and set of measurement tools needed to study and intervene on the HIV CC over a long-term career.

B.4. Behavioral intervention development and evaluation

Didactic Training. I will complete 3 courses in UCSF's CTSI Training in Clinical Research (TICR) program: (1) Biostatistical Methods for Clinical Research III EPI 209, which covers the analysis of repeated measures data from clinical trials; (2) Designing Clinical Research EPI 240, which covers design and analysis of clinical trials; and (3) Translating Evidence into Practice: Theory and Design EPI 245, which covers development and implementation of evidence-based interventions. I will apply to attend the NIH summer institute on randomized clinical trials for behavioral interventions. I will also attend the Adaptive Interventions workshop at the University of Michigan to learn how to develop an adaptive design to optimize the intervention for couples. To supplement my coursework, I will develop a syllabus with my mentors on the design of behavioral interventions for couples in Africa (Dr. Darbes), behavioral interventions targeting engagement in HIV care (Dr. Johnson), and cultural/contextual considerations for Malawi (Dr. Muula). Finally, I will attend the International AIDS Society (IAS) conference to learn about interventions to minimize drop-off along the HIV CC.

Mentorship. Dr. Darbes will provide primary mentorship for this aim given her experience developing a behavioral couples' based intervention in South Africa. Dr. Johnson will provide secondary mentorship given his experience developing behavioral interventions targeting ART adherence. Dr. Muula will provide cultural and logistical support for the intervention and facilitate connections with local and national stakeholders.

Practical Training. For specific aim 3, I will collect qualitative data among couples, community members, and stakeholders to inform a behavioral, relationship-focused intervention for Malawi. I will meet with my mentors to identify the intervention components to include, brainstorm use of existing evidence-based interventions, discuss how to optimize the intervention, and decide on how to deliver the intervention in Malawi.

Competencies. These training activities will provide me with the necessary skills to carry out R-level studies to develop and evaluate behavioral interventions that address dyadic aspects of HIV care and treatment in SSA.

C. Pathway to independence. Table 4.3 summarizes my training activities over the award period. Drs. Darbes and Johnson will oversee my career development as a junior faculty member by including me in NIH grant applications, facilitating my investigator status on other projects, and supervising the development of an R34 grant application. Prior to the end of the R34, I will submit an R01 application to conduct a full-scale randomized trial of the intervention. I will also take advantage of rich career development opportunities at UCSF such as the CFAR mentoring program (e.g., career workshops, leadership retreats), CTSI K-scholars program (e.g., works-in-progress sessions, methodology seminars), and CAPS town halls and seminars.

Table 4.3. Timeline of training activities	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Training activities																
Coursework, workshops, NIH summer institute	√						√		√	√	√				√	
Directed readings and mentorship meetings	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√
HIV grand rounds and meetings at SFGH	√	√		√			√		√		√			√	√	√
Clinic observations and interviews in Malawi		√				√										
Conferences			TPA/ IAS				TPA/ IAR				TPA/ IAR				TPA/ IAS	
IAS=International AIDS society; IAR=International Association of Relationship Research; TPA=HIV Treatment and Prevention Adherence																
Proportion of effort devoted to training activities (% of year)																
Training activities	30				25				20				10			
Research activities	70				75				70				75			
R34 grant application development	0				0				10				15			
Total effort	100				100				100				100			

D. Monitoring of career progress. My K01 award will begin with a meeting organized by Dr. Darbes to review my training goals, research plan, methods, potential challenges, timeline, and target date for the R34 grant submission. Subsequently,

Dr. Darbes will hold annual meetings with me and other mentors to cover progress on activities, methodological and logistical challenges, emerging findings, and status of publications, presentations, and grant development. In advance, I will prepare annual progress supports

summarizing the status of training and research activities. Table 4.4 provides a list of metrics that Dr. Darbes will use to evaluate yearly progress towards my training and career goals.

Table 4.4. Metric to evaluate training competency	Y1	Y2	Y3	Y4
Training aim 1: interpersonal theories on health behavior				
1. Development of a theory-based qualitative interview guide for specific aim 1	√			
2. Development of conceptual framework to understand dyadic aspects of the HIV CC		√		
Training aim 2: methodological skills for dyadic data				
3. Development of a methodological approach to analyze dyadic qualitative data		√		
4. Completion of dyadic analysis for specific aim 2			√	
Training aim 3: healthcare and clinical aspects of HIV/AIDS				
5. Development of a toolkit to measure engagement in the CC in Malawi			√	
Training aim 4: behavioral interventions				
6. Development of behavioral intervention framework			√	
7. Submittal of an R34 grant application to develop and test a behavioral intervention				√

10. SPECIFIC AIMS

Antiretroviral therapy (ART) can substantially reduce mortality and morbidity in HIV+ individuals^{18,19} and prevent new HIV infections in serodiscordant couples²⁰. For these benefits to occur, HIV+ individuals must navigate a complicated series of steps to: (1) link into HIV care, (2) retain in care, (3) initiate ART, (4) adhere to ART and care appointments, and (5) achieve viral suppression. I refer to these steps as engagement in the HIV care continuum (CC). Without adequate attention to the behavioral aspects of the HIV CC, treatment will have limited success. For those on ART, retention in HIV care and treatment is necessary for optimal clinical outcomes, and to prevent treatment failure and the spread of multi-drug resistant strains of HIV²¹. Sub-Saharan Africa (SSA) is currently experiencing a dramatic increase in the number of HIV+ individuals who qualify for ART, calling for immediate attention to strategies that promote optimal use of HIV care and treatment. However, research on the HIV CC in SSA has largely focused on structural and individual-level barriers and facilitators²², resulting in a weak understanding of factors at the relationship level. In other settings, there is evidence that relationship factors cannot be ignored: relationship quality, treatment beliefs, and partner social support play an influential role on ART adherence and virologic control^{23,24}. Thus, a central component of this K01 is the conduct of research on dyadic aspects of engagement in the HIV CC among couples living with HIV.

The proposed research will be situated in Malawi, a resource-poor country in SSA where 11% of adults are HIV-infected²⁵ and an estimated 8,000 adults die each year from AIDS-related illness²⁶. Malawi is widely heralded as a success story of ART^{27,28} and more recently, for the roll-out of test-and-treat policies such as Option B+ for pregnant women²⁹. Despite these successes, large numbers of HIV+ individuals eligible for ART³⁰ and who have initiated ART³¹ continue to drop out of the HIV CC in Malawi. Furthermore, as more HIV+ individuals access ART while healthier, there are growing concerns about long-term adherence to ART³². Given the gaps in knowledge, the overall objective of this K01 is to gain an in-depth understanding of how the relationship context affects engagement in HIV care during the ART period of the CC (steps 3-4 above). The end goal is to develop a relationship-focused intervention to optimize engagement in the HIV CC in Malawi. While I am only studying a segment of the entire CC, I have proposed a feasible project with a comprehensive training plan to provide me with background skills and knowledge to study the entire CC over a long-term career. I will use an iterative mixed-methods study design consisting of the following specific aims:

Aim 1: To describe how the relationship context influences engagement in the HIV CC. To accomplish this aim, I will conduct qualitative interviews with 15 HIV+ individuals and their primary partners (15 couples) at the time of ART initiation and 3 months later. To gain a range of experiences, I will also conduct a single interview with 10 HIV+ individuals who have been on ART for at least one year and their partners (10 couples). Using interpersonal theory and analytic methods learned through my training, I will describe qualitatively how the relationship context (from both partners' perspectives) shapes engagement in the HIV CC.

Aim 2: To identify relationship-level barriers and facilitators affecting engagement in the HIV CC. To accomplish this aim, I will use the qualitative data from Aim 1 to develop a survey on relationship factors, contextual factors, and engagement in HIV care. The survey will be administered to 200 HIV+ individuals on ART (100 women, 100 men) and their primary partner who may also be on ART (200 couples). For partners on ART, I will extract additional clinical data from their medical records (e.g., history of missed appointments) and collect hair samples to measure drug concentration levels as an objective biomarker of ART adherence. Together, the survey, medical record data, and hair samples will be analyzed to identify the most salient relationship-level factors (from both partners' perspectives) affecting engagement in the HIV CC.

Aim 3: To develop a preliminary intervention to optimize engagement in the HIV CC for couples. To accomplish this aim, I will synthesize the findings of Aims 1 and 2 to develop a list of core intervention constructs to target for change and convene a meeting with my mentors to discuss intervention options. I will then conduct 4 focus group discussions with couples from the targeted communities and qualitative interviews with the following community members/stakeholders to elicit feedback on intervention options: (1) behavioral and biomedical scientists; (2) HIV/AIDS policymakers in Malawi; (3) HIV clinic staff in Malawi; (4) *ankhoswe* or traditional marriage advisors; and (5) local traditional authorities. These data will be used to inform the delivery mode, content, format, and evaluation measures for the intervention, tailored specifically to the Malawi context.

The proposed research will provide training in four areas: (1) interpersonal theory on health behavior; (2) methodological skills to collect and analyze dyadic data; (3) healthcare and clinical aspects of HIV/AIDS; and (4) behavioral intervention design and evaluation. The proposed training and research activities will build a strong foundation for a long-term career conducting couples research on the HIV CC in SSA. These activities will culminate in the submission of an R34 grant application to further develop and pilot test a relationship-focused intervention, which will be followed by an R01 application to conduct a full-scale randomized trial.

11. RESEARCH STRATEGY

A. SIGNIFICANCE

Malawi's HIV/AIDS epidemic is among the most severe in terms of its breadth and consequences. In Malawi, approximately 56,000 Malawian adults are infected with HIV each year¹ and HIV prevalence is among the highest in SSA (11%)²⁵. Expansions in ART have greatly prolonged survival, however, an estimated 8,000 Malawians continue to die each year from AIDS-related illness²⁶. In many settings throughout SSA, the majority of HIV infections occur within heterosexual partnerships such as marriage or cohabitation³³. In Malawi, marriage is nearly universal²⁵ and thus, the majority of people living with HIV are either married or in cohabiting unions (78%)³⁴. Within couples affected by HIV/AIDS, partners are more likely to be serodiscordant (9%) than seroconcordant positive (6%)²⁵. The burden of infection within married, serodiscordant couples signifies an urgent need for couple-focused interventions to prevent transmission within the dyad³⁵.

ART can prevent HIV transmission within serodiscordant couples and improve clinical outcomes.

Observational studies^{36,37}, population studies³⁸, and clinical trials²⁰ have shown that suppressive ART prevents sexual transmission of the HIV virus. The HIV Prevention Trial Network (HPTN) 052 trial demonstrated that early initiation of ART can have significant prevention benefits for serodiscordant couples²⁰. More recently, the PARTNER study demonstrated that the risk of HIV transmission through condomless sex in virally-suppressed ART patients was essentially zero³⁷. ART also greatly increases survival rates and decreases AIDS-related mortality^{18,26}. In Malawi, AIDS-related mortality declined by 10% after ART became free in 2005²⁶.

The success of ART depends upon high levels of engagement in the HIV CC. For the benefits of ART to be realized, HIV patients must successfully navigate a complicated series of steps across the HIV CC. Recent changes to WHO eligibility criteria for ART³⁹⁻⁴¹ are expected to substantially increase the number of HIV+ individuals entering the HIV CC. For those not yet on ART, retention in care is critical for treatment of opportunistic infections, ongoing staging, HIV prevention to children and partners, and prompt initiation of ART once indications arise. Patients who initiate ART later in the disease course may not fully recover from low CD4 counts as compared to those who start ART when they are healthier⁴². For those on ART, retention in care is necessary to evaluate medication toxicities, monitor for treatment failure, and ensure adequate adherence to ART. Poor adherence to ART can lead to virologic failure with first-line therapies and the spread of drug resistant strains of HIV²¹. Furthermore, second-line treatments for HIV/AIDS cost roughly double that of first-line treatments⁴³ and are likely to remain out of reach for many Malawians.

Despite the remarkable increase in access to ART in SSA, attrition rates remain high across the HIV CC. Approximately 50% of HIV+ individuals are lost between testing and ART eligibility assessment, and 32% of those who are eligible are lost before they initiate ART⁴⁴. As test-and-treat initiatives gain momentum, there is the potential to dramatically reduce attrition rates between testing and ART initiation. Thus, it will remain critical from a public health perspective to ensure optimal use of care and treatment during the ART period. Indeed, around one-quarter of people temporarily interrupt treatment⁴⁵ and another quarter are lost to follow-up by 3 years⁴⁶. Furthermore, a meta-analysis from SSA revealed that 23% of ART patients did not achieve adequate adherence (range: 2-70%)⁴⁷. In one of the few reports from Malawi, the Ministry of Health reported that 90% of ART patients were 95% adherent to ART⁴⁸; however, the same report raised concerns about the reliability of their pill-count measures, which has been linked to overestimated adherence if patients "pill dump" before clinic visits or forget pills at home⁴⁹. Hair biomarkers offer a promising alternative to pill-count and other self-reported measures^{50,51} and will be explored as an objective measure of adherence in this K01.

Relationship factors may provide important insight into our understanding of the HIV CC in SSA. In resource-poor settings, social relationships help HIV patients buffer the economic obstacles associated with HIV care⁵². In SSA, our research suggests that commitment, equality, trust, intimate partner violence, and communication are key relationship dynamics affecting decisions to test for HIV^{9,10,53,54}. Yet research on the broader HIV CC has failed to adequately study the relationship context, instead, focusing on psychosocial factors at the individual (e.g., stigma, discrimination) and structural levels (e.g., poverty, healthcare delivery)²². In the US, our team's research validates that relationship factors cannot be neglected; relationship quality, treatment beliefs, and partner support play a key role on ART adherence and virologic control^{23,24}. In SSA, a comprehensive understanding of relationship-level barriers and facilitators affecting engagement in the HIV CC is needed to develop effective interventions harnessing the powerful role of primary partners on health⁵⁵.

Couples-based interventions have the potential to improve engagement in the HIV CC. Across many settings, couples-based interventions are a proven approach for reducing HIV risk behavior⁵⁶. In the US, the provision of social support through a couples-based intervention called "SMART Couples" demonstrated significant improvements to ART adherence⁵⁷. In SSA, few couples-based interventions have been employed

to improve engagement in care. There are, however, two ongoing intervention trials that show promising results. *Masivukeni* (“Let’s Wake Up”) is a dyadic-based, multimedia intervention to help HIV patients maintain high levels of ART adherence through education, structured discussions, problem-solving, and communication exercises. Pilot data showed that intervention participants had a 10% improvement in adherence, as compared an 8% decrease in adherence for the control group⁵⁸. *Uthando Lwethu* (“Our Love”) aims to improve relationship dynamics and skills with the goal of increasing uptake of couples’ testing for HIV⁵⁹. Exit interviews with staff and high retention rates (over 90% at 3-month follow-up visit) suggest that couples were highly receptive to the intervention (final results available in August). While these interventions are encouraging, there are gaps that remain. More research is needed on specific interventions for couples that target the HIV CC in SSA (*Masivukeni* was designed for patient/treatment supporter dyads and *Uthando Lwethu* focuses on HIV testing, not care or treatment). Furthermore, both interventions were developed for South Africa, not Malawi. There is strong evidence that culturally-adapted interventions tailored towards specific populations are far more effective than generic interventions⁶⁰.

B. INNOVATION

The proposed project incorporates three innovative features: (1) a dyadic approach to understand engagement in the HIV CC in SSA; (2) the use of hair biomarkers to supplement other measures of adherence; (3) the development of an adaptive, relationship-focused intervention to improve engagement in the HIV CC.

1. Dyadic-level studies provide the opportunity to simultaneously examine the effects of individual, partner, and couple-level factors on health behaviors⁶¹. For *quantitative* data, these methods are advantageous because they allow for the ability to statistically model within- and between-couple differences in interpersonal attributes and behaviors and to potentially mitigate bias and error present in a single partner’s account⁶¹. Methods for analyzing dyadic *qualitative* data are less well developed. With the support of my mentors, I will publish a paper describing the methods developed, thereby contributing to the methodological as well as substantive literature base. Dyadic data will provide a stronger evidentiary basis for a relationship-focused intervention as compared to one couple member studied in isolation. To our knowledge, this study will be the first in SSA to analyze dyadic data on relationship factors affecting engagement in the HIV CC.

2. Superior measures of ART adherence are needed to supplement self-reported measures, which are prone to recall and social desirability biases^{62,63}. Hair specimens offer a promising alternative to existing measures of ART adherence. In the US, ART drug levels found in hair predicted virologic response more strongly than self-reported adherence^{64,65}. There is evidence from SSA that hair collection is feasible and acceptable to local research participants, and may serve as a low-cost biomarker of adherence in resource-poor settings^{50,51}. As far as we are aware, this study will be one of the first applications of hair biomarkers in a behavioral study on engagement in the HIV CC in SSA.

3. There is a need for optimized behavioral interventions that can maximize the impact on health. In South Africa, the results of a peer adherence intervention trial call for interventions tailored towards the most vulnerable groups⁶⁶. The study found no overall difference in treatment outcomes between the control and intervention groups, but a difference by group depending on family dynamics⁶⁶. Adaptive interventions provide an approach to optimize and tailor intervention and delivery using decision rules to link characteristics of individuals to levels and types of intervention components^{67,68}. In this K01, I will consider an adaptive design for couples to improve engagement in care. For example, an adaptive design would start with a less expensive intervention for all couples (e.g., text message reminder) and then apply a more costly and intensive intervention (e.g., a behavioral intervention) only to couples who are considered “non-responsive” (e.g., not engaged in care). For non-responsive couples, I will explore the utility of existing behavioral approaches^{58,59}, to be tailored to the cultural and clinical context of Malawi where similar interventions have not been developed.

C. APPROACH

C.1. Conceptual Framework

We draw upon Karney and colleagues’ Model of Dyadic Interaction⁶⁹ to conceptualize how multiple levels of factors, both proximate and distal, intersect to influence the dyadic interaction (Figure 1). At the center of the framework is the proposition that health behavior is regulated by the dyadic capacity for successful coordination. Starting from the proximate influences on dyadic capacity, I hypothesize that couple communication and relationship quality (e.g., trust, intimacy) will foster a more collectivist effort to support the HIV+ partner’s engagement in care. I also consider the role of social support from primary partners, which has been shown to enable HIV patients to remain on HIV treatment⁷⁰. Conversely, negative couple interactions such as couple conflict or violence could activate psychological stress pathways that may result in missed

doses or clinic appointments. Adherence to medications is generally worse in the presence of spousal or family conflict⁷⁰. Distal influences include partners' individual characteristics, behaviors, and perceptions and beliefs about ART, which will affect the dyad's capacity to engage in successful coordination. For example, partners with positive beliefs and attitudes about ART will be more likely to support their partner in obtaining care and taking medications. Harmful health behaviors such as alcohol use may negatively impact relationship quality and interfere with the provision of social support. Based on the literature⁷¹⁻⁷³, I also hypothesize that there are a host of other contextual factors that intersect with individual- and relationship-level factors to affect the dyad's capacity to engage in care. For example, I will consider how other sources of social support may moderate relationship dynamics and the types of support received from a primary partner. Figure 1 does not provide an exhaustive list of influences or pathways on the dyadic capacity. Using a mixed-methods study design, these will be identified during the qualitative phase and then included in the quantitative analysis.

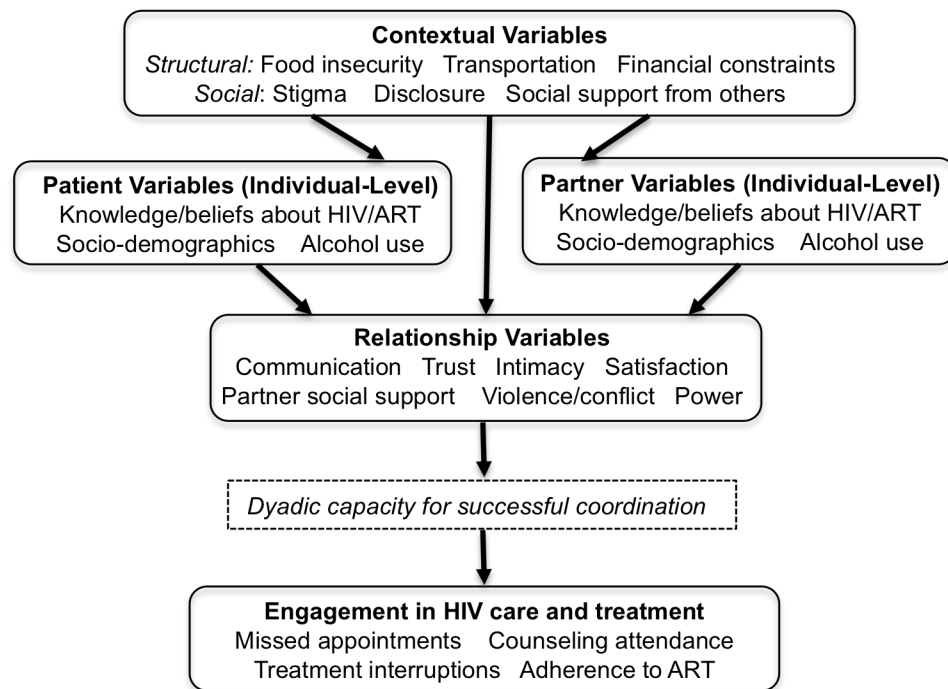


Figure 1. Dyadic framework for understanding engagement in HIV care and treatment (adapted from Karney et al. 2010)

C.2. Preliminary Studies

For the past 6 years, I have been working on projects in southern Malawi—the proposed site for this K01. For my dissertation, I found that relationship dynamics such as relationship unity (e.g., social support and communication), relationship violence, and trust were important factors than influenced decisions to test for HIV¹⁰. More recently, I received a pilot grant through UCSF's Center for AIDS Research (CFAR) with mentors Drs. Darbes and Johnson to conduct an exploratory study in KwaZulu-Natal, South Africa (P30-AI027763). The study was conducted in South Africa (versus Malawi) to leverage the resources and infrastructure of an ongoing couples intervention trial, *Uthando Lwethu*. We conducted cross-sectional qualitative interviews with a sample of HIV+ individuals and their partners (24 couples that were independent from the intervention trial) on ART for various lengths of time to understand how relationship dynamics shape decision-making along the HIV CC and the role of gender in these processes. Data collection is complete and translation of the interviews is underway. Using a subset of available transcripts, preliminary results suggest that the type and frequency of social support provided by a primary partner is highly dependent upon relationship and contextual factors—and their intersection—such as relationship commitment and satisfaction, having children together, living arrangements, employment status and/or migration for work, and problems with alcohol. Preliminary findings do not support the idea of a one-size-fits-all behavioral intervention, but rather a multi-faceted intervention tailored towards the different circumstances and characteristics of couples.

C.3. Methodology

C.3.1. Setting. The proposed research will take place in the Zomba district of southern Malawi, which is one of the most populated districts and is predominantly rural⁷⁴. HIV prevalence in Zomba is among the highest in Malawi at 14.5%^{75,76}. In Zomba, the decentralization of HIV care and treatment services has rapidly increased the number of patients on ART. The proposed study will be conducted at two HIV care facilities. The first site is the Zomba District Hospital, which serves around 22,000 ART patients. The second site is Pirimiti, a small rural hospital that serves around 2,000 ART patients. Data collection will be carried out by the Invest In Knowledge Initiative (IKI), which is a research organization based in Zomba. My mentors, Dr. Van Oosterhout (Dignitas International) and Dr. Muula (Malawi College of Medicine), will provide on-site support for the research.

C.3.2. Overview of Approach. I will use an iterative mixed-methods study design in which each specific aim builds on the next. For Aim 1, I will conduct 25 couple interviews among HIV+ individuals and their partners to describe how the relationship context affects engagement in the HIV CC. For Aim 2, using the information from Aim 1, I will develop a survey for 200 HIV+ individuals and their partners. The survey, supplemented with medical record and hair biomarker data, will be used to assess the relationship-level barriers and facilitators of engagement in the HIV CC. For Aim 3, I will collect qualitative data among the target population of couples and other community members/stakeholders. The combined data from Aims 1-3 will be used to map out a plan for a relationship-focused intervention that targets engagement in the HIV CC for couples in Malawi, which will be further developed and evaluated through an R34 grant application to be submitted in year 4 (see Table 1).

Table 1. Timeline of research activities

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Specific Aim 1 (qualitative)	P	C	C	A	A	M							A	M	M	M
Specific Aim 2 (quantitative)					P	C	C	A	A	M			A	M	M	M
Specific Aim 3 (qualitative)									P	C	A	A	A	M	M	M
Submit/resubmit R34 application													1/7			9/7

P=Preparation for research; C=Data collection; A=Data analysis; M=Manuscript preparation

C.3.3. Aim 1: To describe how the relationship context influences engagement in the HIV CC in couples

Rationale and Design: I will conduct in-depth interviews with HIV+ patients and their primary partners (15 couples) eligible for ART at baseline and 3 months later. While these data will not capture long-term outcomes, I expect that 3 months will allow time for respondents to stabilize on a treatment regimen. ART patients in Malawi are often lost-to-follow-up within months of starting ART⁷⁷; therefore, the follow-up period provides an opportunity to collect information on those who discontinue ART. To supplement this sample with more experienced ART patients, I will also conduct a cross-sectional interview with a sample of 10 couples on ART for at least one year. This adds up to a total of 25 couples, which is a feasible and appropriate number based on our experience with the pilot study (24 couples), other qualitative research on ART⁷⁸, and the recommended number of interviews required to reach data saturation (12 interviews)⁷⁹.

Eligibility and Recruitment: Couples will be eligible if they are: (1) in a relationship for at least six months and together since the start of ART; (2) more committed to each other than any other partner; (3) in a non-polygamous union; (4) age 18 and older; and (5) have an “index patient” eligible for ART (or currently on ART for at least one year, for the cross-sectional couples) who has disclosed their HIV and ART status to their partner. Couples will not be required to be sexually active since we will not capture sexual risk behaviors. However, since the majority of couples will be married, the majority will be sexually active by default. For the 15 longitudinal couples, we will recruit them when they attend ART counseling together (in Malawi, treatment guardians are typically spouses). We will also use passive recruitment strategies by placing study fliers in clinics and invoking the help of staff to inform newly diagnosed individuals about the study. Index patients can give information about the study to their partner, who can contact us if interested. For the 10 cross-sectional couples, we will use the passive recruitment strategy. To obtain a diverse set of experiences that likely differ by gender, we will purposely select half of the HIV+ index patients to be female (the other half will be male).

Data Collection: Prior to data collection, I will spend a month training two interviewers (one male, one female) on probing and listening techniques through role-playing exercises, how to build rapport with respondents, the study procedures, and ethical issues with qualitative research. I have developed training manuals and facilitated trainings for three separate qualitative projects in SSA. The semi-structured interviews will be conducted in Chichewa and audio-recorded. Gender-matched research assistants will interview each partner separately, but simultaneously. Interviews will take place at the IKI research center or in respondents’ homes and will last 60-90 minutes. In consultation with my mentors, I will develop an interview guide based on interpersonal theory. At the first interview, respondents will be asked to talk about their relationships (e.g., how they met, what attracted them to their partner), the circumstances of their own or their partner’s HIV diagnosis (e.g., how disclosure was handled, conversations about HIV), and the events leading up to the start of ART (e.g., medical visits, social support from partner). At the second interview, respondents will further describe their experiences taking ART, including events that occurred between the two interviews. Table 2 provides examples of possible topics and questions to be included in the guide based on my conceptual model.

Analysis Approach: Given that one of my training goals is to learn how to analyze dyadic *qualitative* data, I will focus on the couple as a unit of analysis. I will use the following process, to be refined with Dr. Comfort. First, the couple interviews will be transcribed and translated into English, typed into MS Word, and imported into ATLAS.ti for analysis. Next, with a research assistant, I will code each partner’s interview by assigning a *priori* codes such as “social support” and new codes that emerge inductively to segments of text. After coding

both partners' transcripts, I will write an analytic memo for the couple that summarizes their relationship dynamics, key themes or constructs with quotes, and *within*-couple areas of consistency and discrepancy. I will then code the next set of transcripts and write an analytic memo for the couple, and repeat this process until all 80 transcripts are coded and 25 summary memos (for each couple) are written. I will construct data matrices to compare and contrast codes and themes *between* couples and groups of couples⁸⁰. Each row in the matrix will represent a couple and each column will represent a particular code or theme (e.g., "social support"), which could then be further stratified by variables such as couple ART status. The findings will inform the measures for Aim 2 (in Table 3). For example, I expect that adherence will be affected by partner social support; however, more information is needed on the type of support provided and by whom. Finally, the findings will inform the selection of other intervening variables affecting the dyadic capacity to engage in care.

Table 2. Example topics and questions from qualitative interview guide

Topic/theoretical construct	Item
Couple communication	1. Tell me about a recent conversation you had with your partner about HIV/ART.
Couple conflict and/or violence	1. What happens when you and your partner argue? Probes: Has your partner ever beat you? 2. Has this ever affected your ability to attend clinic appointments or take your ARVs? How so?
Social support	1. How did your partner respond when you disclosed your status? 2. Who helps you with your care and medications, and how? Probes: Does your partner help? Who watches the children? Who helps you pay for transport? Who reminds you of appointments? 3. Who is your treatment buddy and why?
Treatment beliefs	1. What did you initially think about ARVs? Has this changed? Probe: Good things? Bad things? 2. What does your partner think about ARVs?
Treatment-related barriers	1. What was it like when you first started your ARVs? Did you experience any side effects? Did this ever prevent you from taking your pills?
Structural barriers	1. What makes it easy or difficult for you to attend clinic appointments (or take your ARVs)? Probes: Travel issues? Money issues? Lack of food? Who supports you with this and how?
Stigma and disclosure	1. When you found out your status, were you worried what people would think of you? Do you worry that people might find out you are on ARVs? Please explain. 2. Who knows about your status and why?
Engagement in the HIV CC	1. Tell me about a time you missed an appointment (or forgot to take your pills). What happened?

C.3.4. Aim 2: To identify relationship-level barriers and facilitators affecting engagement in the HIV CC

Rationale and Design: Using the factors and pathways identified from Aim 1, I will construct a survey to collect data on 200 ART patients and their partners. In combination with medical records and hair biomarkers, survey data will be used to test for associations between relationship factors and engagement in the HIV CC.

Eligibility and Recruitment: Couples will be eligible to participate if they are: (1) in a relationship for at least six months; (2) more committed to each other than any other partner; (3) are in a non-polygamous union; (4) age 18 and older; (5) have at least one HIV+ index partner currently on an ART regimen for the past 30 days; and (6) the index partner on ART has disclosed their HIV and ART status to their primary partner. We used similar eligibility criteria from two couples' studies on HIV^{24,59}, which have been successful. These criteria will ensure that couples are legitimate (not reporting a false partner) and committed. Since this is a dyadic study, couples must have disclosed about HIV to provide information on the partner's experience of HIV care and treatment. Polygamous unions will be excluded due to analytic challenges. We will use similar recruitment strategies as Aim 1. Of the 200 ART index patients, 100 will be women and 100 will be men. Within couples where at least one partner is HIV+, we estimate that up to 30% may be seroconcordant⁸¹ (thus increasing our sample size to 266 ART patients nested within 200 couples).

Survey Development and Pilot Phase: Many of the relationship measures in Table 3 have demonstrated good reliability and validity for the African context¹⁴. I will make minor modifications to the scales for the Malawi context and tailor the wording to the gender and ART status of the respondent. Once finalized, the pilot survey will be translated into Chichewa and back-translated. Next, I will conduct cognitive interviews⁸² with a small sample (N=20) to ensure the measures capture the constructs of interest, are comprehensible, and culturally-relevant. The revised set of items will be piloted on a convenience sample of ART patients (N=50). Regular meetings with mentors and staff will identify weaknesses of the instrument, translation issues, interviewer errors, and low variability, which will be corrected. Finally, I will evaluate the feasibility of using a mobile device (e.g., tablet, phone) to administer the survey. This has been a successful approach for another couples' study in Africa⁵⁹. As a fallback option, I will administer a paper-based survey.

Data Collection and Measures: There will be 3 sources of data: a survey, medical charts, and hair samples.

Survey. We will setup an appointment with the couple to interview each partner separately, but simultaneously. Gender-matched interviewers will administer the survey to each partner in a private location (e.g., IKI research center). Table 3 summarizes the preliminary measures, which will be finalized after Aim 1.

Table 3. Preliminary Measures for Aim 2

Constructs	Measures/Source
Relationship Variables	
Communication style	Mutually constructive communication ⁸³
Relationship quality (trust, satisfaction, commitment, intimacy, autonomy)	Dyadic trust scale ⁸⁴ ; Investment model scale ⁸⁵ ; Relationship values scale ⁸⁶
Partner-specific social support	HIV care-specific social support scale ⁸⁷ ; Treatment reminders ⁷⁰
Intimate partner violence and conflict	WHO Domestic Violence Questionnaire ⁸⁸ ; frequency of arguments with partner
Relationship power	Sexual Relationship Power Scale ^{89,90} ; Gender Equitable Norms (GEM) scale ⁹¹ ; Relationship values scale (equality subscale) ⁸⁶
Individual Variables	
Treatment beliefs and knowledge	HIV treatment optimism scale for Malawi context ⁶ ; ART beliefs in the African context ^{92,93}
Alcohol use	Alcohol Use Disorder Identification Test (AUDIT) ⁹⁴ ; alcohol use in the past month
Treatment side effects	The self-completed HIV symptom index ⁹⁵
Contextual Variables	
Structural factors	Household Food Insecurity Access Scale ⁹⁶ ; transportation (distance, time, and cost of travel to clinic); amount spent monthly on HIV medication, clinic costs, or missed income
HIV stigma	Internalized stigma ⁹⁷
HIV status disclosure to others	For each additional individual named in the social network questionnaire ⁹⁸ , participants will be asked about whether they disclosed and received HIV-care specific social support.
Social support from others	
Background and Control Variables	
Socio-demographic factors	Gender, age, education, employment status, Household Goods Index (economic status) ⁹
Relationship characteristics	Marital status, cohabitation, relationship length, children together, couple HIV & ART status
Treatment-related variables	Length of time on ART; ART regimen; WHO stage at time of ART initiation (Medical chart)
Engagement in Care Variables	
Treatment interruptions; appointment adherence	Medical chart review
Adherence self-efficacy	HIV-ASES scale ⁹⁹
Self-reported ART adherence	Visual analog scale (VAS) ¹⁰⁰ and partner version of the VAS ¹⁰¹
Drug exposure levels present in hair	Hair samples

Medical chart review. Following the survey, research assistants will locate patients' ART master cards at each health facility, take a digital photograph, and then extract the data into a database at the IKI research center. Master cards contain information such as ART initiation dates, WHO stage at initiation, treatment regimen, and appointment history (with information on missed appointments and treatment interruptions).

Hair biomarkers. I will follow the procedures documented by Gandhi et al.⁶⁵ for hair collection. In brief, around 100 strands of hair will be cut as close to the scalp as possible. The distal end of the hair sample will be marked and placed in aluminum foil to avoid sun exposure. The enclosed foil will be labeled and placed in a sealed plastic bag. Respondents with hair too short will be rescheduled for hair collection 2-4 weeks later. Hair samples will be stored at room temperature in locked cabinets until transported back to UCSF for analysis. Hair assays have been developed for two common antiretroviral drugs in Malawi: Nevirapine and Efavirenz.

Hypotheses and Analysis Approach: I will test the following preliminary hypotheses with key relationship variables, which are the innovation and crux of this research while also facilitating my dyadic analysis training needs. Hypotheses will be added and/or refined based on the findings of Aim 1.

1. Couples with higher intimacy, trust, communication, commitment, and satisfaction will report higher mean levels of social support as compared to couples with lower levels of intimacy, trust, etc.
2. Partners of ART patients in couples with higher intimacy, trust, communication, commitment, satisfaction will provide more social support than partners in couples with lower intimacy, trust, etc.
3. ART patients in couples with higher intimacy, trust, communication, commitment, satisfaction, and social support will be more engaged in care as compared to ART patients with lower intimacy, etc.
4. ART patients in couples with higher relationship violence will be less engaged in care as compared to ART patients in couples with less relationship violence.
5. Relationship power will be associated with engagement in care, but depending upon the more powerful partner's beliefs about ART. For example, if the husband is the more powerful partner, the wife will be more likely to adhere to treatment if her husband is supportive of ART (actor-partner effects with interaction).
6. Both partners' treatment beliefs such as knowledge of ART and level of treatment optimism will be positively associated with engagement in care (actor-partner effects).

To control for non-independence (i.e., degree of similarity between partners) if both partners are on ART, I will employ Kenny et al.'s multi-level regression technique for dyadic data⁶¹ with couple ART status as a between-couple effect. For Hypothesis 1, regression models will include couple averages and the deviation of each partner's score from the couple average to compute between- and within-couple effects. For Hypothesis 2, I will use the Actor-Partner approach to assess the partner effect of HIV care-specific social support on the ART

patient's engagement in care. The Actor-Partner approach is based on the premise that one partner's attributes and behaviors can affect the other partner's outcomes⁶¹. For Hypothesis 3 and 4, regression models will include couple averages for all predictor variables. For Hypothesis 5, regression models will include main effects of both partners' level of power and beliefs about treatment on the ART patients' engagement in care. Because I may be limited by sample size, I will explore interactions between higher power and each partner's beliefs about treatment. For Hypothesis 6, I will use the Actor-Partner approach to test for actor and partner effects of treatment beliefs on engagement in care. Missing data will be handled using multiple imputation with chained equations¹⁰². All models will control for socio-economic factors, relationship characteristics, and treatment-related variables. Other variables may be included as mediators or moderators based on pathways identified in Aim 1. For instance, the level of social support from a primary partner may vary depending on structural barriers or social support from others and therefore, I would include an interaction term in the models. An important training goal of mine involves learning multiple dyadic analysis methods (e.g., mixed models, GEE, SEM) and when to apply them. If the relationship variables are highly correlated, I will consider modeling them as indicators of latent variables using the SEM program *Mplus*.

Sample Size Plan: We will recruit 200 ART index patients, but anticipate up to 30% of partners may also be on ART⁶⁴. To be conservative, my power calculations are based on 200 ART patients with a 50/50 split on gender. Assuming $\alpha=0.05$, power=0.80, and a multiple of R of 0.30 among the independent variables, I used the NCSS PASS software to compute the minimum detectable odds ratio and Cohen's standardized effect size metric h for a binary outcome bounded by base rates of $p_0=0.73$ ⁸⁵ and $p_0=0.90$ ³². For the primary analysis, I will test for associations between gender and ART adherence. The standardized effect size for an ART adherence value of 0.73 was 0.40 with a minimal detectable odds ratio of 2.85. The standardized effect size for an ART adherence value of 0.90 was 0.44 with a minimal detectable odds ratio of 10.84. Benchmarks for standardized effect sizes are 0.20 (small effect) and 0.50 (medium effect)¹⁰³. Thus, the primary analysis will be able to detect effects between small and medium with a tendency towards medium.

C.3.5. Aim 3: To develop a preliminary intervention to optimize engagement in the HIV CC for couples

Rationale and Design: Based on the findings of the preliminary study indicating a need for interventions tailored towards couples' varying needs, we will develop an optimized solution to increase engagement in care using an adaptive intervention design¹⁰⁴. Three sources of input will be required to map out the intervention plan, which will be further developed and tested in an R34 grant application: (1) empirical data from Aim 1 and 2, (2) scientific expertise of my mentorship team, and (3) feedback from the community including the target population of couples (the crux of Aim 3). First, I will synthesize the findings of Aim 1 and 2 to develop a list of core intervention components, which will consist of constructs, variables, or issues that can be directly targeted for change to enhance the dyadic capacity to engage in the HIV CC. An example of a core intervention construct may be couple communication skills needed to coordinate the HIV+ partner's clinic visits. Using this information as a framework for discussion, I will convene a meeting with my mentorship team to brainstorm intervention options. Prior to the meeting, I will compile a list of evidence-based interventions to discuss. Next, I will acquire input from the community and target population of couples to carry out two phases of the ADAPT-ITT model¹⁰⁵: *assessment* (to assess the capacity of local organizations to implement potential interventions) and *decision* (deciding on the preliminary relationship-focused intervention and comparison interventions).

Eligibility and Recruitment: For the *assessment* phase, I will conduct approximately 20 semi-structured interviews with the following groups to obtain input on intervention ideas: (1) behavioral and biomedical scientists from international settings including Malawi; (2) HIV/AIDS policymakers in Malawi; (3) HIV clinic staff; (4) *ankhoswe* or traditional marriage advisors; and (5) local traditional authorities from the targeted communities (e.g., village chiefs, religious leaders). To obtain feedback from the target population of couples, I will conduct four focus group discussions (FGDs) comprised of 5-7 participants each (20-28 respondents total). We will ask couples who participated in Aims 1 and 2 to participate. If they agree, we will provide appointment cards with the date, time, and location of the FGD to be followed-up with a reminder phone call.

Data Collection: For stakeholder interviews that can be conducted in English, I will conduct them in-person. For interviews in Chichewa, a trained research assistant will conduct the interviews. All interviews will use a semi-structured interview guide with questions on staff resources and capabilities, capacity, space, and reactions to several intervention options. The FGDs will consist of separate groups of women and men, facilitated by gender-matched interviewers, and will take place in a convenient and comfortable location such as the IKI research center. The FGD instruments will elicit reactions to intervention ideas based on Aims 1/2.

Analysis Approach: Interviews and FGDs will be audio-recorded, translated into English if necessary, and typed into electronic format. Together with a research assistant, I will code the data for *a priori* themes such as: (1) positive/supportive reactions; (2) negative/unsupportive reactions; (3) couples' needs and concerns; (4)

intervention components, content, and delivery; and (5) cultural considerations. For the *decision* phase, these findings will be discussed with my mentors to decide on the preliminary design of the relationship-focused intervention and the appropriate comparison group (e.g., the standard of care in Malawi). This will culminate in an R34 grant application to refine the intervention approach and the design of the subsequent clinical trial.

C.4. Potential problems and alternative strategies

For Aims 1 and 2, couples will not be selected based on serodiscordant/concordant HIV status. Given that this is a formative study, there is a desire to remain inclusive and flexible in the approach. However, it is possible that higher-functioning couples, including those who formed their relationships based on a shared HIV+ status, may be more likely to enroll. During recruitment, I will closely monitor couple HIV status and incoming data to ensure a sufficient number of serodiscordant couples are enrolled and consult with my mentors to adapt our procedures, if necessary. It may also be difficult to recruit ART patients who recently started treatment, resulting in a biased sample with better engagement. I will closely monitor incoming data on respondents (e.g., length of time on ART) and regularly communicate with staff about any recruitment challenges. If necessary, I will consult with my mentors to modify the recruitment strategy using approaches tailored towards difficult-to-reach populations. For Aim 2, hair samples have not been collected for HIV research in Malawi. Although negative reactions are rare in other African settings^{50,51}, respondents may refuse to provide hair samples. This risk will be mitigated by outreach with the community and close monitoring for high refusal rates. If this occurs, I will assemble an *ad hoc* FGD with ART patients to understand reasons for refusal and ways to increase acceptability before proceeding. If it is not possible to collect hair, our alternative measure of ART adherence, the VAS scale, is a reliable measure of self-report¹⁰⁶ and correlates well with objective measures¹⁰⁰.

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